EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2014
EMA/CHMP/CVMP/QWP/63698/2014
Committee for Human Medicinal Products (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on NIR guideline

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Active Pharmaceutical Ingredients Committee (APIC) of the European Chemical Industry Council (Cefic)
2	Bristol-Myers Squibb International Corporation
3	BUCHI Labortechnik AG
4	European Federation of Pharmaceutical Industries and Associations (EFPIA)
5	Institute of Biotechnology & Bioengineering Centre for Biological & Chemical Engineering Bioengineering Research Group(prof Dr José Cardoso Menezes, Technical University of Lisbon (Portugal)
6	International Federation for Animal Health Europe)
7	Dr. Ralf Marbach (VTT Technical Research Centre of Finland)
8	Merck Sharp & Dohme (Europe) Inc.
9	College ter Beoordeling van Geneesmiddelen/Dutch Medicines Evaluation Board
10	Teva Pharmaceutical Industries Ltd. (content not to be made public)

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

	Stakeholder no.	General comment (if any)	Outcome (if applicable)
G01	1	Please shorten the document; some definitions are too complex and some information seems to be repeated throughout the document.	Comment noted. The guideline covers the regulatory requirements for the development and management of a range of NIRS applications (such as qualitative and quantitative procedures, the use as PAT). We acknowledge that this is not a short guideline. However, efforts have been made to avoid complex definitions and repetitions.
G02	1	In the current guideline, CPMP/QWP/3309/01, tables are used to describe the data requirements (chapter 4). This approach should be re-considered for the revision.	Comment agreed. The data requirements are now summarised in the section 'Summary of general data requirements'
G03	1	This document provides just a basic overview of the different actions/steps. A good NIR guideline should also give you detailed instructions on how to build a NIR method (qualitative or quantitative) in an easy to follow step-by-step format.	The scope of the guideline is to describe the regulatory requirements for marketing authorisation applications and variations which include the use of NIR, it is not our intention to write a manual.
G04	2	We have found the revision of the draft Guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations to be a significant improvement as compared to the earlier Rev1 version. The guideline provides clarity around what the EMA expects from applicants wishing to adopt NIRS, without being overly prescriptive. This guideline will certainly be a valuable reference for practitioners of NIRS in the pharmaceutical industry.	Comment noted.
G05	2	Section 4.3.4 could cause some degree of confusion to readers with regards to what is expected when OOS results are encountered. Clarification around how	Comment agreed. The section on out of specification (OOS) results in routine batch

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		to proceed in the interim stage where the NIR results have been shown to be inaccurate, while the investigation shows that the batch should pass using a reference method, is requested. It appears that the intent of the section is to ensure that one does not flip-flop between the two approved release tests: traditional reference method versus NIRS, however it appears to limit ones' ability to release a batch until the NIRS method has been updated and revalidated, as per Figure 1. How would one proceed to manufacture commercial product in this interim timeframe, which for some methods may be several months, depending upon the complexity of the challenge?	analysis has been updated to clarify that the commercial manufacture can proceed using the reference method while the NIRS method is being updated or revalidated.
G06	3	The revised version of the Guideline on the use of NIRS by the pharmaceutical industry and the data requirements for new submissions and variations is a significant improvement on the previous version. A number of concerns previously raised by industry have been addressed in this revised document, and this is very much welcomed. However, a number of sections require further work, in order to provide further guidance and/or improve clarity to facilitate usefulness and applicability of the guideline. The precise use of language/terminology throughout the guideline will be very important for the correct interpretation of the final document, but editorial comments have largely been excluded to focus on the critical and major issues. Specific comments are presented below, which should help to address these points.	Comment noted.
G07	5	This Guideline essentially prescribes a QbD approach to analytical method development. We think it would be useful to refer it or emphasize it in the Guideline text.	Comment agreed. NIRS is underpinned by the principles of Quality by Design (QbD) and a reference to QbD has been included in the guideline.
G08	5	EMA Guideline states: NIRS Procedure = Method + Model NIRS Procedure = Hard + Soft Components NIRS Procedure = RA + DoE + MVDA + ContImprovment	Comment noted.

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G09	5	This Guideline takes a very interesting perspective (also in line with QbD and PQLI) of Data Collection and Data Interpretation, as information extraction from data (i.e., a knowledge management perspective which will allow better assessment of applicant's prior knowledge). If that is so, the Guideline must consider the process that generates the samples which NIRS will then measure. That will bring a whole other number of issues such as those of NIRS as a process (i.e., PAT) monitoring tool. Such perspective is not explicitly considered in the present text (at least is not explored fully as such). To ignore such link to the process (e.g., process dynamics which may affect the sample's matrix and the method's performance) the Guideline should be a Method's Guideline not a Procedure Guideline.	Comment agreed. A section on NIRS in Process Analytical Technology (PAT) applications has been included in the guideline.
G10	7	This General Comment relates to quantitative modelling, not qualitative modelling. I speak as a private person, not as a representative of any organization. Rev2 is much better than Rev1 and we thank the authors for the effort made. The same fundamental weakness that caused my comment to Rev1, however, is still present in Rev2. The arguably most important property of chemical analysis methods is selectivity (alias specificity). Compromising on this fundamental property is tantamount to playing with fire. The true meaning of selectivity is the "ability to assess unequivocally the analyte in the presence of components which may be expected to be present" (ICH Q2, see also IUPAC). This meaning is still not presented anywhere in the text. Rather, Rev2 still employs a seriously diluted meaning, see the important Section 6.4.3.	Comment agreed. The guideline has been revised to clarify that for specificity, the quantitative procedure should be able to assess unequivocally the analyte in the presence of components which may be present.
G11	8	Merck & Co., Inc, known as MSD outside the United States and Canada, appreciates the opportunity to review this draft of the guidance on NIRS and welcomes the improvements seen in this draft from earlier versions. The consultation of industry via the EFPIA NIRS expert group in 2011 has allowed to use scientific dialogue in the field of NIRS to arrive at a guidance that better balances the need for consistent application with the ability to use the NIRS	Comment agreed. The guideline has been revised to clarify that other approaches to calibration and validation may also be appropriate, if justified.

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		methodology with as much success in the regulated pharmaceutical industry as it has been used in many other industries for years. However we would like to comment on certain aspects of the guidance draft that would require further refinement: Sections on approaches to calibration and validation (specifically the whole of section 6) are written with too much detailed and prescriptive guidance. The approaches outlined for example in section 6.2.3 (choice of sample sets) describe one potential approach but do not in its current form accommodate other proven approaches. In the absence of the ability to create a guidance that serves as a comprehensive guide on how to develop and validate NIR methods – which would be the scope of a more scientifically targeted document – it is suggested to remove much of the level of detail, or alternatively clearly label such that other approaches can be used and justified. If the current wording goes forward there is a high likelihood that it will be regarded as specific requirements by some reviewers of dossiers. There are many NIR methods in successful production use for years which use specific practices that differ from those outlined in section 6.	
G12	8	The requirements around changes outside of the "scope" of the NIR method need further refinement. It is important for the applicability of NIR in the typical GMP production environment to minimize the uncertainty in the process of managing models. Any need to file variations for changes in the NIR method, which typically would not require variation filing for conventional analytical methods (example: changes of software; range of method through based on calibration) will prohibit the use of NIR in routine production as it will add time and (approval) uncertainty to the management of methods. One of the differences that might warrant further exploration is the distinction between "method" and "model" for a NIRS application. With "method" some fundamental aspects of the analytical technology are described, such as NIRS (vs. for example UV), measurement in transmission, etc.. These aspects are likely to not require a flexible change management as they are more set in long terms. The "model", which would encompass the means by which a calibrated	Comment agreed. Section 7 of the guideline has been updated to clarify which changes would lead to a variation application and which would not. Examples will be given in an Annex.

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		NIRS method would be correlated to, for example, reference values, would on the other hand require a change control approach that satisfies the typical use scenario which has been proven to be scientifically valid in many other industries. A "model" will change occasionally throughout the life cycle of the method, which is positively acknowledged in this guidance. As long as the initial requirements and specifications of the method validation are accomplished it should not require any regulatory variation filing to change the model, but rather and internal quality system process which is subject to inspection. One solution would be to minimize the detail required in defining the "scope" of the NIR method. Another solution would be to include a mechanism for the applicant to make future changes that are outside of the scope of the method without filing a variation when the applicant demonstrates a robust internal change management system in the dossier.	
G13	8	Method transfers for NIR methods are very similar in scientific and procedural rigor to method transfers for conventional methods. The requirement to submit a comparability protocol for prior approval of the approach is scientifically unnecessary and puts an additional burden on the use of NIR methods established in one instrument or another manufacturing site, and will hinder the use of NIR in the GMP environment. NIR transfers for both scenarios have been successfully accomplished with many examples and should be regulated, like all method transfers, within the internal quality system of the company, with documentation available upon inspection.	Comment not agreed. Transfer of a NIRS procedure is not a simple process and there are few references to this in the literature. Therefore we believe that the transfer of a NIRS procedure to another instrument should be the subject of an appropriate comparability protocol.
G14	9	The guideline is a practical tool in development of a NIR method for quality control. It is clear what data is required in the application dossier and what steps need to be taken in order to develop the method. Justification is required for all steps in the development. Practical examples are included in all sections. Overall the guideline is written in a clear and stepwise matter. There is however quite some repetition of information over the several sections of the Guideline, which preferably be dealt with by references between these	Comment agreed. The guideline has been updated to bring it in line with the recently revised Ph.Eur. Monograph 2.2.40 on NIR. The section 'Out of Specification (OOS) results in routine batch analysis' has been updated to clarify when a batch can be released in case of an OOS result. Efforts

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		sections. For example, variables affecting the spectral response are listed in the development section but are also included in the robustness studies during validation of qualitative and also quantitative methods. One specific remark concerns the handling of outliers and out of specification results obtained with the NIRS method. The content of sections 4.3.3 and 4.3.4 seems not in line with the Ph Eur Monograph 2.2.40 – Near-infrared spectrophotometry. In the Ph Eur it is stated that if an outlier result by NIRS is combined with a result of another appropriate analytical method within specification, the sample still meets the specification. Hence, release of the batch should be possible, whereas the draft revision of the Guideline forbids this. This apparent disagreement of the draft revised Guideline should be resolved. If the NIRS method concerns the secondary method, the results of the reference method will always be leading. So if the batch complies according the reference method result, it may be released, but the NIRS method should be re-developed using the NIRS results of that batch.	have been made to avoid repetition of information in the guideline.

2. Specific comments on text

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
1	67	5	Comment: CAPS should be on for "Optimisation…"	Editorial comment noted.
			Executive Summary	
2	91	4	Comment: RTRT can be achieved via NIRS (for example) and without any use of the QbD approach. Proposed change : Remove sentence ~~'When used as such, NIRS is underpinned by the principles of Quality by design (QbD)'~~	Comment not agreed. Real time release testing and QbD are linked, as an enhanced control strategy is applied to support real time release testing.
3	98-100	8	Comment: Positive recognition by guidance that life cycle management is critical for success of NIR technology. However concept of connection to "scope of method" needs more definition.	Comment agreed. An example of changes within and outside the scope of a NIRS procedure will be published in a separate Annex.
			1. Introduction	
4	112	1	Comments: The use of "easily" does not add any value to the sentence. Proposed change: Remove "easily"	Comment agreed. "Easily" removed.
5	112-121	4	Comment: There seems to be too much emphasis on "reference methods". In many cases (especially on-line applications of NIR), there are no reference methods which can achieve the same level of performance. The NIR technology should be evaluated on its own merits, and not simply be viewed as an alternative to "reference methods" which may actually be inferior in some or many respects. Proposed change: Expand the scope of this section to enable a scientific and risk based approach to consider the suitability of NIR applications from first principles, and avoid reliance on comparison against potentially	Comment partially agreed. Emphasis on reference method is necessary when NIRS uses a calibration model. Indeed, for PAT NIRS procedures, e.g. dynamic process monitoring of a powder blend where no calibration model is requested, there is no emphasis on conventional reference methods. This is reflected in the updated version of the guideline.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			inferior reference methods.	
6	114-115	4	Comment: It does not take into account that NIRS can be used as a primary method, as well as an alternative method. NIRS can be used qualitatively for numerous applications Proposed change (if any): Remove sentence "~~Consequently, NIRS is not generally used…~~"	Comment agreed. The text has been revised to ensure that the message is clear that NIRS may be used as a 'direct method' under some circumstances and to ensure that NIRS is not portrayed as inferior.
7	116-120	1	Please rewrite/simplify paragraph, some members interpreted this as an indication not to use NIR for batch release	Comment agreed. The text has been rewritten.
8	117-121	8	Comment: Guideline suggests that NIR methods that are based on reference methods are always used for release testing (or in other words does not acknowledge that NIR method for in-process tests, controlling properties that ultimately are tested via a conventional release test later, are also possible). This section might seem to imply that focus of NIR methods and their regulatory consideration is on release testing methods, and the related ability to repeat these tests with conventional analytical techniques, to be repeated by control laboratories. We suggest to clarify this. Also what are expectations on how to submit details on reference methods for such in-process testing (not release or real-time release) methods, reference to expectations set in section 4.2.4 lines 264-276? The term "reference methods developed in conjunction" seems to imply a parallel development of the reference method. Scenarios are possible where reference/conventional methods are already developed, and a NIR method is developed later. This should be possible (vs. the interpretation "developed parallel in time").	Comment noted. The guideline focuses on NIRS procedures used in regulatory submissions and doesn't cover all of those used in development. However, the guideline does not intend to suggest that NIRS procedures can only be used for release.
9	118-120	5	Comment: The statement in these lines is unclear. Specs will be the same irrespective of the methods as long they refer to the same CQAs; reference methods (reference analytics) can	Comment noted. The text has been revised.

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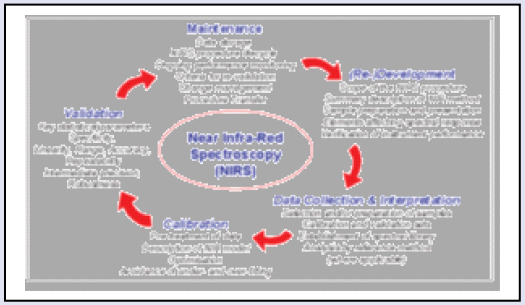
			be mentioned in the applications, but then the applicant has to keep them operational or it suffices to mention the equivalency and comparability of the developed NIRS Procedure to the prescribed reference method?	
10	121-123	1	Comment: Please rewrite/eliminate paragraph; if the purpose is to leave an open space to use spectral standard deviations, this is already mentioned in section 4.6	Comment noted. The introduction of the guideline has been rewritten.
11	122-124	4	Comment: It should be recognised that the lack of availability of "conventional reference methods" may reflect a fundamental shortcoming in such reference methods. For example, the use of NIR for on-line applications such as powder blend monitoring, it is perhaps irrelevant to justify or describe why "conventional reference methods" are not being used since this is simply attributable to the lack of capability of such reference methods. Proposed change: Avoid the apparent dependence of demonstrating suitability of NIR applications against "conventional reference methods".	See comment No 5.
12	122-124	5	Comment: Rewrite these 3 lines, as they don't read well.	Comment noted. The introduction of the guideline has been rewritten. However, the iterative nature of NIRS method development and use is important.
13	130-132	8	Comment: Very positive that the concept of management of models across the life cycle of NIR methods is acknowledged. Would suggest to clarify that the term "recommended" at the end of the statement does not mean that the model needs to be updated every time a new batch is analyzed, but rather only if appropriate. Proposed change (if any): Add "if found appropriate" at the end of	Comment noted. The introduction of the guideline has been rewritten.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			the sentence.	
14	133-142	3	 Comment: In Figure 1: The key statistical parameters of validation should be separated from qualitative and quantitative procedures because the parameters are different. Proposed change: Validation, Key statistical parameters: for qualitative procedures: Specificity, robustness for quantitative procedures: Specificity, linearity, range, accuracy, precision, robustness Limits of detection and quantification.	Comment not agreed. The figure illustrates the concept of lifecycle. Clear instructions regarding validation are outlined in further sections of the guideline.
			2. Scope	
15	155	1	Comment: "finished product" is misleading Proposed change: Substitute "finished product" by "drug product"	Comment noted.
16	156	7	Comment: The draft is ambivalent in the following sense. On the one hand, the draft tries to be general, i.e., apply to *all* calibration methods, by providing isolated phrases to this effect, e.g., the sentence ending in line 156 or the parenthesis "(if used)" in lines	Comment noted. However the guideline is clear in stating that other approaches to those described may be used as long as these are justified.

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			288, 351, 597, and 631. On the other hand, the draft speaks exclusively about the so-called statistical or inverse methods of calibration (PLS etc.). The so-called classical or physical methods like CLS/GLS or SBC, which are based on spectroscopic first principles rather than statistical correlation, are not mentioned at all. Given that the majority of the draft's text is directed at fighting a problem that the classical methods do not have (false correlation) the draft is confusing to readers who intend to use classical calibration methods. They are left to wonder which paragraphs out of the many pages of text apply to them. A clarification is needed. Proposed change: After the sentence ending on line 156, add the following sentence: "This holds in particular for classical calibration methods like CLS/GLS or SBC, which are based on spectroscopic first principles rather than statistical correlation. While the creation of classical calibration models is outside the scope of this guidance, it is recommended that their validation, use, and change management still follow the guidelines below, especially with regard to line 687."	
17	158	4	Comment: Other analytical techniques are not in the scope of this guideline. Delete 158-159 Proposed change: The chemometric principles described within guideline may also be applicable to other analytical techniques	Comment agreed. Indeed, whilst the guideline covers only NIRS, the principles may be relevant and applicable to other methods (e.g. Raman spectroscopy).
			4. General Requirements 4.1.1 Establishing the scope of the NIRS procedure	
18	173-390	9	Comment: this section is extensive although comprehensive.	Comment noted. OOS results should indeed always

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	(324-334)		However, some of the information is already part of guidance and might be removed (for example OOS results in routine batch analysis should always be investigated).	be investigated in routine batch analysis; however for NIRS it is particularly important to emphasise this since it is an important part of the lifecycle of the NIRS procedure.
19	174	4	Comment: There is no general reference to considering a risk based approach. The level of development and/or validation could be different depending on the impact on the control strategy, as defined by ICH Q8/9/10 Points to Consider. Proposed change: Include a general statement on a risk based approach and include a reference to the ICH Q8/9/10 Points to Consider document (as already provided in Section 3, lines 170 - 173).	Comment agreed. A section on Risk Assessment has been added under the general requirements for the development of NIRS procedures.
20	176	5	Comment: Section 4.1.1 has no reference to sampling as an important element of the NIRS Procedure (see our General Comment on use of the Guideline in PAT / Process applications).	Comment agreed. Section 4.1.1 has been updated to include a reference to important aspects of sampling (e.g. sampling interface, probe position and sampling plans.) NIRS procedures are usually sample specific, so the sample type and character should be defined.
21	180-181	8	Comment: Replace term "limitations" with "applicability"	Comment agreed. The term 'limitations' is too vague. It has been deleted.
22	180-181 & 232	10	Comment not made public	
23	181	4	Comment: When discussing limitations of the method, the following are referred to: wavelength range and chemometric algorithm. These are not limitations, in terms of robustness, but are fixed parameters of the method/model. Consider removing these as examples of limitations.	See comment No 21.

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			Proposed change: Remove wavelength range, chemometric algorithm.	
24	181-182	5	Comment: It is very important to note that new samples should fall inside the design-space of the NIRS Procedure; In PAT applications of NIRS it is not sufficient to prescribe that the operating range of validity is defined by analyte concentration range (univariately) as multiple sources of variability are captured by the NIRS Procedure and affect model performance (either in qualification, identification or quantitation). Calibration samples for Model Development should be chosen not on the Y-domain (concentration or reference method domain) but on the X-domain (NIR spectra or PAT data domain). This is stated somewhat in lines 193-194.	This Comment noted. The point is interesting, however we consider the inclusion of such information too detailed for the guideline.
25	189-190	5	Comment: wrong causality Proposed change : The NIRS signal may be directly attributed to the analyte of interest or may be correlated with indirect effects (e.g. specific matrix components related to the analyte of interest).	Comment agreed. The sentence has been revised to make it clear that the NIRS signal may be attributed to the analyte of interest or correlated with light scattering effects or with matrix components. The relationship between the NIRS signal and analyte, attribute or process event should be clearly demonstrated to be relevant, scientifically sound and suitable for the intended purpose of NIRS procedure.
26	192	4	Comment: Where the NIR procedure is used for ID, the method is used to positively identify a material. So it is not a "pre-condition" of the procedure in this case but is the procedure itself. It may be considered a "pre-condition" where the final method is assay. This should be clarified.	Comment agreed. The text is revised to clarify that the NIRS procedure should be able to reject samples in qualitative analysis and that for quantitative analysis, it should be able to exclude from analysis samples that are outside of its defined scope (e.g. out of range, compositionally incorrect).

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			The sample also should not be "rejected". The sample should be "exclude from analysis by the subsequent NIR model". Proposed change: Change to "exclude from analysis by the subsequent NIR model, "	
27	193-194	8	Comment: "NIR procedure should be able…to reject samples that are outside of its defined scope". This statement as written may presume this is done via a technical/software solution, however in many cases this is done in procedural ways (standard operating procedures, specification documents etc.). Suggest to add clarification acknowledging that. Proposed change: add a sentence "This requirement can be accomplished through technology or procedural measures."	Comment not agreed. The word 'reject' refers to the ability of the method to correctly classify an unsatisfactory sample as non-compliant rather than referring to any other procedure in the company.
28	200-201	1	Comment: Chemical interpretation of chemometric models is also an important part of validation.	Comment noted.
29	202	5	Comment: incomplete statement Proposed change: "…independent set of samples or with designed (DoE) samples with which causality not correlation can be established.	Comment noted but it is not considered necessary to add further detail to the guideline.
			4.1.2 Summary description of the NIRS method	
30	204-205	3	Comment: It should not be called the principle of the monochromator Proposed change: (e.g. reflectance, transmission, transflectance), the principle of the spectrometer (e.g.monochromator, interferometer)	Comment agreed. See also comment No 32, 'monochromator' is replaced with 'optical system' and 'the principle of the monochromator' is replaced with 'the light dispersion principle of the optical system'.
31	204-210	8	Comment: Summary description of NIR method is generally acceptable but suggests a lot of details which may change when NIR models (but not methods) are changed. This includes items like "wavelength range used", "signal to noise ratio". It is	Comment agreed. The section on Summary details of the NIRS method has been revised to delete the requirement to provide the signal to noise ratio. The instrument make and model number should be

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			suggested to clarify that these items are needed for the reviewer for an understanding of the initially filed model but may change within change control later in the life cycle, making the initial submission a "snapshot in time" for the NIR method but not an up-to-date document over the life cycle of the method. Specifically signal-to-noise is not typically defined per se for a spectrometer and the calculation relies on certain assumptions. Proposed wording: a) "Elements of the summary description related to the NIR model should be representative of the initial submission but may change over the life cycle of the method with proper change control." b) Suggests to strike "signal to noise" as required element of scope description.	provided.
32	205-206	4	Comment: This states "……the principle of the monochromator (e.g. grating, FT-IR), " An FT-IR system is not a monochromator system. Proposed change: Reword as follows; "……the principle of the optical system (e.g. grating, FT-IR),.... "	Agreed, see comment No 30.
33	206-207	1	Comment: Confusion by mixing of instrument parameters for measurement (setup and procedure how to generate a spectrum) with instrument performance parameters. The wavelength accuracy, precision and the signal to noise ratio are key elements of the instrument test procedures. These parameter are part of the instrument qualification (IQ, OQ, PQ) and not part of the NIRS method! The instrument qualification is a separate document and should not be included here. Proposed change: Exclude parameters of instrument qualification in this document and reference to instrument qualification.	Agreed, however the make and model number of the instrument should be provided so as to capture the difference in the optical bench.

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34	206-207	2	Comment: How does wavelength accuracy and precision or signal to noise ratio relate to a method? Proposed change: Remove ",wavelength accuracy and precision, the signal to noise ratio"	see comments No 31 & 33.
35	206-207	3	Comment: different NIR producers are using different calculation formula for wavelength accuracy and precision, the signal to noise ratio. Proposed change: the spectral resolution, wavelength accuracy and precision, the signal to noise ratio (calculation details should be mentioned).	Not applicable anymore, see comments No 33 and 34.
36	207	4	Comment: Optical bandwith, spectral resolution, wavelength accuracy and prescision, signal-to noise ratio are part of System Suitability test or referenced as part of the system qualification, per Pharm Eur. Thus, these parameters are not part of the description of the NIR method rather than parameters of the instrument qualification. Proposed change: delete: optical bandwith, spectral resolution, wavelength accuracy, prescision, signal-to noise ratio	See comments No 33, 34 and 35.
			4.1.3 Feasibility study	
37	210	4	Comment: The submission of a feasibility study is not considered necessary. The subsequent calibration and the validation of the method demonstrate that the procedure is "suitable for the intended purpose". The feasibility study can be described but it should be stated that it is not a submission requirement.	Comment agreed. The text has been revised to clarify that it is recommended that the feasibility of using NIRS for the intended purpose is considered in development; however the results of such feasibility studies need not be provided in regulatory submissions.
			4.1.4. Variables affecting spectral response	
38	220	1	Comment: Fouling or cleanliness of the sample interface may well be one of the main variables.	Comment agreed. The cleanliness of the sample interface is now mentioned as a possible variable

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			Proposed change: It is recommended to emphasize that, as well as the implementation of procedures for checking the cleanliness and cleaning of the interface.	affecting the spectral response.
			4.2. Data collection 4.2.1. Sample preparation and presentation	
39	228	4	Comment: 'The impact of possible variations of the presentation on the NIRS response should be discussed, supported by appropriate data, and, if shown to be significant, demonstrated to be controlled satisfactorily' → This is part of the validation. Proposed change: Delete: ~~The impact of possible variations in the presentation on the NIR response should be discussed, supported by appropriate data,……..~~	Comment noted. For some users this issue of sample presentation may not be an obvious validation consideration and we believe that it should be included in this section.
40	230 - 232	3	Comment: These sentences "Before any NIRS measurement takes place, it is important to optimise the presentation of the sample to the NIRS instrument. Examples of variables that should be optimised are sample orientation, sample size, optical quality of glassware and environmental conditions." Proposed change: " should be moved to the beginning of this topic line 226".	Comment agreed.
41	233-234	1	Comment: Spectral range is already mentioned in line 205; number of scans can be a part of summary description Proposed change: Merge the relevant content of this paragraph with lines 203-209	Comment agreed. The section has been rewritten.
42	233- 234	4	Comment: Spectral range and number of scans are part of the description of the NIR method.(4.1.2) Proposed change: Delete sentence from 4.2.1 and consider if	Comment agreed. The sentence on the spectral range has been deleted from this section.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			appropriate to add back into 4.1.2	
			4.2.2. Sample population	
43	236-238	1	Comment: The information in this paragraph does not seem relevant Proposed change: Eliminate paragraph	Comment not agreed. It is not considered appropriate to prescribe what the applicant should consider an independent sample to be, since this may change dependent upon the application of the NIRS procedure. An example could be a production scale split into several parts to include variation in compression strength or other parameters. Whilst this is the same batch, the parts of it could be considered independent samples.
44	236 - 238	3	Comment: Samples should be independent. The applicant should define what they understand to be a 'sample' and their definition of an 'independent sample'. These definitions should be justified with respect to the parameter that the intended model is proposed to predict. These sentences are not important and a bit confusing. Proposed change : take these sentences out	Not agreed, see comment No 43.
45	238	5	Comment: What is an 'independent sample' ? As it seems independent samples are key. There should be a definition of what that means and perhaps it should not be left to the applicant to define.	See comment No 43.
46	243 - 244	4	Comment: It is not possible to include "all potential variations that may be encountered in routine production" in the sample population. A more pragmatic solution would be to consider all factors via a risk assessment, and then include pertinent factors as part of the sample population.	Comment agreed. We have deleted the word 'all'.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: The sample population for a qualitative and quantitative procedure should consider ~~all~~ possible variations that may be encountered in routine production. ..	
47	244-245	8	Comment: "Sample population …should cover all potential variation that may be encountered in routine production". This is an unrealistic and unnecessary requirement. The choice of variation included in the model should be based on a risk assessment. This can result in some factors not being included in the model. There are other ways of assuring that a model performs well, for example use of spectral outlier detection to identify if unknown prediction samples contain additional variation over what is in included in the model. Future variation encountered can then be included in the model by change control practices Proposed change: The selection of a suitable sample population for a qualitative or a quantitative procedure should include consideration for anticipated variation that may be encountered in routine production. Including a given source of variation within the sample population may be based on risk assessment tools. Such variation may include for example:	Comment agreed. See comment No 46. We acknowledge the need for a reference to risk assessment in the guideline and a section on Risk assessment has been added to the guideline.
			4.2.3. Pre-treatment of data	
48	258	5	Comment: There is no need for "(but are not limited to)". Just keep writing after "…derivatization, preceded by filtering, scatter correction on modelling of different light components (e.g., absorption and diffuse reflectance)	Comment agreed.
49	258-259	1	Comment: Apparent confusion in terms: "remove unwanted sources of variation prior to treatment", since pre-treatment would generally be considered treatment	Comment agreed.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			Proposed change:"… prior to calibration"	
50	258-260	4	Comment: The variability is not necessarily 'removed' using these data treatments, but rather minimised. Proposed change: Such treatments include (but are not limited to) normalisation and derivation, which are performed in order *to minimise unwanted sources* of variation from the data prior to treatment and to enhance spectral features.	Comment agreed.
51	259	3	Proposed change : "Treatment" to change to "calibration"	Comment agreed.
52	261	4	Comments: It should not be necessary to justify any pre-treatment of data Proposed change: Any pre-treatment of data should be documented	Comment not agreed. The need for pre-treatment should be justified, especially if it is not a standard pre-treatment such as normalisation and derivatisation.
53	261-262	5	Comment: The rationale for choosing a particular pre-treatment and not another should be clearly described.	Comment agreed. It is unnecessary to justify not using other pre-treatments. Sentence deleted.
			4.2.4. Analysis by the reference method (when applicable)	
54	262-275	10	Comment not made public	
55	266	3	Comment#9: The wavelength range to be used for identification is not mentioned. The common practice is to cover "full spectra". However, full spectra could be complete NIR range- 800-2200 nm in some instrumentation or could also be only part of this range – depends on the instrument technology used (in some instrumentation using MEMS technology for example no coverage of 3rd overtone and part of the 2nd overtone – 1900-2200 nm only). - Both could be appropriate from scientific point of view as long as specificity is approved but it should be indicated or discussed in the guideline. In the guide it is mentioned in general that selection of	Comment agreed. The text is revised to clarify that a partial wavelength range may be used instead of the complete NIR range. If a partial range is used, it should be justified from a scientific perspective, and evidence that all relevant chemical/physical information is included in the range should be presented.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			wavelength range should be fully justified and it is a correct requirement but additional discussion on the range should be included i.e. partial range can also be used if all chemical /physical relevant information is included and scientifically justified.	
56	267	5	Comment: incompleteness Proposed change: "…scanning or should be made on the same sample if not at the same time."	Comment agreed. To avoid confusion, the text has been revised to clarify that reference measurements should be made on the same samples used for scanning. Ideally, reference measurements should take place at around the same time as NIR scanning.
57	268-276	8	Comment: Reference method requirements described here appear to assume that a NIR method is either a release method or real-time release method. For NIR methods used in in-process testing, which can be still based on a reference method, there should not be the same expectation for the description of the reference method, as for example conventional in-process testing methods (example moisture by LOD, tablet hardness) are typically not described in detail in regulatory submissions.	It is agreed that for reference methods for which validation data would not normally be provided such as LOD or tablet hardness, validation data would not be required. It is expected that the applicant would be able to justify the absence of such data in the submission to include NIRS.
58	269, 270, 339	1	Comment: Typo in CTD chapter numbering? Proposed change: 3.2.P.5.2~~1,~~ 3.2.P.5.3~~1,~~ 3.2.P.5.3~~2~~	This was a formatting error with footnotes and has been corrected.
			4.2.5 Establishment of a spectral reference library	
59	276-285	3	Comment: The topic of "4.2.5. Establishment of a spectral reference library" should not be written in general requirements, should be mentioned in qualitative procedures topic. Proposed change: Proposed to remove	Comment not agreed. The establishment of a library is part of data collection and therefore should be included under general requirements. We have deleted the term 'reference' from 'spectral reference library' in order to clarify.
60	279-280	2	Comment: Batches used to build a qualitative library or quantitative model do not need to be representative of the marketed product,	Comment not agreed. Batches should be representative of the marketed product since these

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			but need to be suitable for the intended purpose of building a validatable procedure that will be used on commercial marketed product. Proposed change: replace 279-280 by "Suitable batches should be either prepared or selected to ensure the necessary performance of the method as per the scope of the method. "	are those for which the analytical procedure is intended.
61	280	5	Comment: The use of the term "Batches…" is confusing. Maybe the term "samples" should be used instead as NIRS is performed on samples drawn from lots or batches. Many samples can be acquired (e.g., when NIRS is used as a PAT monitoring tool) on the same batch.	Comment agreed. The term samples is used. The spectra should be indexed so that their source/origin may be determined.
62	284	5	Comment: Wrong word "complex". It is not about models becoming less parsimonious and complex; it's about getting the right balance between model generality and accuracy. A more general model will be less accurate; a more specific model will be more robust and accurate (but less general).	Comment agreed. We have deleted 'to avoid calibration models becoming too complex'.
63	284-285	1	Comment: this seems irrelevant and does not add value, the use of a wrong library would have to yield a negative result Proposed change: Remove sentence	See comemnt No 62.
64	284-285	4	Comment: It is assured under the company´s quality system that the correct library is used. Proposed change: Remove sentence "The use of only…."	See comment No 62.
			4.3. Data interpretation 4.3.1. Description of the NIRS model	
65	289	5	Comment: Sec 5.3 and 6.3 need improvement (see below).	Comment agreed. These sections have been revised.
			4.3.2 Statistical spectral quality test	
66	291-304	4	Comment: Section 4.3.2 should only be listed under the quantitative section. Identification and qualitative methods by	Comment agreed. We have added 'for quantitative purposes' to clarify it applies to quantitative NIRS

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			virtue of their purpose utilize effectively the same algorithms used to conduct a spectral quality test. Even for quantitative test methods, this may not be fully applicable because of the specific application or software being used. Proposed change: Either indicate this section is only applicable to quantitative methods or move to the quantitative section 6. Promote this as a best practice but not a requirement to permit the flexibility for situations when the application and/or NIR software does not permit this to be accommodated.	procedures.
67	295	1	Comment: 'Dmodx may be a term proprietary to Umetrics	Comment agreed. The term.'DmodX' has been deleted.
68	298-300	1	Comment: In our view, if a sample is rejected by the spectral quality test, any results obtained should not be considered	Comment noted.
69	299	5	Comment: "…it is poor scientific practice…" please RE WRITE. What is "initial spectral quality" ? Does it mean the raw NIR spectrum is an outlier? Does it refer to spectra after pre-processing ? It may be that a pre-processing chosen at an early stage of the application later in the life-cycle of the application is shown to be sub-optimal (viz., giving rise to occasional outliers) – actually 4.3.3 deals with many of these.	Comment noted.
			4.3.3. Outliers in sample data	
70	304 - 334	3	Comment: The topics of "4.3.3 Outliers in sample data and 4.3.4. Out of Specification (OOS) results in routine batch analysis" should be mentioned after the 4.4 calibration Proposed change: written after the topic 4.4.	Comment not agreed. Outliers and OOS should be in the Data interpretation section.
71	306-324	5	Comment: If a sample spectra is an outlier – and provided that	Comment agreed. A section on Risk Assessment has

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			neither sampling nor the NIRS method have any failure in performance – then that outlier is signalling a process change which is captured (affecting) the NIR spectra. The prior risk assessment (RA) done during method development should have ranked all possible variability sources affecting the NIR spectra and from such RA it should be easy to trace back what process changes occurred (T, particle size, etc).	been added to the guideline to address this. See also comment No 47.
72	317 - 318	3	Comment: the sample may be included in the spectral reference library, the spectral reference library should not be mentioned in the general requirements Proposed change : the spectral reference should be changed to "calibration method"	Comment agreed.
			4.3.4: Out of Specification (OOS) results in routine batch analysis	
73	328-329, 333-334	10	Comment not made public	
74	328-329	4	Comment: "A batch should not be released based on an OOS NIRS result and a within-specification result when tested using the reference method (if available)." This sentence along with the following paragraph creates an unscientific burden upon batch release and is not in line with sound practice. If a scientifically sound failure investigation indicates the NIR method or model was inappropriate for the samples being tested while the reference method has demonstrated samples to be within specification, then the company should be able to release the batch within the controls of the quality system. Model update is a time-consuming process and may involve including the new source of variance introduced by the samples that produced the original OOS. Re-analysis after model update is then redundant as the	Comment noted. OOS section has been revised to clarify the role of reference methods in batch release.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			samples are no longer independent. In summary: the reference method is a validated method. It should be appropriate to use the reference analytical method for release if, after proper investigation, the NIR method or model is proved to be invalid for the samples. The update of the NIRS model and revalidation of it may imply delays that would not be acceptable in production. Proposed change: A batch with an OOS NIRS result and within-specification result when tested using the reference method should only be released after a scientifically sound investigation with the conclusion that the NIRS method or model was not appropriate for the sample.	
75	324-334	2	Comment: See general comment. Lines 325-328 nicely lay out expectations that a batch should not be rejected or released until an investigation has determined a root cause for the NIRS based OOS. However, 333-334 "the re-analysis undertaken such that the batch may be released within specification for both the NIRS procedure and the reference method of analysis" is potentially confusing. This is clearly discussed within section 5.1 of the EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release), 29 March 2012, EMA/CHMP/QWP/811210/2009-Rev1. Proposed change: recommend that a reference to decision trees as part of the site quality management system pertaining to batch disposition be made and that one should follow decision trees so	Comment not agreed. The guideline is about the data to be provided in submissions rather than focussing on GMP. Any such decision trees are part of the requirements of quality systems and should not form part of this guideline.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			that while the NIRS method is being updated/revalidated the commercial manufacture can proceed using the reference method (of other alternate test) as a primary release test is valid.	
76	328-329	1	Comment: Current guidelines set forth by the United States Pharmacopeia and the European Pharmacopeia suggest that the release of a batch of material with outlier or OOS NIRS results is an acceptable practice when analysis by an appropriate reference method yields in-specification results for that batch. Per USP 34 <1119> Near-Infrared Spectroscopy: *"Outliers—Sample spectra that produce an NIR response that differs from the qualitative or quantitative calibration model may produce an outlier. This does not necessarily indicate an out-of-specification result; but rather an outlier indicates that further testing of the sample may be required and is dependent on the particular NIR method. If subsequent testing of the sample by an appropriate method indicates that the property of interest is within specifications, then the sample meets its specifications. Outlier samples may be incorporated into an updated calibration model subsequent to execution and documentation of suitable validation studies."* Per Ph. Eur. 7.5, 2.2.40 Near-Infrared Spectrophotometry: *"Outliers. Outlier results from NIR measurements of a sample containing an analyte outside the calibration range indicates that further testing is required. If further testing of the sample by an appropriate analytical method gives the analyte content within the specifications, this may be accepted and considered to have met*	Comment noted. Section 4.3.4 refers to out of specification results rather than outliers whereas the previous section refers to outliers. The section has been revised to clarify that while the NIRS method is being updated/revalidated, its use should be suspended. The commercial manufacture can proceed using the reference method (or other alternate registered test). In the meanwhile the Ph.Eur. chapter on NIR has also been revised.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			the specifications. Thus an outlier result generated by NIR measurements of the sample may still meet specifications for the analyte of interest." Proposed change: The practice described in 4.3.4. *Out of Specification results in routine batch analysis* is inconsistent with Pharmacopeia guidelines. For consistency among all guidelines, please revise lines 328 and 329 to suggest a similar practice to USP and Ph.Eur.	
77	331-335	8	Comment: This section essentially says one has to update the NIR model in order to release the batch if there is an OOS for the NIR result even if a passing result is obtained for the reference method. While this approach may be scientifically desirable it puts a premium on the ability to update NIR models in an efficient way with respect to internal and external (regulatory oversight) change control. A typical turn-around time for a model update on a high-volume product, including scientific work and GMP change control, is and has to be within 3-5 days in order to allow the continuation of production.	Comment noted.
78	333-334	1	Comment: The process of handling outliers and the importance of NIRS method lifecycle management is understood. However, the release of material is extremely time-critical and the ability to release will be negatively impacted by the amount of time required to analyze the batch by two methods of analysis, update the NIRS method, and reanalyze the batch on the updated NIRS method. In addition, lines 333 and 334 suggest releasing the batch on the updated NIRS method that has been updated to contain that same batch. In	See comment No 76.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			essence, the batch would be tested against itself. A more appropriate practice would be to analyze the outlier samples by an appropriate reference method, and release the material on the reference method results (provided they are within specification). At that point, the outlier NIRS results can then be used to update the NIRS method for future analysis on different batches while allowing release of in-specification material in a timely manner. Proposed change: Revise procedure of handling NIRS outliers	
79	333-334	4	Comment: "… and re-analysis undertaken such that the batch may be released within specification for both the NIRS procedure and the reference method of analysis…" Proposed change: Remove sentence: The NIRS procedure….method of analysis. (see above comments for lines 328-329).	See comment No 76.
			4.5 Validation	
80	340-343	5	Comment: To require that an intrinsically multivariate method such as NIRS – a true PAT monitoring tool (multi-parametric) – be regulated by a univariate regulations, will force NIRS to be used as HPLC replacement and not as a PAT tool when needed. Moreover, lines 340-343 imply that most of what follows in this Guideline about NIRS Procedures that do not require a calibration – and at the same can and should be proven, documented and validated – will not be in compliance to the existing regulations referenced in these lines.	Comment noted. Chemometric validation is different from method validation. This note for guidance includes guidance as to how ICH objectives of validation are to be met with respect to the application of chemometric analysis.
81	344-345	5	Comment: But the independent samples need to be within the design-space defined for the NIRS Procedure and that will require a	Comment noted.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			priori checking (done up front); so some degree of knowledge on the independent samples will be acquired unintended.	
82	359-378	1	Comment: It is presumptive to assume that this document is a good starting point for PAT applications. What about other strategies, like ASTM D3764, or D6122? It is clear that the guidance is written with laboratory release testing in mind and that should limit the scope of the document. No discussion around establishing fitness for purpose criteria. No discussion of QbD or risk assessment, although Q9 is referenced.	Comment noted. A section on risk assessment has been added to the guideline. We tried to cover various NIRS applications, however it is not within the scope of the guideline to cover all aspects of QbD.
			4.6 NIRS in Process Analytical Technology (PAT) applications	
83	362	5	Comment: Sampling must be adapted to process dynamics. Proposed change: "… individual manufacturing processes (e.g., sampling frequency adapted to process dynamics)."	Comment agreed.
84	374-375	1	Comment: Inconsistency. Unit ops and CQAs mixed up in one sentence	Comment implemented.
85	374 - 375	3	Comment: drug product manufacturing process steps such as granulation, blending, tablet hardness and coating Proposed change: drug product manufacturing process steps such as granulation, blending, tableting and coating	Comment agreed.
86	375	5	Comment: Inconsistency. Unit ops and CQAs mixed up in one sentence. Proposed change: "…steps such as blending, granulation, compression and coating."	Comment agreed. See comments No 84 and 85.
			4.7 Summary of general data requirements	
87	379	1	Comment: Method setup and design space is not referenced in this section	Comment not agreed. NIR can be applied without design space; therefore it is not considered necessary

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
				to include additional wording here.
			5.1. Development	
88	406	4	Comment: Remove "of several samples of several batches of different substances present". This is very ambiguous. Identification can take place for a single substance in a reference library, where the procedure shows adequate specificity. Proposed change: Remove and replace … is based on the comparison of spectral data of the substance with spectral data in the reference library.	Comment noted. See validation section.
89	408 – 409	3	Comment: The appropriate confidence level of the conclusion should be justified. "if PCA based methods are used, the spectral residual can be used to justify the confidence in the conclusion. Proposed change: add "if PCA based methods are used, the spectral residual can be used to justify the confidence in the conclusion".	Comment agreed.
90	424	2	Comment: Is this supposed to be a category heading?	Formatting comment.
91	426	5	Comment: "… as the conformation of characteristics..." Proposed change: "…as conformity to characteristics.."	Comment agreed. This guideline uses the term conformity as the conformation of characteristics in accordance with a certain degree of similarity to a specified standard.
92	433	5	Comment: Incomplete explanation. Proposed change: "… analysis or because conforming to a process signature is sufficient to ensure batch-to-batch consistency.	Comment noted.
			5.2.1 Sample collection and population	
93	452-453	4	Comment: "all known potential suppliers" is not practical, or necessary. It is important that all suppliers of that material which is delivered to the site are included. Further suppliers may be used to extend the robustness of the method during lifecycle. Proposed change: "all used suppliers "	Comment agreed. The text has been revised to clarify that for procedures used to identify or qualify substances on receipt, samples from all suppliers used should be incorporated into the library.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
94	454	5	Comment: Exaggeration and over-arching. It is unrealistic what is stated in 453-454. In view of the Risk Assessment findings it should be known what sample CQAs may realistic change throughout the NIRS Procedure life-cycle. Moreover a company will be able to retrieve samples from retention samples of historical lots and use its supply chain to assemble a sample population (size and diversity) that will span the critical quality attributes in ranges that match the intended use of such samples; to prescribe that "all known potential suppliers" be contacted and samples obtained is not realistic and may not even be required if the intended use of the NIRS procedure and the RA previously done are considered.	See comment No 93.
			5.2.2. Number of samples	
95	457-460	1	Comment: The intensity of the analyte signal is the most essential point here and missing so far. If the analyte signal is very large even a very complex matrix will not interfere the qualitative analysis. So a complex sample matrix does not necessarily lead to the use of more samples. You will perhaps need even more samples for a simple matrix, when your analyte signal is very low.	Comment agreed. We have clarified in the guideline that the intensity of the analyte signal should be taken into account in the decision on the number of samples to be included in the library.
96	460	5	Comment: "…the sample matrix…" Proposed change: "…the more complex the sample matrix, the more matrix effects are likely (e.g., less spectral selectivity). Hence the more though needs to go into using designed samples with which indirect correlations and matrix effects can be avoided. A properly considered sample planning may reduce the amount of nominal samples needed to be measured to ensure that normal variability of nominal samples is captured."	Comment noted. The proposed change goes too much into detail for this guideline and seems to be too restrictive. However, we have clarified in the guideline that in general, the more complex the sample matrix and the more interference from the matrix, the more samples will be required to cover the statistical population.
97	462	1	Comment: The number of batches or samples a validation should be based upon is not that easy to assess. There is always the risk	Comment not agreed. Because of the complexity of the model building it is not possible to give a specific

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			that the 'next' batch is just a little bit different. Is it possible to add numbers for guidance; say at least 5 independent batches?	number, an assessment and a justification from the applicant is needed.
98	462-463	5	Comment: Necessary but not sufficient. If this Guideline is to be seen as a QbD proposal on setting up NIRS Procedures, then these lines imply that the developed procedure works well in the operating nominal space (not the entire Procedure design-space); only when normal production operation is moving around all DS locations in a short time span, will the prescribed practice provide such guarantee.	Comment noted.
			5.2.3 Composition of sample sets	
99	464-467	3	Comment: 'In order to develop, optimise and validate a calibration model for a typical qualitative NIRS procedure used for identification or qualification, 'two' sets of samples are required: Proposed change : a) Should be 'three' sets b) to add: the third bullet point: - a calibration set for creating the calibration model - a calibration test set (internal validation set) - an independent validation set for (external) validation of the proposed chosen model.	Comment agreed in principle. Both concepts, 2 or 3 sets, could be used for developing, optimising or validating the calibration model.
100	471-475	1	This was already mentioned, although with less detail, but information is duplicated – it is unnecessary in this section	Comment noted. The paragraph gives further information on dealing with spectral libraries.
101	477-478	5	Comment: place these two lines after line 468	Editorial comment.
102	479-480	8	Comment: The requirement that validation samples should be "entirely independent" of the calibration samples should be interpreted that they are different samples, but not independent batches. For the production of "off-range" or placebo samples it is	Comment noted. Off range samples or placebo samples are not entirely part of the concept of independent samples. These samples could be additionally used in the library.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			impractical to produce separate batches of such samples for calibration and validation samples.	
103	480 - 482	3	Comment: "The selection of an appropriate calibration model may be aided by so-called 'internal validation' methods. 'Internal validation' is the application of resampling statistics to cross-validate and provide an 'internal check' of the performance of the model for the purposes of optimization." It is not really correct saying that internal validation is used for cross-validation. Proposed change: Internal validation set is a sample set that chosen separately from the calibration set to check the performance of the model for the purposes of optimization.	See also comment No 99.
104	480-484	4	Comment: The use of this terminology and concept of 'internal validation' and 'cross-validate' within the qualitative section may be confusing. It generally is only used within the context of quantitative methodology. While someone may use this practice to aide in optimizing the calibration model, is it necessary to include it as a paragraph in this section at all. Proposed change: Delete the paragraph lines 480 – 484.	See also comment No 99 and 103.
105	480, 488	5	Comment: "… positive and negative …" A very low frequency of false negatives and false positives can be only be achieved by developing a model on a larger space than the nominal space of in spec samples (NIRS procedure control space – or space of nominal variation). This comment is meant to support the previous note on lines 462-463 above.	See also comment No 98.
			5.3 Calibration	
106	496 - 497	3	Comment: Cluster Analysis (dendrograms) dendograms is a plot type. The output of many algorithms can be visualised as	Comment agreed. The word 'dendrogram' has been deleted.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			dendograms. Proposed change: take out (dendrograms).	
107	498	5	Comment: In my view it is very unfortunate that the Guideline opens the way for poor method development and to ignoring that spectroscopy used for quantitation is about linearity and additivity of signals, to be compensated by means of nonlinear and over-parameterized modelling strategies which more often than not, are used by non-experts whom will produce non-robust and overfitted models. Proposed change: remove reference to ANN and SVM methods in lines 498 and 661	Comment agreed. Reference to KNN-analysis and SVM have been deleted since the guideline intends to be as flexible as possible.
108	499	5	Comment: "…distance match." Proposed change: "…distance match, CUSM and Shewart charts.""	Comment noted. The text is changed into: "…correlation algorithms such as distance-match or Shewart charts".
109	503	3	Comment: should be stated, explained and justified in the validation report. It should be calibration report, not validation report. Proposed change: should be stated, explained and justified in the calibration report.	Comment agreed. To remove confusion on this point (the information should be included but this may be in a calibration or validation report), 'in the validation report' from line 503 has been deleted. In addition, it is suggested that a graphical representation could be provided to support and explain the calibration model and its validation.
			5.4. Optimisation	
110	504 - 506	3	Comment: 'In general, the optimisation of a qualitative procedure is confined to the selection of the samples included in the model and the choice of pre-treatments and the calibration algorithm.' It is not important to mention here.	Comment noted.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			Proposed change: take this topic out.	
			5.5 Validation (internal and external)	
111	507	5	Comment: incompleteness Proposed change: "…and the choice of spectral pre-treatment, wavenumber or wavelength selection and the calibration algorithm."	Comment not agreed. The title will become long and less impactful as a result of the proposed change, we propose to leave this as it stands.
112	509-514	4	Comment: The use of this terminology and concept of 'internal validation' and 'cross-validate' within the qualitative section may be confusing. It generally is only used within the context of quantitative methodology. Spectra used in the development of the library and contained within the library for an identification or qualitative method are directly used to confirm the methods are appropriate. An 'internal validation' may not be necessary and therefore is not a needed step. Proposed change: Reword this paragraph to indicate that spectra used in the calibration can be used to the same effect as being implied by the "internal validation".	Comment partially agreed. Cross validation will be changed to internal validation to avoid multiple terms. However, it is not agreed that internal validation is used only in the context of quantitative methods. Internal validation is necessary in the context of calibration (both qualitative and quantitative). The use of qualitative method without a calibration is acknowledged but it is out of scope of optimisation section.
113	510	5	Comment: Correction / clarification needed. The performance being tested here is not that of the spectral reference library but that the correct model structure was derived so that it can describe the spectral reference library. Proposed change: "The objective of internal validation is to help define the best model structure."	Comment agreed. This section has been reworded.
114	510 - 511	3	Comment: Generally, this <u>is</u> evaluated by testing the samples of the spectral reference library using cross validation techniques or where necessary, a discrete set of samples Proposed change: Generally, this <u>can be</u> evaluated by testing the samples of the	Comment noted. Section reworded

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			spectral reference library using cross-validation techniques	
115	515	5	Comment: add for clarification Proposed change: "…tolerances. The internal validation step will demonstrate that the model structure is suitable to describe the spectral reference library used in the calibration step.	Comment noted. This has been taken on board as part of comment No113. Therefore it is not considered necessary to make further revision here.
116	518	5	Comment: add for clarification Proposed change: "…library. The external validation step will provide evidence that the calibrated model is general and can be used in routine for new samples within the space spanned by the reference library samples."	Comment noted. This wording is acknowledged and it is agreed that this issue is covered in the guideline under general considerations.
117	519	3	Comment: regarding the confidence limits, as mentioned on the comment of line number 408-409 "if PCA based methods are used, the spectral residual can be used to justify the confidence in the conclusion" Proposed change: add "if PCA based methods are used, the spectral residual can be used to justify the confidence in the conclusion".	Comment noted. However the drafting group would prefer not to give guidance that is specific only to certain methods.
			5.2.3 specificity	
118	523-540	10	Comment not made public	
119	531-532	4	Comment: Use of a 'risk assessment' is an extreme measure for something that may be clearly documented with basic justification. Proposed change: change sentence to "A 'review' of the goods-in and manufacturing operations should be used to justify the analogues and challenges presented to the model."	Comment agreed, 'risk assessment' has been changed to 'review'.
120	537 – 539	4	Comment: The NIR method may not need to be equivalent to the replacement method as long as it meets the intended use for the primary method. Proposed change: "The results of the validation of the NIRS	Comment noted. The word 'effective' in this context does not mean 'equivalent', rather that the NIRS method should be as good for the intended purpose of the test as the reference method. An analogy

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			procedure should demonstrate that for each tested parameter, the procedure is sufficiently selective to discriminate between batches that comply with the tested parameter and batches that do not.	could be made to LOD and KF, which both may be used for determination of water content but measure different things.
			5.5.3. Robustness	
121	542	4	Comment: This section should mention a risk based approach, as well as suggesting a structured approach to risk assessment (e.g. FMEA and/or MSA). This should not be mandated but recommended as good practice.	Comment not agreed. It is the choice of the applicant as to which approach is most appropriate for them to take. It is not considered necessary to revise the wording of the guideline.
			6. Quantitative procedures	
122	548	5	Comment: one line on the importance of DoE is too short, in view of the potential benefit obtained from planned (DoE) synthetic or real but modified samples, to examine all sources of variability identified during Risk Assessment of the Procedure. Proposed change: (see comments made to lines 202 and 460)	Comment not agreed. This guideline is about the data requirements for NIRS and is not intended to go into detail regarding the importance of DoE.
			6.2.1 Sample collection and population	
123	559-562	4	Comment: The SAME manufacturing procedure may not be available to create lab samples to address linearity. Proposed change: "Where laboratory samples are required to expand the narrow range of production samples to properly assess linearity in line with specification limits, such samples should be prepared using ~~the same~~ a manufacturing procedure that provides acceptable samples."	See comment No 125.
124	560-561	2	Comment: "using the same manufacturing process". This seems somewhat constraining, especially if using pilot scale equipment	See comment No 125.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			where the process may appear "similar" but not necessarily identical. Proposed change: "should be prepared using similar manufacturing procedure and any changes should be justified with regards to their impact on the NIRS model".	
125	560-561	5	Comment: to many things at stake in this paragraph; new samples to extend the range is one thing; checking the model is still holding for the extended range is another thing; checking that linearity / additivity is still holding, yet another thing. Reference to a linearity requirement between spectra and reference analytics is inconsistent with lines 498 and 661 which make reference to non-linear calibration methods being acceptable (in my view it is potentially disastrous that the Guideline opens the way for poor method development to be compensated by means of non-linear modelling strategies) Proposed change: "laboratory samples are required to expand the narrow range of production samples, such samples should be prepared using the same manufacturing procedure."	Comment agreed. The words 'same manufacturing procedure' have been replaced with 'same manufacturing procedure, or any changes should be justified with regards to their impact on the NIRS model'.
126	564-565	4	Comment: Wording comment with regards to "in the application of regression correlation statistics" Proposed change: Replace the text by: "in the application of regression/correlation-related statistical methods."	Comment agreed. Section has been reworded.
127	566-567	5	Comment: "…uniform distribution of samples throughout the range of potential variation …". The space spanned by the samples should be defined in the NIRS domain (PAT tool domain – as NIR will capture and be affected by other sources of variability other than	Comment noted.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			the CQA of interest). This is a prerequisite for method robustness and should be prescribed as part of the NIR Procedure development and life-cycle management. For example, if the space spanned by the samples changes (as seen by NIR spectra of such samples) over the Procedure life-cycle, due to specific sources of variability changing (e.g., T, moisture, particle size) then calibration update will have to have that into consideration. That calibration update need may become necessary even if the samples are within the pre-existing analytical range defined based on the reference method.	
128	569	5	Comment: Incompleteness Proposed change: "… signal of the analyte of interest, spectral selectivity and potential matrix effects."	Comment agreed. The words 'spectral selectivity and potential matrix effects' have been added to the text.
129	573-574	4	Comment: The use of "DOE correlated" is confusing here and should be removed. Proposed change: "The choice and number of samples should be justified with respect to the intended purpose of the procedure."	Comment agreed. The text has been revised to reflect that the choice and number of samples should be justified with respect to the intended purpose of the procedure. Sample collection and population may be addressed effectively and efficiently using an appropriate DOE approach.
130	574-575	5	Comment: Very much so. However this should be stressed also in the other text places where reference to the possible beneficial use of DoE is addressed.	Addressed in comments No 122 and 129.
			6.2.2 Number of samples	
131	576-577	8	Comment: Consider rewording the sentence for clarity. Some calibration approaches might not be captured by this statement.	Comment agreed. The problem seems to be with the term 'principal components'. The term 'principal components' (when used as a generic term) has been changed into 'latent variables or equivalent'.
132	577 - 579	3	Comment:	See comment No 131.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			To avoid bias, the number of samples used to develop the calibration model should be very much greater than the number of principal components used. Proposed change: take out this sentence because the number of principle components should not be mentioned here (and never been mentioned or introduced earlier).	
133	577-581	5	Comment: I find that this paragraph needs clarification. Proposed change: "Calibration algorithms are generally based on the correlation of variance in NIR spectra via their principal components (PCs) with a reference data set. The number of samples used to develop the calibration model should be much greater than the number of PCs used, and the number of PCs (model rank or model order) should be comparable to the number of detectable significant sources of variability found during the RA step. The system rank and model order should be comparable to prevent overfitting (of a good model structure) or model mismatch (wrong model structure found). In all cases, the number of samples used to develop the calibration model should be justified."	Comment agreed. See comment No 131 and 47. Reference is made to the new section on risk analysis. The text has been reworded as follows: "Calibration algorithms are generally based on the correlation of variance in NIRS spectra, via their latent variables (or equivalent; see 'definitions' section), with a reference data set. The number of samples used to develop the calibration model should be much greater than the number of latent variables used and the number of latent variables should be comparable with the number of detectable significant sources of variability found during the risk assessment step".
134	583	1	Comment: See comment above to Lines 457-460. The intensity of the analyte signal is the most essential point here and missing so far. If the analyte signal is very large even a very complex matrix will not interfere the quantitative analysis. So a complex sample matrix does not necessarily lead to the use of more samples. You will perhaps need even more samples for a simple matrix, when your analyte signal is very low.	Comment agreed. Section reworded.
135	585-589	5	Comment: This paragraph is specific. For a more general discussion	Comment agreed. See comment No 134.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			of those issues, spectral selectivity, specificity and sensitivity should be used instead.	
136	588	5	Comment: Incompleteness Proposed change: "… components or a more careful wavelength selection or spectral pre-processing may be required, …"	Comment agreed. Section has been reworded
			6.2.3 Composition of calibration set, calibration test set and validation set of samples	
137	591-628	1	Comment: this paragraph is complex and not easily understood Proposed change: simplify and shorten	Comment noted. Section has been reworded
138	591 - 628	4	Comment: Section 6.2.3 – this section does not fully acknowledge that the technique of "cross-validation" is frequently used in lieu of splitting the calibration and calibration test set into 2 parts – especially when the number of samples available is limited. In fact, it is more often the case that the available calibration set is limited and therefore using all available variability is preferable to optimize the method. Therefore the same set is used for both calibration and to conduct the cross validation optimization exercise. Proposed change: modify the wording through the section to fully embrace that the same set can be used for both calibration and cross validation technique is used.	Comment agreed. Section has been updated to reflect that the same set can be used for both calibration and cross validation technique, however that both options (using the same set or not) are possible.
139	594-599	8	Comment: The use of three sample sets assumes the use of step two "calibration set for optimization of calibration model". This practice is not generally needed and variations are acceptable as long as an independent validation set is used. The second step is correctly labelled as "if used" to make it optional. With this in mind the first sentence should remove the requirement to have exactly 3 data sets. Proposed change: Reword the first sentence to say "To	Comment agreed. 'Three sets of samples' has been replaced with 'the following sets of samples'.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			develop…,the following sets of samples are required." This will remove the requirement for 3 sets.	
140	598	5	Comment: consistency, "calibration test" should be replaced by "internal validation" Proposed change: "the internal validation test set as criteria for model structure and model calibration optimization.	Comment not agreed since the current wording is considered more clear and simple.
141	599-601	10	Comment not made public	
142			Comment #5: No indication in this section that out of spec samples (OOS of concentration level i.e. spectral data- within the range, prediction result- out of range) can be used to expend the range of the calibration model created. Additionally in linearity and range studies of validation the required range to be validated is not mentioned usually the practice is to validate at least 50%-150% of the spec. Also the use of special chemometric software to simulate Synthetic calibration samples should be discussed (creation of mixture spectra by chemometric software)	Comment not agreed. There is no need to inlude OOS samples in the model since these should be flagged by the procedure as being OOS. It is not considered acceptable to include OOS product within the scope of the procedure. These should be out of scope. Synthetic samples simulated by the software would not be accepted.
143			Comment #6: No indication of tools for quantitative model evaluation ("how good is the model ") for example: after creating the quantitative model we receive values of R^2, bias, SEC etc. during the development the user creates many versions of models - tools should be given in order to help the user decide which model is the best : R^2- it is not indicated what is the recommended R^2 usually the range would be 0-1, while the relevant values of acceptance would be 0.9-1.0- but is 0.9 enough? (especially for PAT data) . SEC VS SEP values- the closeness of values of SEC and SEP can	Comment noted. See comment No182.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			indicate that it is a good model (Calibration VS prediction of different set of data). SEC values VS concentration range Dependency of SEC values in concentration levels for example SEC 0.2% for impurity spec NMT 1% versus Assay around 100% spec with the same SEC value. SEP limits -it is not indicated what is good value for the obtained SEP (relative value depend on concentration range and laboratory error of current used reference method) usually we use a rule of thumb 1.4 SEL (the lab error of currently used method e.g.HPLC if method variance acceptable)- not mentioned Also lines 668-670- no feasible parameters are given (reference to 6.2.3 section) in section 6.4.2 SEL is mentioned with no indication of the relevant ration between SEL and SEP Curve resolution techniques for further evaluation of the created model should be included.	
144	603 -616	4	Comment: It seems from this text that the choice of model is entirely empirical. We recommend not excluding the option for scientific basis/rationale to support a particular choice of model, which may be supplemented with empirically derived data. Proposed change: Amend the text to take into account a science based approach to model calibration.	Comment not agreed. It is unclear how model calibration can be based on scientific rational without empirical data
145	603-616	8	Comment: The practice outlined for 'calibration optimization' using a second "calibration test set" is not generally accepted or needed. Calibration optimization can be accomplished in several different	Comment agreed. See comment No 138.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			ways. Suggest to strike this whole section as it goes into too much detail. Alternatively this guidance should be very significantly de-emphasized.	
146	616	5	Comment: Consider adding a statement on good modelling practices after line 616. Proposed change: "The applicant should bear in mind that especially for dynamic PAT applications an acceptable model must first be capable of tracking the trend found in the samples' reference analytics values, and second be accurate in its predictions over a broad range of (i.e., when other potential variability sources are also changing).	Comment partially agreed. Section 4.6 specifically addressed PAT and has been revised to address this comment. The section on modelling has been revised but no reference to good modelling practices.
147	618-619	1	Comment: Samples manufactured at production scale across the specified range will typically not be available for validation. For the validation of linearity and accuracy at the upper and lower limits are typically covered by using lab or pilot scale batches. Refer also to chapter 4.2.2 (line 239-242) where batches representative for commercial process are required. Proposed change: delete "…and should include production-scale batches, where possible" & replace with: "batches representative for the commercial process, where possible."	Comment noted. In principle, the external validation set should cover all variation seen in the commercial process and should include production scale batches, where possible.
148	621-625	4	Comments: "The validation set of samples is used to validate the calibration model and is used to generate the statistical parameter, the Standard Error of Prediction (SEP), which is an indicator of the validity and predictive ability of the calibration model. An SEP will also have been generated for the calibration test set, however this is used as an initial indicator of the predictive validity of the model only. The SEP for the external validation set of samples is the	Comment agreed. Lines 621-625 have been moved to a new section about statistical criteria. See comment No 182.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			pivotal statistical parameter for the model." This level of detail provided in draft guidance is not required since there are other scientifically appropriate approaches. Proposed change : Remove "An SEP will also have been generated for the calibration test set, however this is used as an initial indicator of the predictive validity of the model only. The SEP for the external validation set of samples is the pivotal statistical parameter for the model." and add that details provided for SEP are only an example and other approaches are acceptable when justified.	
149	622-624	5	Comment: Oversimplified. The criteria for model acceptance should not be based on one lumped or averaged (i.e., over the entire model range) statistical figure of merit alone. Again, consider adding a statement on good modelling practices, in this paragraph. A good model must be evaluated both also as being able to capture the trends of predicted x experimental and also the residuals (model mismatch) should be randomly distributed across the entire analytical range of interest with a magnitude that in part is captured by SEP (but SEP subdues outlying residuals).	Comment agreed. The criteria for model acceptance have been reviewed, see section 6.3 "calibration model assessment".
150	625	5	Comment: wording Proposed change: "… indicator of model validity only."	Comment noted. See comments No 148, 149 and 182.
151	625	7	Comment: The definition of SEP in the formula on page 28 is different from the notation used in other standards, e.g., ISO 12099, where the term RMSEP is used instead and where the term SEP is reserved for describing the prediction error after bias correction. Proposed change: After the sentence ending on line 625, add a parenthesis: "(The mathematical definition of SEP as applied in this	Comment noted. The SEP as defined in this guideline does not contain a bias correction. However, the definition of statistical parameters used by applicants should be stated in the dossier.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			document is given on page 28. Note that the definition is different from that used in other standards because the SEP defined here does not contain bias correction.)"	
152	626 -627	3	Comment: "An analyst may choose not to apply 'internal validation' methods during development and optimization of a calibration model." Proposed change: add "in case of cross-validation" at the end of the sentence.	Comment noted. This section has been reworded to adress use of cross validation.
153	627-629	5	Comment: correction Proposed change: "The applicant may choose not to make an 'internal validation´ assessment …"	Comment agreed. This has been reworded.
154	632	3	Comment: the NIRS procedure. Proposed change: *change to be: the NIRS method.*	Comment not agreed. The text refers to the NIRS procedure.
155	632	5	Comment: correction Proposed change: "…method used."	Comment not agreed. The text refers to the NIRS procedure.
156	634	5	Comment: clarification Proposed change: "performance of the NIRS Procedure."	Comment not agreed. The text refers to the NIRS procedure.
157	635-636	5	Comment: "…presented graphically." Will this be in the procedure application ? If yes, what happens during the Procedure life-cycle (LCA) and its continuous improvement? Data sets will change (grow in size). Do these graphical justifications need to be updated throughout LCA or it suffices to note differences if needed? How the much thorough the retrospective (cumulative) efforts should be in regard to keep dragging older data through the LCA of a Procedure ?	Comment not agreed. Graphical presentations are required for the purposes of assessment and demonstration of method understanding. These graphical presentations need only be presented to support any relevant changes made to the procedure by way of variation application.
158	637	3	Comment: Standard error of laboratory (SEL) should be mentioned. Proposed change: to add Standard error of laboratory (SEL) should	Comment noted. See Section 6.3. Full validation data for the reference methods is stated to be required in

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			be mentioned.	Section 4.2.4.
			6.3.1 Software	
159	641-642	5	Comment: "… carefully pair and match these data..:" is this about on-line applications where reference analytics take place at a lower frequency than the high-frequency of measurement of PAT tools such as in-line NIRS.	Comment agreed.
160	644	5	Comment: correction Proposed change: "Such software statistically correlates variation within the data."	Comment agreed. The wording is changed into "Such software empirically correlates variation within the data".
161	645	1	Comment: The correlation between reference method and NIRS using principal components is made through PCR Proposed change: 'PCR' instead of 'PCA'	Comment agreed.
162	645	2	Comment: this may simply be a typo but PCA is not a multivariate regression technique, maybe Principal Components Regression (PCR) was the intent?	Comment agreed. See comment No 161.
163	645	3	Comment: latent variables for PLSR or principal components for PCA). Proposed change: latent variables for PLSR or principal components for PCR).	Comment agreed. See comment No 161.
164	645	4	Comment: Should refer to quantitative PCR rather than qualitative PCA. Proposed change: Change "PCA" or "PCR" to reflect regression.	See comment No 161.
165	646	5	Comment: correction Proposed change: "…latent variables for PLS regression)."	Comment agreed. "PLSR" is replaced with "PLS regression"
			6.3.2 selection of principal components	
166	646-664	10	Comment not made public.	
167	646-664	1	Comment: No reference is made to the use of Cross-Validation	Comment agreed. Optimisation of the model is by

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			technique to choose the number of principal components (compromise between predictive capability and over fitting). Proposed change: Include reference to Cross-Validation technique	appropriate selection of PCs and cross-validation.
168	647	5	Comment: correction Proposed change: "6.3.2 Selection of Model Order"	Comment not agreed. The drafting team does not agree with this new term.
169	648	5	Comment: correction Proposed change: "The rank or model order (e.g., number of PCs to use in a PCR model to describe the required variability in the data set) is of critical importance to avoid under- or over- fitting of the data by the calibration model."	Comment not agreed. The drafting team does not agree to make this change since it will create confusion with the readers. The term 'rank' or 'model order' is not sufficiently established and the guidance is considered clear.
170	653	2	Comment: The reference to co-linearity is confusing. The main advantage of using latent variable regression methods is that it can deal with co-linearity in the data by projecting the raw data into a set of orthogonal factors / principal components - there's no co-linearity in the latent variable space since each variable by definition is orthogonal.	Comment noted. The term principal component is used generically rather than specifically. It is recognised that the use of this term generically is not ideal. It has been replaced by latent variables
171	658	5	Comment: "The analyst" consider replacing with "The applicant" as in line 627	Comment agreed.
172	659	5	Comment: incompleteness Proposed change: "…the feasibility study, which should have included a risk assessment, and the known.."	Comment agreed. The feasibility study should include a risk assessment.
173	660	1	In our experience, the use of neural networks for NIR method development typically leads to highly overfitted models and in our view should not be used over PCR/PLS algorithms Proposed change: Remove reference to neural networks	Comment agreed. Reference to neural networks has been deleted.
174	661	5	Comment: Warning. In my view it is potentially disastrous that the Guideline opens the way for poor method development and ignoring that spectroscopy used for quantitation is based on linear and	Comment agreed. See comment No 173.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			additivity of a signal, to be compensated by means of non-linear and over-parameterized modelling strategies which most often are used by non-experts. Proposed change: remove ANN reference	
175	665	5	Comment: Completeness Proposed change: "…also be reported when assessing predicted x experimental values."	Comment agreed.
			6.3.3 Optimisation of the NIRS model	
176	666-667	1	Comment: irrelevant/repeated information Proposed change: Remove first sentence, start paragraph at optimisation	Comment noted.
177	667-668	5	Comment: Wordiness Proposed change: remove first sentence and start at "Optimisation…".	Comment agreed. See comment No 176.
178	674	5	Comment: clarity Proposed change: "… under- and over-fitting of 'models'. Any…"	Comment agreed and implemented.
			6.4. Validation	
179	678	5	Comment: As mentioned earlier there are other equally very important statistical figures of merit. Consider creating a small section on "Statistical Figures of Merit" which can be referred from different parts of the Guideline and in which there is clear mention to the three most important ones: (1) SEP (viz., RMSEC, RMSECV, RMSEP), (2) slope and intercept with graphical analysis (for outlier detection) of predicted x experimental, and (3) a residual analysis of model mismatch to observations (check on model structure and further accuracy assessment).	Comment agreed. See comment No 182.
180	680-687	1	Overly extensive/unclear description of SEP, and it is not clear why	Comment agreed. See comment No 182.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			only refer to SEP in "General Considerations"	
181	681	8	Comment: Another important element to be evaluated with such off-target samples is accuracy and robustness.	Comment noted. Accuracy and robustness have been addressed under validation section.
182	683-687	5	Comment: This entire whole paragraph needs careful consideration and rewriting to be clearer and more accurate than it is now. I would simply delete most of the first four lines and start after that. Proposed change: "A statistical acceptance criterion is used as a measure of the model's ability to predict the correct quantitative result. This is SEP, …"	Comment noted. See section 6.3 Calibration model assessment.
183	683-684	8	Comment: "Since quantitative NIRS analysis relies upon reference data obtained from a reference method or very rarely". Proposed change: delete the term "rarely". Many NIRS application exist for both liquids and solids applications where adequate standards can be built by volumetric or gravimetric analysis.	Comment agreed.
			6.4.2. Standard Error of Prediction (SEP)	
184	689	3	Comment: The SEP and the SEP/range ratio should be determined for the external validation set. Proposed change: Take out "the SEP/range ratio"	Comment not agreed. SEP/range is considered a key element of external validation. External validation should cover the full range of the procedure.
185	689	4	Comment: Level of detail provided in draft guideline is not required since there are other scientifically appropriate approaches. Proposed change: Add that details provided for SEP are only an example and other approaches are acceptable when justified.	Comment agreed. See comment No 179.
186	690	5	Comment: "range" undefined Proposed change: "The SEP and the SEP/method range ratio should be …"	Comment agreed. The definition of range, especially with respect to 'regulatory range' has been clarified.
187	690-693	5	Comment: According to this Guideline the Procedure is not static	Comment noted. The comment this is discussed

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			and may change and need updating over its life-cycle. What type of model monitoring over the LCA is needed and at which point in the LCA should it be done (only when changes are made, when changes are not intentionally made but are detected ?)	under Section 7.1.
188	691	2	Comments: Sentence "These are considered pivotal statistical parameters." appears overly strong, particularly when referring to SEP/range ratio. If it is pivotal then one needs further supporting data to illustrate why, or guidance on how to use them.	Comment agreed. See comment No 182.
			6.4.3. Specificity	
189	697-700	7	Comment: See the general comment above. As a minimum change, I ask to please insert the correct definition of selectivity. Proposed change: Delete lines 697 – 700 and replace with: "For specificity, the procedure should be able to assess unequivocally the analyte in the presence of components which may be expected to be present."	Comment agreed and implemented.
			6.4.4 Linearity	
190	708-719	4	Comment: There appears to be some disconnect in the linearity and accuracy sections. The guidance discusses demonstrating linearity (ICH is establishing) and establishing accuracy (which should be demonstrated). For the models, linearity is established for the calibration model. This does not require validation set samples covering the full concentration range. Proposed change: Merge chapter Linearity and Range Linearity and range have to be demonstrated during the establishment of the calibration model. No corresponding samples in the validation set are mandatory for linearity and range. Linearity	Comment agreed. The chapters on linearity and range have been merged.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			can be adequately confirmed and validated with accuracy standards that cover the range of linearity. Delete 717-719	
			6.4.5 Range	
191	715-718, 681	7	Comment: In the opinion of this author, Range should be treated as an input specification, and not as a parameter to be separately validated. See also the existing text in lines 709 and 720. Proposed change: Delete lines 715 – 718 and change the ending of the sentence ending in line 681 to ".. demonstrate selectivity and linearity over a specified range."	Comment noted. The range is considered part of the scope of the NIRS procedure. However linearity should be demonstrated over a specific range.
192	718	2	Comment: Why should such results be highlighted as outliers? If the spectra are perfectly valid with no unusual Q residual then the model would indicate that the sample just has excess active, for example. The results should not be discounted, but would clearly prompt an investigation into the nature of the property which may then lead one to determine that it is an outlier.	Comment noted. Section on 4.3.2 on outliers has been updated.
193	718-719	8	"Validation samples having analyte content outside of the calibration range should appear as outliers when tested by the NIRS procedure." Comment: It should be clarified (see earlier comment on line 193-194) that this requirement is not expected to be fulfilled necessarily through the software/automation but can also be satisfied in a procedural way (standard operating procedures, specifications).	Comment noted. See comment No 192
			6.4.6 Accuracy	
194	719-723	1	Comment: In the current guideline CPMP/QWP/3309/01 SEP is recommended as a parameter to determine accuracy. In the new draft there are separate chapters for SEP and accuracy. There is no reference in the SEP chapter to accuracy. Accuracy is not	Comment noted. We don't consider it necessary to merge the sections on SEP and accuracy.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			specifically described. At least the SEP chapter should include a reference to accuracy (or vice versa).	
195	722	5	Comment: Clarification / correction Proposed change: "… intended use. For a well developed NIRS procedure the (SEP) is comparable to the reference method's accuracy (SEL). NIR methods using parsimonious models not overfitting the calibration data set, can be more accurate than reference methods. Those special cases deal with reference methods of low precision and with a particular noise structure (viz., random or white noise) and strong linearity between the chosen spectral regions and the analyte signal by the reference method. In these cases, a well developed and validated model will show greater accuracy than the reference method."	Comment noted.
196	722-724	8	"In some case, the NIRS procedure may have a higher error than the reference method. In such cases, limits may be set that are tighter than those set for the reference method". Comment: If the RMSEP is used a primary means of determining accuracy, one must remember that the statistic is a measure of the APPARENT accuracy of the method and will include the variance of the reference method. The true accuracy (as defined by sample-specific confidence intervals or ASTM formulae for subtracting the reference method varaince from the RMSEP) can be equal to, or better than the reference method. There should be no justification for setting tighter limits for the NIRS method relative to the reference method.	Comment agreed. The sentence has been deleted.
			6.4.7. Precision	
197	725	4	Comment: SEP and Bias are not measures of precision. These are measures of accuracy (how close to true) rather than a measure of	Comment agreed. See Calibration model assessment section.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			distribution/ spread. SEP has been discussed heavily in 6.4.2. Bias"as close to zero as possible" is not scientific. Proposed Change: Remove "and the SEP" and move sentence on Bias to Accuracy 6.4.6 or 6.4.2. Bias should be documented, explained and justified.	
198	725 - 734	4	Comment: There is no need to demonstrate intermediate precision where there is no sample preparation. Proposed change: Include a statement to state "Where there is no sample preparation (e.g. on-line application) it is not necessary to demonstrate intermediate precision."	Comment not agreed. Intermediate precision should be demonstrated even if there is no sample preparation to take into consideration parameters such as environmental position, sample position, etc…
199	730-731	4	Comment: The sentence "Repeatability should be demonstrated across the range of sample variation" is unclear. Repeatability can be demonstrated using multiple measurements of a single sample. The description should be updated to reflect this. Proposed change: Repeatability should be demonstrated through the analysis of replicate measurements at the expected level.	Comment agreed. This sentence has been removed.
200	733	1	Comment: In some cases, samples will degrade with time. Performing the intermediate precision across days becomes non feasible. Proposed change: "over different days (unless samples degrade)"	Comment noted. The guideline has been updated to reflect that the suitability of the determined precision of the NIRS procedure should be discussed and justified.
			6.4.8 Robustness	
201	735	4	Comment: The statement "Generally, the reference methods used to generate the reference data for quantitative NIRS procedures measure chemical or physical properties of samples whereas the vibrational characteristics measured by NIR spectral analysis take into account	Comment agreed. The sentence deleted. See also comment No 202.

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			both physical and chemical properties." The 'vibrational characteristics' are also based on physical and chemical properties of the substances measured with NIRS. The explanations given in lines 738 - 746 appear sufficient to address the robustness. Proposed change: Delete the statement in lines 735 - 737.	
202	736-738	8	"Generally, the reference methods used to generate the reference data for quantitative NIRS procedures measure chemical or physical properties of samples whereas the vibrational characteristics measured by NIR spectral analysis take into account both physical and chemical properties". Comment: Confusing and not a scientifically valid statement. The main difference is that NIRS typically does not involve sample preparation and therefore the measurement may be impacted by changes in the sample matrix. All analytical methods are impacted to varying degrees by changes in the physical and chemical properties of the sample. These changes could impact the sample preparation procedure or the measurement itself. Example: HPLC coupled with UV detection. The electronic absorption of molecular chromophores in the column effluent is affected by both chemical and physical properties of the solution (Temp, flow rate, ionic strength, etc.). It is the separation of sample components that imparts specificity. Proposed change: Recommendation: Re-word to: "If the NIRS method does not involve sample preparation, the measurement may be impacted by changes in the physical or chemical properties of the sample matrix".	Comment agreed. Sentence reworded.
203	740	5	Comment: Completeness	Comment agreed.

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			Proposed change: "…sampling and spectra pre-treatment."	
204	743	5	Comment: Completeness Proposed change: "… Response). The use of risk analysis and DoE will help support knowledge about the procedure performance and robustness, for all combined sources of variability influencing the procedure."	Comment not agreed. The use of risk assessment has been addressed in previous sections. Reference is rather made to method development in general.
			7. NIRS procedure lifecycle and post-approval requirements	
205	750	3	Comment: 7. NIRS procedure lifecycle and post-approval requirements. The wording "lifecycle" can be confusing, because it might mean difference. Proposed change: The iterative process of NIRS procedure and post-approval requirements	Comment not agreed. It is recognised that development and maintenance are iterative processes but the word "lifecycle" is considered appropriate because it reflects much better the idea that the procedure is set in long terms and is embedded with the manufacturing process.
			7.1. Management of the NIRS procedure lifecycle	
206	751	3	Comment: 7.1. Management of the NIRS procedure lifecycle As commented on the line 750. Proposed change: 7.1 Management of the NIRS iterative process	Comment not agreed. See comment No 205.
			7.2. Changes to approved NIRS procedures	
207	759	3	Comment: 7.2. Changes to approved NIRS procedures Proposed change: 7.2. Changes to approved NIRS methods	Comment not agreed. It is clearly stated in section 4.1.1 that the NIRS procedure is the combination of the NIRS method and NIRS model. In this perspective procedure is broader than method and is considered the appropriate wording.
208	764	3	Comment: 7.2.1. Changes within the defined scope of the NIRS procedure Proposed change: 7.2.1. Changes within the defined scope of the NIRS method	Comment not agreed. See comment No 207.
			7.2.1 Changes within the defined scope of the NIRS procedure	

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209	766-771	5	Comment: In practice this means that the RA done up front for procedure development will have to contemplate all types of post approval changes within the application's scope (cf. lines 183-184).	Comment noted.
210	771-777	1	Comment: What is the intention and additional benefit of the mentioned change management tests? If changes are fully documented and the NIRS method and procedure have been validated there is no need to change management tests and periodic re-evaluation of change management tests. Proposed change: Delete lines 771-777.	Comment not agreed. The fact that changes are documented does not preclude the need to have change management tests. Change management tests are tools used as part of change validation. Their periodic re-evaluation is necessary because they should reflect the actual quality of material and classes of substances used on the manufacturing site.
211	779	5	Comment: "Quantitative NIRS procedures should only be used within the calibrated concentration range…" this statement is only true when the NIRS procedure is to be used as an analytical method for release; for NIRS as a PAT tool the procedure's design and operating spaces should be evaluated in a MV way looking at the PAT domain (e.g., NIR spectra PCA projection after pre-processing and wavelength selection of spectra) – as indicated by us before (comment to lines 181-182). The Guideline statement in line 779 in summary takes a step-back on the use of NIRS as a PAT tool and detracts from the initial Guideline intended QbD approach to analytical method development (intrinsic to QbD is the consideration of multivariate effects).	Comment not agreed. It should be clear for industry that the guideline addresses "regulatory methods" used for in process control and/or product release. It is then expected that the scope of those methods are clearly defined. Any PAT application intended for process knowledge and /or non-regulatory purpose is out of the scope of the guideline and needs no justification in terms of "scope " definition.
			7.2.2. Changes outside of the defined scope of the NIRS procedure	
212	779-793	8	Comment: The requirements around changes outside of the "scope" of the NIR method need further refinement. It is important for the applicability of NIR in the typical production environment to	Comment not agreed. In the context of NIR, the range covered by NIR should reflect at least the method specification. Changes to the ranges related

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			minimize the uncertainty in the process of managing model. Any need to file variations for changes in the NIR method, which typically would not require variation filing for conventional analytical methods (example: changes of software; range of method through based on calibration) will prohibit the use of NIR in routine production as it will add time and (approval) uncertainty to the management of methods. An example in the current section is the change of the "range" of the NIR method, which could easily change by the addition or subtraction of samples to calibration and validation set. This is typically done in a way not to narrow but if at all widen the range and well acceptable. Proposed change: Reconsideration of this section.	to changes to specification should be submitted for regulatory approval (see line 790). Other changes to the range that are not related to change in the specification would not require a variation but need to be documented and justified according to internal change management system.
213	783	3	Comment: 7.2.2. Changes outside of the defined scope of the NIRS procedure Proposed change: 7.2.2. Changes outside of the defined scope of the NIRS method	Comment not agreed. See comment No 205.
214	787 - 789	4	Comment: This could be interpreted that adding additional materials to an ID library that are not spectroscopically similar etc would necessitate a variation rather than GMP only. Proposed change: …would be considered sufficient and does not need a variation application.	Comment agreed.
			7.3. NIRS procedure transfer between NIRS instruments	
215	793	3	Comment: 7.3. NIRS procedure transfer between NIRS instruments Proposed change: 7.3. NIRS method transfer between NIRS instruments	Comment not agreed because the transfer includes the transfer of the model.
216	794	3	Comment: The aim of NIRS procedure transfer is to ensure that the calibration model generated on one NIRS instrument will work on	Comment not agreed. Comment cannot be implemented, because the transfer includes the

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			another instrument, based on the validation parameters detailed in Sections 5.5 and 6.4 of this guideline. Proposed change: procedure to method	transfer of model.
217	794-829	4	Comment: Section does not appear to address the scenario where the transfer between instruments is successful and does not require any compensation. In such a case, the comparability protocol would be sufficient. Proposed change: Recommendation to include explicit language to clarify that if the transfer of the model from one instrument to another meets comparability acceptance criteria, options 1 (correction) and 2 (recalibration and validation) do not apply.	Comment not agreed. The comparability protocol is not an alternative to option 1 and option 2. The transfer will be performed using option 1 or option 2. The comparability protocol should in both cases show successful transfer.
218	796-797	3	Comment: "Samples analysed on the original 'master' instrument should give equivalent results on all additional instruments to which the calibration model is transferred." It is not necessary to use the same samples analyzed on all instruments because validation is needed and mentioned in Sections 5.5 and 6.4. Proposed change: take this sentence out	Comment agreed. Section updated.
219	799	3	Comment: hardware (e.g. identical spectrometer type and measuring set-up) Proposed change: hardware (e.g. similar spectrometer technologies and measuring set-up)	Comment not agreed. Identical does not mean similar.
220	802	3	Proposed change: interfaces (e.g. probes, waveguides and fiber optics)	Comment agreed and implemented.
221	813 - 814	3	Comment: "Calibration transfer models may be developed using a small but representative number of calibration samples that are run on both instruments (the master and the additional instrument)." If FT-NIR is used, the NIR method can often be transferred without	Comment not agreed. The stakeholder claims that if FT-NIR is used, NIR method can be transferred without developing calibration transfer models. However this claim is not supported by any scientific

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			developing calibration transfer models. Proposed change: add: If FT-NIR is used, the NIR method can often be transferred without developing calibration transfer models.	or technical argument.
222	821-822	5	Comment: This paragraph motivates the need to document sample leverage (individual importance) in model development and also to store the spectra of high leverage samples to facilitate throughout the Procedure life-cycle to find comparable samples. There is a very interesting consequence from this point which is: the possibility of managing a spectral data-base of high-leverage samples, rather than samples themselves! This opens the way for synthetic samples to be built to intentionally resemble such high-leverage samples (our 2nd Patent Application with ROCHE PZ).	Comment not agreed. The example given by the author is a specific example that cannot apply in general to all types of applications. In principle the guideline is flexible enough and does not preclude the proposed solution.
223	823-829	8	"In both cases (1) and (2), the transfer of an NIRS procedure to another instrument should be the subject of an appropriate comparability protocol." Comment: Method transfers for NIR methods are very similar in scientific and procedural rigor to method transfers for conventional methods. The requirement to submit a comparability protocol for prior approval of the approach is scientifically unnecessary and puts an additional burden on the use of NIR methods established in one instrument or another manufacturing site, and will hinder the use of NIR in the GMP environment. NIR transfers for both scenarios have been successfully accomplished with many examples and should be regulated, like all method transfers, within the internal quality system of the company, with documentation available upon inspection. Proposed change: Reword whole section to remove the need for comparability protocol.	Comment not agreed. The transfer of an HPLC method between instruments is not similar to the transfer of a NIRS procedure between instruments. This argument has been extensively developed with industry. Industry failed to provide real examples of successful transfer that need no correction or recalibration. Hence the comparability protocol should be submitted prior to NIRS transfer between instruments. See also comment No 217.

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224	824-828	1	Comment: During the break-out session to discuss the comments of revision 1 it has been agreed that method transfer is subject to GMP in case the results of the comparability protocol demonstrate negligible differences. Proposed change: The above-mentioned statement should be added to this section to clearly address this assessment.	Comment not agreed. See comment No 217.
225	827-829	4	Comment: It is not considered appropriate to always "register the transfer" by variation, particularly if transferring between equivalent NIR methods, without the need for transfer algorithms or mathematical compensation. This should be covered within the company quality system and subject to GMP inspection. Variation should only be considered if moving outside the scope of the procedure. NIR procedure transfer should not be automatically considered as outside of the defined scope of the NIRS procedure. Proposed change: Transfer is handled under the GMP system of the company and does not require a variation application.	Comment not agreed. A change of instrument is automatically associated to a change in hardware and /or software and/or interfaces. This will more or less have an impact on models and/or methods and will at least necessitate mathematical compensation. See comment No 223. One has to keep in mind that changes in instrument will not occur often. On the other hand, industry can also chose the option to develop the procedure on more than one instrument if the transfer of the procedure is foreseen as part of the product lifecycle.
			8. Glossary	
226	GLOSSARY	5	Comment: in the definition of "Chemometrics" Proposed change:" Mathematical multivariate methods to analyse, compare or model data from chemical or physical methods."	Comment partially agreed. Sentence has been reworded and reads "Mathematical methods to analyse and compare data". See also comment No 236.
227	GLOSSARY	5	Comment: in the definition of "DoE". What is the need to give the specific definition for 2-factor full factorial designs? Keep it general. Proposed change: "A strategy to gather empirical knowledge from the analysis of data obtained from experiments run with predefined/intended variation in their most important variability sources (factors) established through RA. It is an effective way to	Comment agreed. A more general definition is given.

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			establish in a quantitative way, data-based mathematical models describing a system, to be used in furthering process understanding and establishing desired process operating ranges"	
228	GLOSSARY	5	Comment: there should be entries for MVDA, QbD and RA Proposed change: "MVDA – Opposed to classical descriptive statistics focused on the analysis of multiple samples but only one variable at a time, MVDA works on both dimensions of a given problem: in the samples direction (e.g., time or observation domain) and in the variables direction. In doing so MVDA is very effective in analyzing and comparing data from PAT tools and dynamic processes. MVDA often uses projection methods for dimensional reduction and the use of the main variation directions in a data set. " "QbD – A systematic approach to process development that begins with predefined objectives and emphasizes product / process understanding and uses process control based on sound science and quality risk management. " "RA – Risk assessment is a knowledge-based methodology used in quality risk management (e.g., ICH-Q9) that can aid in identifying which relevant influencing sources of specific responses. A properly done RA is a requirement to achieve well-designed DOEs within QbD whether for analytical procedure/method development of other purposes."	Comment not agreed. There is no need to define these terms in this guideline.
229	GLOSSARY	5	Comment: Wrong definition for PLS (PLSR). PLS is a regression method on Latent Variables (PLS = Projection into Latent Structures)	Comment not agreed. In various fields of chemometrics (especially NIR) the abbreviation is used for the term 'Partial Least Squares' (Regression). It is acknowledged that the term is also

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				used for 'Projection to Latent Structures' (based on the PLS method developed by Herman and Svante Wold).
230	GLOSSARY	5	Comment: Wrong definition of "PCA or LV". Principal components are orthogonal to each other (the PCA algorithm generates them that way); LVs are not exactly orthogonal the aim is to have the LVs to span the maximum variance of the NIRS space and a different set on the analyte reference method measurements space. This must be corrected or will be subject of dispute by many chemometricians and analytical chemists using chemometrics, worldwide. Proposed change: Define PCAs (current definition should be clarified), then define LVs as above for example.	Comment agreed. A definition for latent variable has been added.
231	829 (page 25)	3	Comment: Calibration test set The set of samples, which are drawn from the same population as the calibration set, but were not used to generate the calibration model. In practice, the calibration set often consists of two thirds of the available sample population. The calibration test set is the remaining third. <u>It can be called internal validation set</u> Proposed change: add: "It can be called internal validation set" at the end of the sentence.	Comment agreed. 'Internal validation' has been added into brackets.
232	829 (page 26)	3	Comment: Internal validation "The application of resampling statistics such as cross-validation. Subsets of the calibration data set are subjected to a variety of statistical processes to identify which calibration model may best fit the available data. Each model is characterised by a statistical parameter. For cross-validation, the entire data set of samples is split into individual samples or groups of samples, which are	Comment not agreed. The proposal applies to the calibration test set only.

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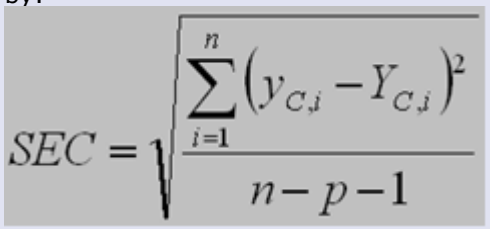
			removed individually from the rest of the samples and tested as unknowns against a calibration model constructed using the rest of the samples. The characteristic statistic is the Standard Error of Cross Validation (SECV)" Comment: internal validation does not mean only for cross-validation. It can be like calibration test set. Cross-validation should not be mentioned here. Proposed change: (writing similar to calibration test set): The set of samples, which are drawn from the same population as the calibration set, but were not used to generate the calibration model. In practice, the calibration set often consists of two thirds of the available sample population. The calibration test set is the remaining third.	
233	829 (page 26)	3	Proposed change: The definition of NIRS method should read: "Describes the key elements that enable the NIRS measurement of the analyte of interest. This includes for example, the equipment and spectrophotometer type (e.g. interferometer (FT), monocrometer, etc), the sample measurement interface (e.g. probe, sample stage etc), the number of scans or measurements and the spectral range of the instrument."	Comment agreed. Examples of the spectrophotometer type (e.g. FT, grating, etc) have been added to the definition.
234	829 (page 27)	3	Comment: Ratio of performance deviation (RPD) has never been mentioned before. Proposed change: take it out	Comment agreed.
235	829 (page 28)	3	Comment: Standard Error of Prediction (SEP) Comment: the formulae written in the guideline is wrong. It is called Root mean square error of prediction (RMSEP). Proposed change:	Comment not agreed. The SEP formulae in the NIR guideline is considered appropriate. If applicants use other formulae they should justify it in their application and explain the differences between the

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			$SEP = \sqrt{\frac{\sum_{i=1}^{n}(Y_{wi} - Y_{ri} - bias)^2}{n-1}}$	formulae.
236	Glossary	1	Comment: incomplete definition of chemometrics Proposed change: … from chemical of physical methods	Comment not agreed. See comment No 226.
237	Glossary	1	Comment: extensive definition of DoE Proposed change: remove references to 2x2 factorial design and keep it general	Comment agreed. See comment No 227.
238	829	4	Comment: "Chemometrics: Mathematical multivariate methods to analyse or compare data". It is important to consider that methods of chemometrics are not necessarily multivariate. Proposed change: Remove "multivariate".	Comment agreed. The word 'multivariate' has been deleted.
239	829	4	Comment: "Standard Error of Prediction (SEP): A statistic measuring the difference between the NIRS procedure and reference method quantitative analyte values of the calibration test set and the independent validation set. The SEP derived from the independent validation set is considered a pivotal statistical parameter." Extra detail not required in the glossary Proposed change: Remove "The SEP derived from the independent validation set is considered a pivotal statistical parameter."	Comment agreed. The sentence has been deleted.
240	829	4	Comment: "Ratio of performance deviation (RPD)…": Only available as a definition in the glossary, never mentioned in the document. Proposed change: Either mention in the document (in the validation part), or remove from glossary. If decided to be mentioned in the document, then please specify rule of use and how to interpret its acceptance	Comment agreed. The definition of ratio of performance deviation has been deleted. See also comment No 234.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			criteria or limits.	
241	829	4	Comment: Standard deviation. Should be "Y" for "y = reference method value" Proposed change : Should be "Y" for "y = reference method value"	Comment agreed.
242	829 (Glossary)	4	Comment: RMSEP, RMSECV and RMSEL are the more common terminology. Proposed change. Use the terminology RMSEP, RMSECV and RMSEL	Comment not agreed. Statistical parameters other than those described in the guideline can be replaced by other commonly used statistical parameters provided that differences in the formulae are explained in the application.
243	829 (Glossary)	4	Comment: The glossary should be improved and completed. Proposed change: Formula of Standard Error of Calibration (SEC) should be replaced by:  Standard Error of Prediction corrected for bias (SEP(C)) should be provided after SEP in the glossary: with:	Comment not agreed. The SEC formulae in the NIR guideline is considered appropriate. If applicants use other formulae they should justify it in their application and explain the differences between the formulae.

nr	Line no.	Stake-holder no.	Comment and rationale; proposed changes	Outcome
			$$SEP(C) = \sqrt{\frac{\sum_{i=1}^{n}\left(y_{V,i} - Y_{V,i} - Bias_V\right)^2}{n-1}}$$ with: $$Bias_V = \frac{\sum_{i=1}^{n}\left(y_{V,i} - Y_{V,i}\right)}{n}$$	