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Overview of comments received on ICH guideline on Q2(R2) Validation of analytical procedures (EMA/CHMP/ICH/82072/2006)

Please note that comments will be sent to the ICH Q2(R2) EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Andrea Gaggioli - ISS. ITA	0	0	many	Terminology issue related to Accuracy. I think the more suitable term here is Trueness (as allowed in the Q2R1 version: No more allowed in the R2 version). In fact the definition is: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional **true** value or as an accepted reference value and the value measured. (ICH Q2). I would use Accuracy for the combination of Precision and Trueness, which is called here TAE (new term, see comment below and .pptx file submitted in cell G85).	
APIC	0	0		uncertainty is not part of the validation whereas it has a reality in practice and part of the discussion between laboratories	
APIC	0	0		Measurement uncertainty resp. Total analytical error (TAE) is missing. The TAE is only named in the glossary Since this is calculation from accuracy and precision study, many validation reports include this calculation.	
EFPIA	0	0	General Comment	Linkage of Q2 to Q14: Improved linkage is required between Q2 and Q14, both in terms of the relationship between the guidelines and the agreement of the terms and concepts utilised. See inidividual entries as detailed.	Closer alignment of the guidance titles (see Q14 comment). Additional text providing cross referencing to Q14 in introduction (lines 4, 35) Ensure use consistent use of term ‘performance criteria’ (lines 321, 357, 571) ‘Duration’ to be included in robustness (line 418) Clarifications to Figure 1 (line 84) to align terminology and clarify the use of ‘appropriate’ development data (proposal will be made available)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	0	0	General Comment	Working and Reportable Range: Additional clarity is required in relation to working and reportable ranges. Greater flexibility is necessary on the definition of working range to cater for application to multiple types of analytical method. However, greater focus should be given to the validation of the reportable range, with scope provided to use a working range in this regard where required. See inidividual entries as detailed.	Revise the text introducing the concept of range (215 – 218) Remove reference to 'working' range (59, 64, 214, 222, 254, 331) Revision of range definitions (531 – 543) Removal of 'specificity' (implicit from acc. and precision, 101) Clarification of Table 2 as examples only Clarification that QL / DL should only be required when working close to the lower limits of the procedure (267) Add text to enable extrapolation where justifiable (218)
EFPIA	0	0	General Comment	Provide more examples for multivariate analytical procedures using different models (e.g., Principal Component Analysis, Partial Least Squares, etc.) to help readers better understand the validation and lifecycle management of multivariate analytical procedures	
EFPIA	0	0	General Comment	consistency in the document: method vs procedure. Eg page 28 - 661 - method is used instead of procedure	harmonise to "analytical procedure" in the whole document
European Association of Nuclear Medicine	0	0		The European Association of Nuclear Medicine welcomes the review of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) draft guidelines Q2(R2) on Validation of analytical procedures and Q14 on Analytical procedure development, recently released for public consultation.	
European Association of Nuclear Medicine	0	0		These guidelines represent a general and commonly accepted basis for the development and validation of analytical methods for most of drug substances and products.	
European Association of Nuclear Medicine	0	0		However, in the ICH guideline Q14 it is also stated that "Approaches other than those set forth in this guideline may be applicable and acceptable with appropriate science-based justification. The applicant is responsible for designing the validation studies and protocol most suitable for their product", thus recognizing that the suggested analytical methodology may not be fully applicable in special cases. Although they are not specifically mentioned in ICH texts, radiopharmaceuticals are certainly a special case and should therefore be excluded of the scope of the ICH analytical procedures guidelines.	
European Association of Nuclear Medicine	0	0		Indeed, these guidance documents (ICH Q2 and ICH Q14) do not fully address all the specific tests required for the analysis of radiopharmaceuticals.	
European Association of Nuclear Medicine	0	0		Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides included for a medical purpose. The radioactive compounds in radiopharmaceuticals may contain simple salts, metal complexes, small organic molecules or large molecules as the active pharmaceutical ingredient. As for any other pharmaceutical, their quality (i.e. identity, strength, and purity) needs to be controlled before administration to patients, to ensure that their characteristics are suitable for the intended purpose. However, for quality control of radiopharmaceuticals specific aspects which differ from conventional pharmaceuticals must be taken into account:	

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European Association of Nuclear Medicine	0	0		· The strength of a radiopharmaceutical is defined by its radioactivity content, or radioactivity concentration, and it follows the decay law; thus, the strength of a radiopharmaceutical decreases with time.	
European Association of Nuclear Medicine	0	0		· Radioactive standards for the drug substance or radiochemical impurities are not available, the radioactive drug substance itself cannot be isolated.	
European Association of Nuclear Medicine	0	0		· Whilst analytical techniques used to determine the content of non-radioactive components of radiopharmaceutical preparations are generally the same as those used for conventional pharmaceuticals, radioactivity determination requires specific techniques, which make use of dedicated instrumentation capable of specifically detecting, discriminating and quantifying the radioactivity in the sample.	
European Association of Nuclear Medicine	0	0		As a special class of medical products, radiopharmaceuticals require their own guidelines. In this respect, the EANM, in cooperation with EDQM, has recently developed a guideline on the validation of analytical methods for radiopharmaceuticals. This includes recommended approaches to validate analytical methods for radiopharmaceuticals.	
European Association of Nuclear Medicine	0	0		As such, the Nuclear Medicine community does not see the need for radiopharmaceuticals to be covered by these Q2 and Q14 analytical guidelines, and should be explicitly exempted, but would rather call for a recognition by the ICH of the EANM guidelines on this matter.	
European Association of Nuclear Medicine	0	0		Reference: Gillings, N., Todde, S., Behe, M. et al. EANM guideline on the validation of analytical methods for radiopharmaceuticals. EJNMMI radiopharm. chem. 5, 7 (2020). https://doi.org/10.1186/s41181-019-0086-z	
European Association of Nuclear Medicine	0	0		Reference: European Directorate for the Quality of Medicines & HealthCare: Revised guidance for elaborating monographs on radiopharmaceutical preparations: new section on validation of methods : https://www.edqm.eu/en/-/revised-guidance-for-elaborating-monographs-on-radiopharmaceutical-preparations-new-section-on-validation-of-methods	
FUJIFILM Diosynth Biotechnologies Denmark	0	0		Thank you for drafting an update to Q2 (R1). There are a lot of improvements in the guideline with respect to claryfying issues from R1 and making the guideline substantially more unambigious. In generel, the examples included in Tables 3 - Tables 11 are highly appriciated. However, almost 30 years have passed since the first version of Q2A was published and among other developments, statistical software to design and evaluate validation studíes has developed tremondously during this time (if they at all existed in 1993). Thus, it should be taking into consideration that in 2022 it is possible to design validation studies by DOE and gain more knwledge with use of fewer resources. Thus, the guideline should take this into account. Examples are inclueded below.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
FUJIFILM Diosynth Biotechnologies Denmark	0	0		Even though Q14 "analytical procedure development" is referenced and it is stated that Q14 should be considered during validation studies, the Q2 R2 draft version still does not fully implement Q14, e.g. knowledge and risk assessment when designing validation studies. In section 4 "Validation tests, methodology and evaluation", especially in section 4.3.2 "precision" there is too much "minimal approach" and too little "enhanced approach".	
FUJIFILM Diosynth Biotechnologies Denmark	0	0		A statement that the analytical procedure should be validated "under actual conditions of use" is missing in the guideline. That sentence is stated in ICH Q7 12.80. It should nevertheless also be stated in ICH Q2	Include a statement "the analytical procedure should be validated under actual conditions of use"
Guerbet	0	0		Please consider the possibility to harmonize the use of the words 'trueness' and 'accuracy' with the ISO 5725 standard.	Use trueness instead of accuracy and reserve the term of accuracy to describe the combination of trueness and precision
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	All	ISPE found several sections in the ICHQ2(R2) draft revision challenging to follow because information on related validation points is split among different sections, and in some cases the details are not aligned well between sections (e.g. introduction vs body of text vs Glossary).	We suggest streamlining the organization of information across the sections by grouping related concepts and harmonizing Q2(R2) text details with the associated Q2(R2) Glossary terms. Specific ISPE suggestions are provided in each section's comments.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	All	While ISPE appreciates the desire to minimize redundant presentation of common principles, it is not consistently clear throughout Q2(R2) which validation elements and recommended data are related to multivariate analytical procedures versus traditional analytical methods. For example, it is not clear that cross-validation is a key concept applicable to multivariate analytical procedures, while technology transfer is a key concept for traditional analytical methods.	We suggest consistently separating out validation elements and recommended data that are applicable to multivariate analytical procedures versus traditional analytical methods, even if it requires repetition of certain common principles. Section 3.4 and the Glossary are well organized in this respect, with clear separation of issues relevant to multivariate analytical procedures. For similar organizational clarity, all other Q2 sections should clearly distinguish elements related to multivariate analytical procedures from those related to traditional analytical procedures.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	0	0	All	While some sections (especially the Annexes) have greatly improved understanding of Q2 principles for methods used with biological products, ISPE notes several specific recommendations provided in the guidance still appear biased towards terminology, methods and applications suited to chemical products.	Specific ISPE suggestions to better clarify elements relevant to biological product methods are provided in each section's comments.
Keng Siak Lam	0	0		For given quality attributes, we want to see a large portion of the finished product or API is wtihin specifications. What if you want to be 95% sure that the interval captures at least 95% of the population? Such a quality on coverage provides a high degree of assurance of the consistency in the manufacturing process, and most importantly provides us a greater confidence that the manufactured products are both safe and effective. In short, TI describes the population or process from which the pre-defined number of samples are selected. Whereas PI predicts the results of a future sample from the same population. Hence, PI has a shorter interval. TI is widely published in the literature and only fit for this intended use for analytical procedure validation.	Combined accuracy and precision can be evaluated by use of a tolerance interval (to assess the proportion of all future reportable values that will fall within the acceptable range). Other approaches such as prediction interval may be acceptable if justified.
Medicines for Europe	0	0		The document is mentioning "Reportable range" in section 3.2 that it should be validated for accuracy, precision and specificity. However, in the validation methodology sections, it doen't explain how to implement the concept for specificity (4.2). Also, section 4.2 is titled as "Working Range" which is confusing.	Please provide more specific methodology for reportable range validation. E.g., Is it allowed to select one to validate (reportable range or working range)?

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	0	0	3	We often have sample matrix changes caused by manufacturing process changes, and in this case, addendum method validations of existing anytical methods have been planned. In this regard, we would like to know if the minimal requirements of the performance characteristics can be proposed for the addendum method validation strategy.	Addition of the validation strategy for the addendum method validation of sample matrix changes compared to its initial method validation results.
Moderna	0	0	General comments:		1. Please provide the method validation guidance for Karl Fischer water determination methods
Moderna	0	0	General comments:		2. Robustness – Please provide guidance on how to determine quantitively if an HPLC method is robust or not. Provide recommendation on specific statistical analysis which can be used for robustness evaluation. Provide any criteria (robust vs. not robust) which can be used as references.
Moderna	0	0	General comments:		3. Please provide recommendation for acceptance criteria for accuracy (% recovery) and precision (% RSD) for complex biological HPLC purity methods (e.g., mRNA purity method). All examples in ICH Q2R2 are small molecule related methods.
Moderna	0	0	General comments:		4. For % peak area purity/impurity HPLC methods where no sufficient separation is achieved between impurities and main peak, please provide guidance on how the method specificity will be demonstrated in system suitability. For small molecule methods, this can be done by monitoring the resolution (e.g., setting no less than 1.5) of a critical peak pair. Some regulatory agencies suggest using theoretical plate numbers. However, peak shape will vary from time to time which will impact theoretical plate numbers but not necessarily separation for biological samples.
Moderna	0	0	General comments:		5. For % peak area purity/impurity HPLC methods, if the impurities are not available, please provide additional guidance on how the QL is determined for those impurities.
Moderna	0	0	General comments:		6. For % peak area purity/impurity methods, please provide guidance on how the accuracy is evaluated for main component. Also, if the impurities with high purity are not available, please provide guidance on how the accuracy will be evaluated for these impurities.
PPTA	0	0	General comments:	Overall, a welcome positive update, with additional clarifications needed on expectations, as well as precisions for validation and strategy and biological methods (see comments below).	

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ProPharma Group, Liesbeth van Rooijen	0	0	General comments:	In Table 1 and section 4.2 the term "Working Range" is used as a typical Procedure Performance Characteristic. In the examples in Annex 2 the performance characteristic is typically called "Reportable Range" and in section 7 Figure 2 it is called "Range". Another example: in Table 4 the performance characteristic mentioned is "Reportable Range" and in column next to it, it is called "Working range". In my opinion the relationship between "Working Range" and "Reportable range" as presented in section 4.2 only holds if the Reportable range is a concentration/content range and sample dilutions have a direct impact on the test result; for analytical procedures like for instance DLS where the reportable range is a particle size range, the text in section 4.2 *"Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range will lead to a specific working range"* is confusing: in this case the sample preparation does(/should) not lead from the reportable range to a working range. In summary: the terminology used with regard to Range seems to be inconsistent, incomplete and sometimes incorrect.	Please consider including additional clarification on this topic, in combination with a more consistent use of the correct terminology throughout the whole document.
ECA Foundation / European QP Association	0	0	General comments:	ICH have failed to write a single integrated document to provide an encompassing approach to procedure development, validation and operational use	Integrate ICH Q2 with Q14
ECA Foundation / European QP Association	0	0	General comments:	ICH Q2 does not integrate with ICHQ14 - Figure 2 is too simplistic	Integrate ICH Q2 with Q14
ECA Foundation / European QP Association	0	0	General comments:	There is no mention of validating the analytical procedures against the intended use as defined by an ATP.	Include the ATP and how it defines the intended use of the method
ECA Foundation / European QP Association	0	0	General comments:	No mention of analytical procedure life cycle	A lifecycle diagram showing the three stages: development, validation and use
ECA Foundation / European QP Association	0	0	General comments:	The Analytical Target Profile does not feature in Q2(R2) apart from the glossary	
ECA Foundation / European QP Association	0	0	General comments:	There is no complete analytical procedure life cycle described in either Q2 or Q14	
ECA Foundation / European QP Association	0	0	General comments:	The operational phase of the life cycle is omitted entirely from both documents. There is zero mention of the most important and longest phase of the life cycle	Rewrite the two documents: USP <1220> is far superior
ECA Foundation / European QP Association	0	0	General comments:	Regulatory issues about validation that should be in ICH Q2 are actually found in ICH Q14 Section 10	Transfer Section 10 from ICH Q14 into Q2

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISCT	1	688	All	This document (ICH Q2 (R2)) expands upon and updates the earlier document (ICH Q2 (R1)). It articulates very well with ICH Q14, and clearly explains the relationship between ICH Q2 & ICH Q14. The scope and purpose of the document, and how the procedures and data should be used for regulatory purposes are clearly outlined and useful. The document is well thought out and thorough. It appropriately covers procedures for biological/biotechnological products.The examples include cell based assays for determination of potency relative to a reference (Table 7). The document has utility for cell and gene therapy.	None
EFPIA	2	8	1	Linkage of Q2 to Q14: Additional text providing cross referencing to Q14 in introduction	This guideline presents a discussion of elements for consideration during the validation of *analytical procedures* included as part of registration applications submitted within the ICH member regulatory authorities. Analytical procedure validation is an exercise forming part of the analytical procedure lifecycle, as described within ICH Q14. Q2(R2) provides guidance and recommendations on how to derive and evaluate the various *validation tests* for each analytical procedure**.** This guideline includes a collection of terms, and their definitions. These terms and definitions are meant to bridge the differences that often exist between various compendia and documents of the ICH member regulatory agencies.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	9	12	1	"Section 1: Introduction" is clear from lines 1-24, ISPE appreciates the added concept of leveraging supportive method performance data generated in studies conducted under ICHQ14. ISPE suggests one minor addition to the second paragraph (lines 9-12) to further enhance understanding of the role of Q2(R2) in terms of the total analytical method lifecycle described in Q14.	Currently (lines 9 – 12): "The objective of validation of an analytical procedure is to demonstrate that the analytical procedure is suitable for the intended purpose. A tabular summary of the characteristics applicable to common types of analytical procedures is included (Table 1). Further general guidance is provided on how to perform validation studies for analytical procedures." Suggested addition (in italics) (lines 9 – 12): "The objective of validation of an analytical procedure is to demonstrate that the analytical procedure is suitable for the intended purpose. *ICHQ2(R2) method validation, which confirms the accurate, reliable performance of an analytical procedure within pre-determined acceptance criteria, is part of the method lifecycle defined in ICHQ14.* A tabular summary of the characteristics applicable to common types of analytical procedures is included (Table 1). Further general guidance is provided on how to perform validation studies for analytical procedures."
ECA Foundation / European QP Association	13	43	2	In the scope it is stated that the guideline applies drug substances and drug products and refering to the documenation for registration according to ICH M4Q. In spite of ommitting the term "drug substance and drug products" It only refers to analytical procedures for submission but not for other analytical prodcures, e.g used for the testing of starting materials (with reference to Q11), By the way: The validation protocol is a GMP document but not submitted.	Scope should be clearly extended to all analytical procedures included into a synthesis according the GMP reqirements and their respective ATP (not only for submission)

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EFPIA	13	13	1	"provides an indication....which should be presented". It seems to be contradictory to me to have the term "indication" followed by "which should be presented". Indication seems to be just an incomplete listing of things that are required. But if required how can the listing be incomplete in this doc?	Recommend to replace "indication" by "guidance"
EFPIA	18	20	1	Validation data from earlier phases of clinical development (phase-appropriate strategy) should also be acceptable, as performance characteristics should not have to be repeated in subsequent validations if the method, analyte, and matrix does not change.	Of note, suitable data derived from development studies (see ICH Q14) and clinical development can be used in lieu of validation data.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	20	21	1	ISPE appreciates the inclusion in "Section 1: Introduction" (line 20-21) of a platform method concept and abbreviated validation (when justified) as a highly beneficial addition to Q2(R2). ISPE suggests minor edits to line 20-21 to further clarify what is meant by using platform method for "a new purpose" by providing examples.	Currently (line 20-21): "When an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified." Suggested addition (in italics) (line 20-21): "When an established platform analytical procedure is used for a new purpose, validation testing can be abbreviated, if scientifically justified, *such as when they are applied to the same product in different formulations, or when they are applied to different products which are molecularly similar and in similar formulations."*
Medicines for Europe	23	25	1,1	"… submission of analytical procedure development…" this statement contradicts the line 11 "This guideline is intended to complement ICH Q2…". It should be clear that the purpose of this guideline is to provide information for the development of analytical method, by pointing out how risk assessment and analytical knowledge may be helpful on finalizing methods appropriate for specific applications, not to prepare parts for CTD that is out of its scope.	This part could be rephrased to: "The guideline also describes how to document analytical procedure develpoment and related lifecycle information that is not part of CTD format (ICH...) but may be shared to support the appropriateness of the analytical methodology for specific application".
EFPIA	24	24	1	define what a "protocol" is, especially if it refers to pre-approved acceptance criteria. Suggestion to define in the glossary	define "protocol" in the glossary
EFPIA	25	25	1	Line 25 – please adjust to 'suitably characterized materials', to avoid potential confusion with reference standards	Suitably characterized ~~reference~~ materials, with documented identity

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	25	35	1	ISPE notes that "Section 1: Introduction" lines 25 – 35 contain four major topics that would each benefit from being moved into the body of the text to allow sufficient elaboration of each, particularly in relation to multivariate analytical procedures versus traditional methods. The four topics are (1) the nature of materials that may be used in validation studies, (2) the ability to efficiently design experiments to simultaneously generate data on multiple validation parameters, (3) the nature and use of system suitability tests during validation, and (4) development and confirmation of method robustness. ISPE recognizes that points (1) and (2) are currently in the Introduction section of Q2(R1), but we believe Q2(R2) has an opportunity to improve communication on these key topics, along with topics (3) and (4). Furthermore, Q2(R2) has an opportunity to clarify considerations for all 4 points with respect to multivariate analytical procedures.	Suggested edits (lines 25-35): -Please end the Introduction section at line 24 (i.e., remove lines 25-35). -Please relocate lines 25-35 from the Introduction section to relevant sections within the body of the text; specific suggestions are provided in each recommended section's comments. -Within the proposed relocations, ISPE also suggests adding further information for each point with respect to how they should be considered in multivariate analytical procedures. Specific ISPE suggestions for line relocations and additional clarifications are provided in the relevant section's comments.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	25	27	1	ISPE suggests that "Section 1: Introduction" lines 25-27 concerning materials used in validation studies could be relocated to "Section 3 Analytical Procedure Validation Study" (lines 77-81) because it is a major element to consider in designing appropriate validation studies for traditional and multivariate analytical procedures. Also, ISPE recommends the discussion of materials used in validation studies could be further separated into considerations for traditional methods versus multivariate analytical procedures. ISPE notes that "Section 3.4. Considerations for Multivariate Analytical Procedures" (lines 136 – 138) already contains a statement on the assignment of values or categories to samples used in the validation of quantitative or qualitative multivariate procedures. Therefore, it would be useful to connect the statement in 3.4. to the relocated information in Section 3 to be included in validation protocols on materials used in validation experiments.	Currently (Introduction lines 25-27): "Suitably characterized reference materials, with documented identity and purity or any other characteristics as necessary, should be used throughout the validation study. The degree of purity necessary for the reference material depends on the intended use." And: Currently (Section 3, lines 77 – 81): "Prior to the validation study, a validation protocol should be generated. The protocol should contain information about the intended purpose of the analytical procedure, and performance characteristics and associated criteria to be validated. In cases where pre-existing knowledge (e.g., from development or previous validation) is used appropriate justification should be provided. The results of the validation study should be summarized in a validation report."

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	25	27	1	ISPE suggests that "Section 1: Introduction" lines 25-27 concerning materials used in validation studies could be relocated to "Section 3 Analytical Procedure Validation Study" (lines 77-81) because it is a major element to consider in designing appropriate validation studies for traditional and multivariate analytical procedures. Also, ISPE recommends the discussion of materials used in validation studies could be further separated into considerations for traditional methods versus multivariate analytical procedures. ISPE notes that "Section 3.4. Considerations for Multivariate Analytical Procedures" (lines 136 – 138) already contains a statement on the assignment of values or categories to samples used in the validation of quantitative or qualitative multivariate procedures. Therefore, it would be useful to connect the statement in 3.4. to the relocated information in Section 3 to be included in validation protocols on materials used in validation experiments.	Combined to: Suggested edits (Section 3, lines 77 – 81; ***dark italics are the relocated Introduction lines*** ; *regular italics are proposed additions):* "Prior to the validation study, a validation protocol should be generated. The protocol should contain information about the intended purpose of the analytical procedure, and performance characteristics and associated criteria to be validated. The protocol should also include information on the materials to be used in the validation study. *For traditional methods* ***, suitably characterized reference materials, with documented identity and purity or any other characteristics as necessary, should be used throughout the validation study*** *. Traditional analytical procedures that do not utilize a reference standard or calibration curve for generating reportable results may utilize appropriately characterized materials reflective of the intended test samples. For multivariate analytical procedures, materials used for validation should be reflective of the attributes relevant to the nature of the measurements (refer to Section 3.4.1.).* ***The degree of purity necessary for the reference*** *or test* ***material depends on the intended use*** *.* In cases where pre-existing knowledge (e.g., from development or previous validation) is used appropriate justification should be provided. The results of the validation study should be summarized in a validation report."
PPTA	25	27	1	The term "reference material" is not contained in the glossary. Moreover the wording suggests that this is limited to chemical reference materials. It does not consider biological reference materials for which assignment of potency, but not purity is critical.	Please add "reference material" to the glossary. Please adapt wording to include biological methods and biological reference materials.
EFPIA	28	31	1	It's not clear if the sentence is refering to the devlopment or to the validation work	Change to "In practice, the experimental work performed during development can be designed....."
Guerbet	28	31	1	Proposition of clarification, addition of Total Analytical Error and use of the term of Trueness	the appropriate validation tests can be performed to provide sound, overall konwledge of the performance (e.g. the Total Analytical Error) of the analytical procedure by evaluating : specificity/selectivity, trueness and precision over the reportable range.

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International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	28	31	1	ISPE suggests that "Section 1: Introduction" lines 28-31 on efficient designs of validation experiments could be relocated to "Section 4 Validation Tests, Methodology, and Evaluation" (lines 146-151) because it is a major element to consider in designing efficient validation experiments for traditional and multivariate analytical procedures. Also, ISPE suggests further elaboration of experimental designs that generate simultaneous data on multiple validation parameters by separating into considerations for traditional methods versus multivariate analytical procedures. ISPE notes that "Section 3.4 Considerations for Multivariate Analytical Procedures" (lines 118 – 144) already describes experimental methodologies for validation of multivariate analytical procedures. Therefore, it would be useful to add reference to Section 3.4. to distinguish them from the experimental designs applicable to traditional analytical methods.	Currently (Introduction lines 28-31): "In practice, the experimental work can be designed so that the appropriate validation tests can be performed to provide sound, overall knowledge of the performance of the analytical procedure, for instance: specificity/selectivity, accuracy, and precision over the reportable range." And: Currently (Section 4, lines 146 - 151): "In the following chapters, experimental methodologies to evaluate the performance of an analytical procedure are described. The methodology described is grouped by the main performance characteristic the analytical procedure was designed for. However, it is acknowledged that information about other performance characteristics may be derived from the same dataset. Other approaches may be used to demonstrate that the analytical procedure meets the objectives and related performance criteria, if justified."
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	28	31	1	ISPE suggests that "Section 1: Introduction" lines 28-31 on efficient designs of validation experiments could be relocated to "Section 4 Validation Tests, Methodology, and Evaluation" (lines 146-151) because it is a major element to consider in designing efficient validation experiments for traditional and multivariate analytical procedures. Also, ISPE suggests further elaboration of experimental designs that generate simultaneous data on multiple validation parameters by separating into considerations for traditional methods versus multivariate analytical procedures. ISPE notes that "Section 3.4 Considerations for Multivariate Analytical Procedures" (lines 118 – 144) already describes experimental methodologies for validation of multivariate analytical procedures. Therefore, it would be useful to add reference to Section 3.4. to distinguish them from the experimental designs applicable to traditional analytical methods.	Combined to Suggested edits (Section 4, lines 146-151; ***dark italics are the relocated Introduction lines*** ; *regular italics are proposed additions):* "In the following chapters, experimental methodologies to evaluate the performance of a *traditional* analytical procedure are described. *Experimental methodologies to evaluate the performance of multivariate analytical procedures are described in Section 3.4.* The methodology described is grouped by the main performance characteristic the analytical procedure was designed for. However, it is acknowledged that information about other performance characteristics may be derived from the same dataset. ***In practice, the experimental work can be designed so that the appropriate validation tests can be performed to provide sound, overall knowledge of the performance of the analytical procedure, for instance: specificity/selectivity, accuracy, and precision over the reportable range*** . Other approaches may be used to demonstrate that the analytical procedure meets the objectives and related performance criteria, if justified."
EFPIA	29	29	1	"Performance"	"Performance characteristics"

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EFPIA	30	31	1	Clarification requested for "the precision over the reportable range" which is not aligned with the design described in 4.3.2.1 for repeatability (minimum of 6 determinations at 100% of the test concentration).	
EFPIA	32	32	1	Line 32 implies that a singular SST is always required	Adjust 'the system suitability test' to '*a system suitability test*'
EFPIA	32	33	1	In general, there is insufficient data to set valid criteria for the SST parameters under development. All relevant SST parameters can be screened, but the final parameters and criteria should be determined based on data generated with the final method.	Indicate that the final set of SST-parameters and criteria should be based on data e.g. from the validation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	32	33	1	ISPE suggests that "Section 1: Introduction" line 32-33 on system suitability tests could be relocated to "Section 3 Analytical Procedure Validation Study" (lines 82-83) because it is a critical element used to assess the controlled operational performance of a test method, which is a key feature of analytical lifecycle management. Along with reference to ICHQ14, ISPE feels it would be beneficial to include reference to leveraging appropriate system suitability criteria from prior knowledge or platform methods, where justified. ISPE notes that" Section 3.4. Considerations for Multivariate Analytical Procedures" (lines 118 – 144) does not currently contain information on system suitability tests used with these procedures. Therefore, ISPE also recommends clarification on aspects of system suitability tests with multivariate analytical procedures.	Currently (Introduction line 32-33): "As described in ICHQ14, the system suitability test (SST) is an integral part of analytical procedures and is generally established during development as a regular check of performance." And Currently (Section 3, line 82-83): "Figure 1 shows how knowledge can be generated during analytical procedure development as described in ICH Q14 and aid the design of a validation study." Combined to Suggested edits (Section 3, line 82-83; ***dark italics are the relocated Introduction lines***; *regular italics are proposed additions)*: "Figure 1 shows how knowledge can be generated during analytical procedure development as described in ICH Q14 and aid the design of a validation study. ***As described in ICHQ14, the system suitability test (SST) is an integral part of analytical procedures and is generally established during development as a regular check of performance***. *Acceptance criteria for SSTs established during method development or leveraged from prior knowledge or platform methods should be confirmed in method validation studies. System suitability tests (SST) should be designed and utilized as appropriate for traditional analytical methods or multivariate analytical procedures."*
FUJIFILM Diosynth Biotechnologies Denmark	34	34	1	"Robustness typically should be evaluated as part of the development…." must be aligned with the text in line 417 "should be considered during development" and Q14, line 180	Agree on the same wording in both guidelines and within the guidelines
GE Healthcare, Oslo	34	34	1	Sentence is difficult to read.	Rearrange beginning of sentence to read: Robustness should typically...

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	34	35	1	ISPE suggests that "Section 1: Introduction" line 34-35 on method robustness could be relocated to "Section 3: Analytical Procedure Validation Study" (lines 74-76) because it would allow clarification of robustness optimization strategies described in ICHQ14 and the robustness data provided to support ICHQ2(R2). Along with reference to ICHQ14, ISPE feels it would be beneficial to include reference to leveraging appropriate robustness information from prior knowledge or platform methods, where justified. ISPE notes that "Section 3.4. Considerations for Multivariate Analytical Procedures" (lines 118-144) does not currently contain information on robustness considerations for calibration or validation. Therefore, ISPE also recommends clarification on aspects of robustness optimization and confirmation with multivariate analytical procedures.	Currently (Introduction line 34-35): "Robustness typically should be evaluated as part of development prior to the execution of the analytical procedure validation study (ICH Q14). And Currently (Section 3, line 74-76): "The objective of the analytical procedure, appropriate performance characteristics and associated criteria and appropriate validation tests (including those excluded from the validation protocol) should be documented and justified." Combined to Suggested edits (Section 3, line 74-76; ***dark italics are the relocated Introduction lines***; *regular italics are proposed additions)*: "The objective of the analytical procedure, appropriate performance characteristics and associated criteria and appropriate validation tests (including those excluded from the validation protocol) should be documented and justified. ***Robustness typically should be evaluated as part of development prior to the execution of the analytical procedure validation study (ICH Q14)***. *Assessment of method robustness may be leveraged from prior knowledge or platform methods. Critical elements of robustness may be confirmed during method validation, if necessary. For multivariate analytical procedures, robustness should be evaluated and confirmed as appropriate."*
Medicines for Europe	34	35	1	If the robustness is as part of the development, is it necessary to attach the study to the validation study or iis it enough to cite the identification number of the study or is it needed to summarize the conclusion of the robustness in the validation study?	Attach to the line 34-35 a new sentence about it: e.g. the conclusion of the robustness (performed during the development) should be the part of the validation study.
PPTA	34	35	1	ICH Q2(R2) describes: "Robustness typically should be evaluated as part of development prior to the execution of the analytical procedure validation study (ICH Q14)." But there is no hint or comment describing what expectations have to be fulfilled to bridge method of development lab (performing extended robustness assessment) with received method in the QC lab (performing validation study and then routine testing of product). It has to be noted that a method developed and set up in the development lab might be slightly different to the method details received in the QC lab. E.g. due to availability of instrument (versions, updates) it is not always possible to have identical instrument types in both labs....	Takeda suggests to add the following text proposal after line 35: "If applicable adequate transfer studies are performed between transferring development lab and receiving QC lab to ensure comparability of the methods and being able to fully rely on robustness studies performed in the development lab. This bridging study can also be performed as part of the analytical procedure validation study."
EFPIA	35	35	1	Linkage of Q2 to Q14: Additional text providing cross referencing to Q14 in introduction	Finally, the analytical validation strategy is grounded on knowledge of performance expectations to ensure the quality of the measured result, in alignment with ICH Q14.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ECA Foundation / European QP Association	39	39	2	In the scope it is stated that the guideline applies for biological/biotechnological products. However, all guidance given is still centered around chemical products. E.g. for the determination of accuracy, there is no "true value" for a biological product as it is not possible to obtain a 100% pure product. Orthogonal methods measure different characteristics an cannot give a true value.	Suggest to add examples that apply to biological/biotechnological products
EFPIA	39	39	2	Delete biotechnological	No consensus definitions differentiating between "biological" and "biotechnological", and none provided in text
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	39	43	2	ISPE appreciates the statement that ICHQ2 principles may be used to conduct phase-appropriate method validation during clinical development. It provides valuable conceptual alignment with statements in ICHQ7 and regional guidances on the evolving nature of method validation during clinical development. ISPE also appreciates the statement that ICHQ2 principles can be applied to other analytical procedures following a risk-based approach. By further enhancing this statement, ISPE believes ICHQ2(R2) has an additional opportunity to improve conceptual alignment with several regional regulatory authorities that require 'method qualification' to demonstrate that an analytical procedure is scientifically sound for its intended use. Therefore, ISPE encourages adding a statement that ICHQ2 principles may also be used to conduct method qualification studies, if they are required by regulatory authorities.	Currently (Section 2, lines 39-43): "The guideline can also be applied to other analytical procedures used as part of the control strategy (ICH Q8-Q10) following a risk-based approach. The scientific principles described in this guideline can be applied in a phase-appropriate manner during clinical development. This guideline may also be applicable to other types of products, with appropriate regulatory authority consultation as needed." Suggested edits (Section 2, lines 39-43; addition in italics): "The guideline can also be applied to other analytical procedures used as part of the control strategy (ICH Q8-Q10) following a risk-based approach. *ICHQ2 principles may also be applied to method qualification studies, when necessary.* The scientific principles described in this guideline can be applied in a phase-appropriate manner during clinical development. This guideline may also be applicable to other types of products, with appropriate regulatory authority consultation as needed."
ProPharma Group, Ewelina Czerniec-Michalik	41	42	2	It would be beneficial for alignment of the approach to provide more specific recommendations on the validation parameters in relation to the clinical phases of drug products.	Please consider linking validation parameters requirements with specific clinical phases for drug products.
EFPIA	42	42	2	The scientific principles described should apply not necessarily only during *clinical* development. Suggest changing to 'drug development' or 'product development'.	Suggest changing to '*drug development*' or '*product development*'.
EFPIA	42	43	2	Delete 'This guideline may also be applicable to other types of products, with appropriate regulatory authority consultation as needed'. If retained the reference for requirement for regulatory consultation should be removed.	Really not sure that this sentence is helpful. What types of product - do you have any in mind? If yes, an example would help with clarity. What pathway should you use for regulatory consultation? Do we really want to have to go to HAs to discuss method validation? Delete, or soften to 'The guideline may also be applicable to other types of products (e.g. x, y) with appropriate justification, as needed'.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	44	46	2	ISPE would like to highlight an example in "Section 2: Scope" (lines 44-46) to enhance the relevance to biologics with slight edits to the statement regarding common purposes of analytical methods. Many of the current terms used in lines 44-46 convey a bias towards methods typically used with chemical products. Though the differences may seem subtle, for purposes of understanding ICHQ2 principles they can be significant. For example, with biological products the term 'assay' is not related to 'potency'; 'assay' is more like 'content' or 'concentration'. Methods for 'purity' are typically for 'total purity/impurities', though there are also stand-alone 'impurity' methods for process residuals (as quantitative or limit tests). Therefore, ISPE suggests adding reference to some of these common terms would signal further relevance of ICHQ2(R2) to biological products. Also, because multivariate analytical procedures are included in Q2(R2), it is recommended to specifically note them as part of the Scope.	Currently (lines 44-46): "The guideline is directed to the most common purposes of analytical procedures, such as assay/potency, purity, impurity (quantitative or limit test), identity or other quantitative or qualitative measurements." Suggested edits (lines 44-46; addition in italics): "The guideline is directed to the most common purposes of analytical procedures, such as assay/potency, purity, impurity (quantitative or limit test), identity or other quantitative or qualitative measurements, *as well typical purposes for biological products such as relative potency, product-related purity/impurities, content/concentration, and process impurities. The guideline also directed to purposes where multivariate analytical procedures are utilized."*
PPTA	45	45	2	The terms "assay" or "potency" are missing from the glossary.	Please add to the glossary the terms "assay" and "potency".
EFPIA	48	49	3	Validation does not mean the method is robust, rugged or reproducible. Nor does it assure that a method will continue to work outside of the tightly controlled parameters for the study.	"analytical procedure meets it objectives at a given time in the procedure lifecycle. It does not ensure continued method performance, hence a suitable SST and continued monitoring etc etc"
EFPIA	54	54	3	It would be more accurate by adding "type of"	Changed to "and the type of measured product attributes"
EFPIA	58	60	3	Table 1: Clarify that the limit test is quantitative; add Product Quality Attribute	
EFPIA	58	59	3	specificity - selectivity is missing	add "selectivity"
EFPIA	58	59	3	suitability of the calibration model: + in quantitative columns which suggests that all quantitative procedures have a calibration model while it is not necessarily the case (eg area/area procedures).	please add, "+ if relevant"
EFPIA	58	59	3	reproducibility is missing in the table	add "reproducibility test"
FUJIFILM Diosynth Biotechnologies Denmark	58	66	3	Disagreement between wording in table 1 and in the body text in the guideline. E.g. "suitability of calibration model" should be applied in 4.2.1 "Response"	Make sure the same terms are used consistenly and unambigiously everywhere in the guideline

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	58	72	Table 1	ISPE is concerned that Table 1 remains heavily biased towards chemical products in the terms used in the header for product attributes. Although Table 1 is very efficient, it is challenging to interpret the limited set of attributes and performance characteristics for typical biological product measurements. Also, it is not clear which elements in Table 1 apply to traditional analytical methods and which are applicable to multivariate analytical procedures. Therefore, ISPE believes Table 1 could be made more substantially more effective if it were slightly expanded to denote product attributes and types of measurements commonly applied to biological products. For example, methods for identity may have quantitative elements; methods for content/concentration often utilize reference standard calibration curves; methods for relative potency usually require dose response curves of a reference standard and a test sample. ISPE also suggests Table 1 should include a column for multivariate analytical procedures to better clarify which performance parameters are associated with these types of measurements. ISPE appreciates that ICHQ2(R2) now clarifies the elements of Range by defining Working Range and Reportable Range ("Section 3.2. Reportable Range (lines 98-106), "Section 4.2. Working Range (lines 214-218), and "Section 5. Glossary" (lines 531-543). To provide further clarity on validation elements for Working Range and Reportable Range, ISPE recommends that Table 1 incorporate both elements of Range where appropriate for performance characteristics of certain methods.	Suggested edits to Table 1 (highlighted in gray) - please see embedded PDF file for best clarity. Image aso added in Row 85.
Medicines for Europe	58	59		For the validation test "Precision" in the Table 1 a reference to the note (5) is missing.	The note should be renumbered as (4, 5).
Medicines for Europe	58	59	3	The "Table 1: Typical performance characteristics and related validation tests for measured product attributes" uses the terminology "Suitability of Calibration Model" while the "Figure 2: Selection of validation tests based on the objective of the analytical procedure" uses the terminology "Validation of Calibration Model". Both terms seem to denote the same meaning, thus, should be aligned throughout the guideline to avoid confusion. (Or additional clarification should be provided if those two terms were used to carry different meanings)	The terminology for the calibration model should be consistent throughout the guideline (Or additional clarification should be provided if those terms were used to carry different meanings)
PPTA	58	72	3	Table 1: Combined line for "Working Range Suitability of Calibration model Lower Range Limit verification" is confusing for Impurity tests as a Lower Range Limit in this context suggests for Limit tests a sort of need for determination of a Range. This impression is also further reinforced with Figure (line 656-658) where for a Limit Test Validation of Range Limits is suggested as Validation Tests (See Comment below for line 656)	Please separate into two lines: -Working Range/Suitability of Calibration model -Quantitation & Detection Limit

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	58	72	3	Note (3) as described in line 69: "(3) a combined approach can be used alternatively to evaluating accuracy and precision separately" is put at line "Specificity" of Table 1 rather then at line "Accuracy" and "Precision". It is proposed that the concept laid out in line 401-415 Section 4.3.3 "Combined approaches for accuracy and precision" is also mirrored in Table 1 as this table is a central point of reference and overview.	Please add Note "(3)" also to the line "Accuracy" and to the line "Precision" of Table 1
ANMV	59	59	Table 1	Note (3) does not report to specificity	Note (4) should be set next to specificty
ANMV	59	59	Table 1	Note (4) does not report to accuracy	Note (3) should be set next to accuracy
ANMV	59	59	Table 1	Note (4) does not report to precision	Note (3) should be set next to precision
ANMV	59	59	Table 1	As defined in ICH Q14, the robustness should be studied when developing an analytical method, along with the system suitability testing parameters and acceptance criteria. The study of the robustness of an analytical method helps to identify critical parameters that can impact the analytical performance. It helps to define suitable SST criteria, adequate to alert the user on the risk of a possible lack of performance of the system and to take preventive actions to garantee the analytical performance before getting out of specifications results. Robustness provides knowledge and comprehension on the critical parameters of the analytical method. If the robustness of the system is not adequately studied, analytical method perfomance characteristics, such as precision can be affected. Therefore, it seems important to us to include robustness in the list of mandatory characteristics to be demonstrated/reported in the validation of analytical methods. To our point of view, robustness should be included in table 1 as performance characteritics to be demonstrated during analytical method validation and should be perfomed or checked when validating quantitative analytical methods for assay or impurity determination.	Include Robustness in table 1 with + in the columns corresponding to Quantitative impurity measurements and assays, with a note under the table "(x) data can be reported from the development of the analytical method"
APIC	59	59		The table 1 shows the typical performance characteristics. 1. The selectivity is missing in the table 2. In many cases the stability of solutions (reference solution, sample solution etc.) is an important validation parameter e.g. to show the suitability of autosamplers.	
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	59	71	3, Table 1	in conjunction with line 69 – 71: It seems that footnotes 3 and 4 are mixed up as specificity is linked to a combined approach evaluating accuracy and precision while accuracy and precision are linked to a lack of specificity.	Line 70 – 71 should be footnote 3 Line 69 should be footnote 4
ECA Foundation / European QP Association	59	59	3	Table 1. There is no mention to the upper range limit which is as important for impurity test where the analyte in question increases over time. E.g. aggrgates in monoclonal antibody products or host cell proteins in upstream in-process samples	Suggest adding Upper range limit to the table if a footnote to be evaluated if applicable.
EFPIA	59	59	3	Working and Reportable Range: Table 1: Adjust wording from 'working range' to 'reportable range'	
EFPIA	59	72	3	Last row “Precision”: the “-“ and “+” entries are repeated for repeatability and intermediate testing, although there is no difference.	No repetition necessary.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GE Healthcare, Oslo	59	59	3	Last test in table 1: "Intermediate" and "precision test" looks to be two separate tests.	Change formatting to indent last line.
Gilead	59	71	3	Footnote for specificity and accuracy/precision in Table 1 are switched.	
Medicines for Europe	59	60	3	table 1: working range for quantitative test of impurities: lower range limit is defined only as QL (quantitation limit). As later on (table 2, rows 107 - 108) reporting threshold is mentioned it should be at least added; DL is really not justified for a quantitation method	Change form QL (DL) to: QL or RT (reporting threshold)
Moderna	59	60	Table 1 Limit test		Reconsider the characteristics defined for limit tests for impurities. Currently, these are detection limit and specificity. However, most limit tests are based on quantitation limit and not detection limit.
PPTA	59	59	3 (Table1)	The expression "calibration model" is apparently used for the dose-response curve. In biological methods secondary reference standards are calibrated against primary reference standard in a separate study. The obtained result is then assigned to the secondary standard	The different meanings of "calibration" in biological and chemical methods be addeed to be adressed to avoid confusion. Please clarify.
ProPharma Group, John den Dunnen	59	60	3	Last row table 1 layout "Intermediate Precision Test".	Please correct lay-out.
ProPharma Group, Liesbeth van Rooijen	59	60	3	Since in the remainder of the guidance in most cases the term "Specificity/Selectivity" is used, please consider using that term in Table 1 as well.	Please consider using the term "Specificity/Selectivity" in Table 1 as well.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	60	72	Table 1 footnotes	ISPE notes that Table 1, footnote #5 (line 72) states that reproducibility and intermediate precision can be performed as a single set of experiments. However, there seems to be a conflict between the inclusion of concepts of Reproducibility in ICHQ2 and the intended applications of ICHQ2: - "Section 1: Introduction" (line 13-14) states ICHQ2 provides an indication of the data which should be presented in a regulatory submission. - But "Section 4.3.2.3. Reproducibility" (lines 390-394) states that reproducibility (interlaboratory trials) is usually not required for regulatory submissions; it is usually conducted for standardization of analytical procedures for inclusion in pharmacopeias. Therefore, ISPE recommends removing references to experimental designs for Reproducibility from Table 1 footnotes to prevent confusion on the scope of ICHQ2(R2) with respect to standardization of analytical procedures outside of regulatory submissions.	Suggested edit (line 72): -Please delete Table 1, footnote #5 to remove reference to experimental designs for Reproducibility
EFPIA	62	62	3	Brackets are used throughout the Table 1 in various contexts, which can be confusing.	Suggest switching to another notation, maybe †

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ProPharma Group, John den Dunnen	62	62	3	"()" is not used in table 1.	Please remove.
EFPIA	64	64	3	Working and Reportable Range: Adjust wording from 'working range' to 'range'	
APIC	69	71	3	N/AP	Footnotes 3 and 4 seem to be swaped between them
APIC	69	71	3	comment (3) and (4) should be reversed	comment (3) should be about specificity and comment (4) should be about accuracy and precision
ECA Foundation / European QP Association	69	71	3	Text in footnote (3) corresponds to footnote (4) and viceversa	(3) lack of specificity of one analytical procedure could be compensated by one or more other supporting analytical procedures (4) a combined approach can be used alternatively to evaluating accuracy and precision separately
EFPIA	69	69	3	rephrase and clarify that this is the Total Analytical Error approach	change to "a combined approach can be used alternatively (Total Analytical Error) instead of accuracy and precision separately"
fUJIFILM Diosynth Biotechnologies Denmark	69	71	3	The text for notes # 3 and # 4 seems to be switched	Please coorect
GE Healthcare, Oslo	69	71	3	The text in footnotes (3) and (4) have been switched.	Switch the content of (3) and (4).
Guerbet	69	71	3	Notes 3 and 4 seems to be inverted	(3) lack of specificity of one analytical procedure could be compensated by one or more other supporting 70 analytical procedures. (4) a combined approach can be used alternatively to evaluating accuracy and precision separately
Katarzyna Piechota (Mrs.)	69	71	3	Remarks (3) and (4) are swapped.	(3) lack of specificity of one analytical procedure could be compensated by one or more other supporting70 analytical procedures. (4) a combined approach can be used alternatively to evaluating accuracy and precision separately.
Medicines for Europe	69	70	3	The comments of the remarks (3) and (4) are mixed up	comment for remark (3): lack of specificity of one analytical procedure could be compensated by one or more other supporting analytical procedures. Comment for remark (4): a combined approach can be used alternatively to evaluating accuracy and precision separately
Medicines for Europe	69	69		The note for tests "Accuracy" and "Precision" is incorrectly numbered as (3).	The note should be numbered as (4).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	69	71	3	The footnote #3 and #4 for "Table 1: Typical performance characteristics and related validation tests for measured product attributes" is mismatched with the content labelled in the Table 1. (3) a combined approach can be used alternatively to evaluating accuracy and precision separately -> This footnote is assigned to specificity in the current draft. (4) lack of specificity of one analytical procedure could be compensated by one or more other supporting analytical procedures. -> This footnote is assigned to accuracy and precision in the current draft.	The order of footnote #3 and #4 for Table 1 should be switched or should be correctly assigned to the corresponding performance characteristics.
Medicines for Europe	69	69	3	Typo error of (3)	It should be (4)
Moderna	69	70	3 Analytical procedure validation study	(3) a combined approach can be used alternatively to evaluating accuracy and precision separately 69 (4) lack of specificity of one analytical procedure could be compensated by one or more other supporting 70 analytical procedures. The contents of these two notations do not match with where they are placed on Table 1.	Consider to switch the contents of notations (3) and (4) to match with the positions they are placed on Table 1.
Orion Corporation	69	71		In Table 1 the footnotes 3 and 4 should be other way around.	
PPTA	69	71	3	Footnote (3) and footnote (4) sentences are switched.	Please adapt as follows: Footnote (3) should be "lack of specificity of one analytical procedure could be compensated by one or more other supporting analytical procedures." Footnote (4) should be "a combined approach can be used alternatively to evaluating accuracy and precision separately."
ProPharma Group, Liesbeth van Rooijen	69	71	3	The description of the footnotes 3 and 4 should be interchanged: it is not aligned with Table 1	(3) lack of specificity of one analytical procedure could be compensated by one or more other supporting analytical procedures. (4) a combined approach can be used alternatively to evaluating accuracy and precision separately.
Medicines for Europe	70	70		The note for validation test "Specificity" is incorrectly numbered as (4).	The note should be numbered as (3).
ECA Foundation / European QP Association	72	72	3	Footnote (5) says "Reproducibility" but what is ment is "repeatability" as the term "Reproducibility" is not in the table	(5) Repeatability and intermediate precision can be performed as a single set of experiments.
EFPIA	72	72	3	Change Reproducibility to Repeatability	In the table Precision is described by Repeatability test and Intermediate Precision test
Medicines for Europe	72	72	3	The comment of remark (5) refers to reproducibility and intermediate precision, but the table is only defining repeatability and intermediate precision and the asterisk is set by intermediate precision. The terms and definition should be used strongly consequent and clear.	To the term intermediate precision should be added in brackets "(reproducibility = interlaboratory trial)".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	72	72		Since "Reproducibility" determination includes simultaneous testing of effects of many more variables than "Intermediate Precision" (such as different laboratory, different analysts, different reagents, different staff etd.), statement should be written more clearly.	We suggest to add the statement from currently effective »ICH Topic Q 2 (R1) Validation of Analytical Procedures: Text and Methodology«: "In cases where reproducibility testing has been performed, intermediate precision is not needed".
EFPIA	74	76	3	Sentence is confusing. Recommended to rephrase to exclude validation tests and repeated words (e.g. and).	" The objective of the analytical procedure and associated performance characteristics with corresponding criteria (i**ncluding those excluded from (?)** the validation protocol) should be documented and justified."
Medicines for Europe	74	76		The paragraph does not describe in sufficient detail where all the mentioned information is intended to be recorded. Currently, all this information is clearly stated in the registration dossier. In addition, we do not understand the purpose of justification of absence of validation tests from the protocol - especially if the ICH guideline does not require some test to be performed(considering the type of measured product attribute). For example - why would it be required to justify absence of accuracy, precision and working range testing for identification tests.	We suggest to remove this paragraph or to clearly state that only absence of the validation tests that are required considering the type of measured product attribute in the Table 1 (lines 58, 59) should be documented and justified.
ECA Foundation / European QP Association	75	76	3	This sentence is unclear: "(including those excluded from the validation protocol)" why do we want to document validation tests that are not included in the protocol?	Please, specify what validation tests are not included in the validation protocol. Are you referring to robustness or development work?
EFPIA	77	86	3	Linkage of Q2 to Q14: Clarification to text and to Figure 1 to align terminology with Q14, add clarity regarding validation strategy vs validation study, and clarify the use of 'appropriate' development data. Figue 1 should be additionally updated to align with the intent of the updated text, to specifically mention the use of platform data and to expand the acronym 'AP' to Analytical Procedure.	Prior to the validation study, a validation protocol should be generated detailing the intended validation strategy. The protocol should contain information about the intended purpose of the analytical procedure, and performance characteristics and associated criteria to be validated. Validation of performance characteristics may be demonstrated through use of prior knowledge or through the generation of additional validation data. In cases where prior knowledge (*e.g.,* from appropriate development, previous validation or platform analytical procedures) is used, appropriate justification should be provided. The outcome of the validation should be summarized in a validation report, including the evaluation of prior knowledge and validation data.
Medicines for Europe	77	81		Intended purpose of the analytical procedure should be clearly recognisable since the very beginning of the analytical procedure development phase. Furthermore, we also believe that the evidence should also be recognisable from its title and specification. Purpose of the validation protocol is to state the validation tests to be performed, acceptance criteria and especially to clearly state the procedure for the analysts how to perform the testing, since deviations from the analytical procedure that is to be validated have to be made. Therefore, stating and justifying the purpose of the analytical procedure in the validation protocol seems meaningless and unnecessary.	We suggest to remove the sentence "The protocol should contain information about the intended purpose of the analytical procedure".
ProPharma Group, Ewelina Czerniec-Michalik	78	79	3	Can the mentioned "pre-existing knowledge" be derived from the legitimate scientific publications and sources or should is be based only on the experience of the laboratory involved in the validation studies?	Please clarify.
Gilead	84	84	3	Figure 1, other than robustness, what data from development study is considered acceptable?	Suggest adding a footnote like e.g. robustness, forced degradation, etc.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	84	85	3	For ease of understanding and clarification in Figure 1, please define the acronym "AP".	Please add "(AP)" after bullet for "Analytical Procedure".
PPTA	84	85	3	In left text box, second bullet for Figure 1, please include the word "to" before "Q2" to improve readability.	Please include the word "to" before "Q2".
ECA Foundation / European QP Association	86	97	3,1	This section refers to validation during the life cycle but it only addresses changes to procedures, co-validation and cross-validation. It does not address continuos performance verification of the analytical procedure nor establish a link to ICH Q14. Trending is a requirement by EU GMP vol 4. chapter 6.9	Please add reference to ICH Q14 in continuos performance verification or add text in this section.
GE Healthcare, Oslo	86	88	3,1	Spacing between header and text is different from surrounding headers.	Remove blank line 87 and add space after paragraph.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	86	97	3,1	ISPE notes that numerous concepts in "Section 3.1. Validation during the lifecycle of an analytical procedure" are extensively covered in ICHQ14 (eg revalidation, co-validation, method transfer, method bridging). Therefore, ISPE recommends deleting section "3.1. Validation during the lifecycle of an analytical procedure" from ICHQ2(R2) to minimize redundancies of information on these lifecycle elements between the two guidances.	Suggested edits (lines 86-97): -Please delete section "3.1. Validation during the lifecycle of an analytical procedure"
EFPIA	88	91	3.1	Principles described in ICH Q14 may be used to define the extent of validation, add cross reference.	Changes may be required during the lifecycle of an analytical procedure. In such cases, partial or full revalidation may be required. Science and risk-based principles (see ICH Q14) can be used to justify whether or not a given performance characteristic needs revalidation. The extent of revalidation depends on the analytical performance characteristics impacted by the change.
Medicines for Europe	88	91	3,1	It is not clear which are the minimum analytical procedure performance characteristics to be demonstrated in "Partial Validation"	Maybe an additional information in table 1 on line 58-59 with +/- with the needed characteristics for partial validation
Moderna	89	89	3.1 Validation during the lifecycle of an analytical	Word choice: *revalidation* , if a study was designed based on assisstting development data and passed within the initial validation; this validation is then valid. If there are addition information either from development or through testing from Quality Control, the method is then re-evaluated for certain parameters. This work should be worded as s*upplemental validation* .	Please consider to change *revalidation* to *supplemental validation*

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	92	97	3,1	Method Transfer: It should be clarified in ICHQ2 that method transfer is a change in the context of analytical procedure lifecycle, (in line with ICH Q14) and that co-validation can be between laboratories and rather than sites. Add new text to emphasize that co-validation data can be used in leiu of method transfer data and cross-referencing Q14.	Co-validation can be used to demonstrate that the analytical procedure meets predefined performance criteria by using data from multiple sites laboratories, and removes the requirement for additional method transfer experiments. Transfer of a validated analytical procedure should be considered in the context of analytical lifecycle changes in line with ICH Q14 (Chapter 7). When transferring analytical procedures to an alternative different laboratory, a subset of validation experiments is often performed.
EFPIA	92	97	3,1	Cross-validation has a different meaningh for multivariate analytical method. It will be best to add a sentence stating its specific meaning for multivariate analytical method to avid confusion.	Propose to add a sentence that there is a differnt meaning of cross validation in the context of chemometrics
Guerbet	92	94	3.1	When implementing a new analytical procedure in several laboratories at the same time, a co-validation replaces the experimental work that would be needed for the analytical transfer.	Co-validation can be used to demonstrate that the analytical procedure meets predefined performance criteria by using data from multiple sites, replacing that way the analytical transfer.
Medicines for Europe	92	94	3,1	The guideline states that a subset of validation experiments is often performed for co-validation when transferring analytical procedures to a different laboratory. Additional guidance on the subset of validation experiments needed for the co-validation in such case would be helpful to prevent unnecessary experiments. For example, if the laboratories' system (i.e. material, reagents, software, machines, etc.) are equivalent, the validation results from multiple sites are expected to be equivalent. In that case, confirming the reproducibility is considered sufficient. Is "Co-validation" available for the initial validation right after development, or is it only available for transferring analytical procedures to different laboratory which had been fully validated already?	Additional clarity in what subset of validation experiments are necessary for co-validation when transferring analytical procedures throug addition of statement "If the laboratories' system are considered equivalent, confirmation of the reproducibility would be sufficient" would be greatly appreciated.
Medicines for Europe	92	94	3	An example of the necessary experiments during co-validation (method transfer) would be helpful	When transferring analytical procedures to a different laboratory, a subset of validation experiments is often performed (eg Precision, system suitability test and verification of the QL)
EFPIA	96	96	3,1	Insert the term "interchangeably" when we talk about cross-validation? This may tie into ICH Q12 a bit more in how procedures are registered, their criteria and the notification process if switched from one to another.	Cross-validation is an approach which can be used to show that two or more analytical procedures can be used interchangeably for the same intended purpose.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	98	106	3,2	ISPE appreciates clarification of Range with the inclusion of concepts and definitions of Reportable Range versus Working Range in ICHQ2(R2). ISPE suggests a few edits to Section 3.2 (lines 98-106) to improve clarity and consistency in the terminology and descriptions across ICHQ2(R2) sections "3.2. Reportable Range" (lines 98-107, section "4.2. Working Range (lines 214 – 218) and section "5. Glossary" (lines 531 – 543)	Current (lines 98 - 100): "3.2. Reportable Range The reportable range is typically derived from the product specifications and depends on the intended use of the procedure." Suggested edit (line 98 - 100) (highlighted in italics): "3.2. **Reportable** Range *The range of an analytical procedure is the interval between the lowest and highest results for which the analytical procedure exhibits suitable performance. Range is comprised of two elements: Reportable Range and Working Range. The Working Range of a method is discussed in Section 4.2.* The Reportable Range of test samples is typically derived from the product specification acceptance criteria and depends on the intended use of the procedure."
Medicines for Europe	98	103	3,2	Analytical procedure performance characteristics required for the confirmation of reportable range is not aligned with the requirement listed in other section of the guideline. Line 98-103: Accuracy, precision, and specificity Line 535-537: Precision and accuracy	The analytical procedure performance characteristics required for the confirmation of reportable range should be consistent throughout the guideline.
ECA Foundation / European QP Association	99	107	3,2	While the ranges specified in table 2 might be ok for chemical products, they are too narrow for biological/biotechnological products. Often, during development phases or during stability, either specifications are not yet established or values above and below the ranges described in table 2 are obtained. The analytical procedure should be able to accurately and precisely quantify stability samples in order to establish proper shelflife specifications.	Add that ranges should also cover any forsiable stability data or values outside specifications and that the ranges described in the table are a minimum guidance - not just recommended
EFPIA	99	99	3,2	Doesn't make sense for the specifications to drive the reportable range - should be the other way around. Methods need to be designed to support the intended purpose/specifications.	The reportable range must support the product specifications and depends on the intended use of the procedure. (Delete 'is typically derived from').
APIC	100	101	3,2	The reportable range is confirmed by demonstrating that the analytical procedure provides results with acceptable accuracy, precision and specificity. In R1 the specificity was not mentioned but linearity was.	Replace the sentence by: The reportable range is confirmed by demonstrating that the analytical procedure provides results with acceptable accuracy, precision, linearity and specificity.
EFPIA	101	101	3,2	Working and Reportable Range: Removal of 'specificity' (as this is implicit from acc. and precision)	
ECA Foundation / European QP Association	102	102	03/Feb	clear wording should be chosen	replace reporting limit by reporting threshold
EFPIA	107	107	3,2	Working and Reportable Range: Clarification of Table 2 as examples only	Table 2: Examples of typical reportable ranges for common uses of analytical procedures
EFPIA	107	108	3.2	Dissolution / Low end of reportable range: missing word "lowest" from term dosage strength. Rephrasing recommended for clarity.	"Immediate release: Q-45%, considering the lowest dosage strength at first timepoint Modified release: QL"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	107	108	3.2	Dissolution / High end of reportable range: the upper value of 130% is unlikely to be achieved by most formulations with a label claim of 100%. Considering many immediate release formulations may not release 100% at the Q time, especially medicines with low-solubility drugs. Besides that, for extended release medicines, the formulation often releases the drug in amounts close to the tolerance at the last timepoint. The upper limit of 130% additionaly represents a fundamental change from the current guideline (+/- 20%), which is not technically justified.	"**%Label claim +20%,** considering the highest dosage strength, or +20% of the highest reportable value at the last timepoint, considering the highest dosage strength". The 2 options should be included and be considered appropriate to either immediate release and modified release. They are selected based on product dissolution behavior.
EFPIA	107	107	3.2	Table 2: Low end of reportable result changed from -20 % (ICH Q2 R1) to "Q-45 %(immediate release) of the dosage form strength first measurement time point or QL (modified release)". Is that harmonized with other guidelines (e.g. USP)? The wording Q-45% (immediate release) of the dosage form strength first measurement timepoint or QL (modified release) is ambiguous. It is unclear whether the words "first measurement timepoint" belongs to immediate release formulation or to modified release formulations.	Proposed change: For Column "Low end reportable range" 1. Dissolution Immediate release (IR) One point specification: Q-45% of the dosage form strength Multiple point specification and/or dissolution profiles: Q% value of the first measurement timepoint must be included in the reportable range 2. Modified release (MR): Multipoint specification: Q% value of the first measurement timepoint must be included in the reportable range (extended release (ER)) Quantification limit (QL) (delayed release (DR)) 3. Dissolution profiles: Q% value of the first measurement timepoint must be included in the reportable range
EFPIA	107	108	3,2	High end of reportable range for a purity test is listed as 100% of the specification.	If the specification is 95% purity the reportable range would be limited to 95% based on this recommendation. For purity methods the reportable range would be to the maximum purity the method is able to report. It would be expected to exceed the specification limit.
EFPIA	107	107	3.2	In Table 2, both impurity testing and purity testing are mentioned. It would be useful if these terms were defined in the glossary	Suggests to add Impurity testing and Purity testing to the glossary
EFPIA	107	107	3,2	Table 2: dissolution testing - "or" missing between "strength" and "first"	
GE Healthcare, Oslo	107	108	3,2	Table 2 is difficult to read due to spacing between words.	Align left.
Gilead	107	108	3,2	Is purity specifically for biologics, such as antibody? It is not very clear what this purity referes to. For small molecules, using "nominal concentration" will be more appropriate than "specification limit".	Indicate what purity applies to, biologics or small molecule drugs.
Gilead	107	108	3,2	It seems impractical to prepare spiked samples representing 80% of specification limit for the purity testing by area %. This means adding 28% of impurities if the purity specification is NLT 90%. If this interpretation is not correct, please update for clarity.	Suggest to state 80% of the nominal concentration. For upper level 120% of the nominal concentration.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	107	107	Table 2	ISPE appreciates the inclusion of a table to provide guidance on typical Reportable Ranges for common uses of analytical procedures. ISPE suggests a minor edit to the entry of Assay to better assure relevance in how the term in used for biological products. Also, although we particularly appreciate the inclusion of potency, ISPE suggests a few edits to clarify the entry to better reflect potency terminology and reportable ranges typical for biological products.	Current Table 2, Row 1, Column 1: "Assay of a drug substance or finished (drug) product" Suggested edit (highlighted in italics): "Assay, *content, or concentration of an excipient*, drug substance, finished (drug) product" Current Table 2, Row 2, Column 1: "Potency" Suggested edit (highlighted in italics): "*Relative* Potency" Current Table 2, Row 2, Column 2: "Lowest specification acceptance criterion -20%" Suggested edit (highlighted in italics): "Lowest specification acceptance criterion -20%" *"80% of specification limit"* Current Table 2, Row 2, Column 3: "Highest specification acceptance criterion +20%" Suggested edit highlighted in italics): "Highest specification acceptance criterion +20%" *"120% of specification limit"*
Medicines for Europe	107	107		The high end of reportable range for dissolution testing (130 % of declared content of the dosage form) should be harmonised with the requirement in the Table 5 (120 %).	We suggest to change the requirement for the high end of reportable range for dissolution testing from 130 % to 120 %.
Medicines for Europe	107	107	3	Reportable range: Table 2.: Dissolution testing (Immediate release): Low end of reportable range: Q-45%. What is the reason for this requirement? According to the pharmacopeias, at S3 level, any value below Q-25% is not acceptable.	
Medicines for Europe	107	107	3	Reportable range: Table 2: Purity testing (as area%): It is not clear the type of analytical procedure: Is it a purity test of a main component with area normalization method where the specification requirement is for only the main component: e.g. min. 90%? In this case does the expected reportable range prescribed by guide (80-100% of specification limit) mean 72-90%? Since methods of this kind are impurity methods indirectly, and it is necessary to use some kind of reporting threshold as the integration limit for the evaluation, is it not necessary to use a reportable range from the reporting threshold to the specification limit of the main component? Is it enough to use the main component?	
Medicines for Europe	107	107	Table 2	For "Potency", low/high end of reportable range is expressed as '+/- 20% of specification'. Does it mean, %? or %p? e.g., specification for potency assay is 80-120%. The reportable range is 60-140%? or 64-144%?	N/A

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	107	107	Table 2	Purity testing (as area%)' is newly added in Table 2. If the specification is targeting 'purity', is it prioritized to reporting the QL based on purity? e.g., SEC-HPLC is targeting monomer% (as area%) and monomer% is evaluated by subtracting impurity% from 100%. In this case, if assay is targeting purity, reportable range would be 78-100% (specification is equal to or more than 98%) and the QL would be evaluated to some value at the lower range, 78%. But in terms of impurity, reportable range would be 2-2.4% and the QL would be evaluated as different value.	N/A
Orion Corporation	107	108		There is a typo in Table 2 in the Dissolution accuracy requirement (130%). In the example in Table 5 the requirement is 120%. There is a contradiction between the requirements. Should the requirement be 120% in both tables?	Dissolution testing: 120% of declared content of the dosage form
PPTA	107	107	3,2	What is the meaning of the "or" in 80% of declared content or 80% of lower specification limit? 80% of the lower specification limit is lower than 80% of the declared content. What is the meaning of Q-45%? Reporting Threshold = Quantitation Limit?	Please clarify.
EFPIA	108	116	2.1.2	Demostration of stability indicating properties, mentions use of physical and chemical stress conditions but does no mention ICH Q1A or B.	Add reference to ICH Q1A and B. Would also need to add to line 654 if mentioned as references.
GE Healthcare, Oslo	108	108	3,2	Spacing between header and table above is different from surrounding headers.	Add space above header.
PPTA	108	108	3,3	Biological methods focus on one analyte, therefore selectivity is not applicable or synonymous to specificity	Footnote (4) should be "a combined approach can be used alternatively to evaluating accuracy and precision separately."
ECA Foundation / European QP Association	109	116	3,3	If a quantitative analytical procedure can detect changes, it should also be demonstrated that the change, e.g. for a stability sample, can be distinguished from the analytical variation in order to establish theat the analytical procedure is stability indicating. It is not enough to demonstrate specificity, the change should be quantifiable and linearity/accuracy demonstrated for these stability indicating samples	Suggest adding a table with the performance characteristics that are relevant for a stability indicating procedure and sample
ProPharma Group, John den Dunnen	109	111	3,3	If a procedure is a validated quantitative analytical procedure that can detect changes in relevant ICH Q2(R2) Guideline quality attributes of a drug substance or drug product during storage, the procedure is considered a stability-indicating test. More clear if "test" is removed.	If a procedure is a validated quantitative analytical procedure that can detect changes in relevant ICH Q2(R2) Guideline quality attributes of a drug substance or drug product during storage, the procedure is considered stability-indicating
EFPIA	111	115	3,3	Use of forced degradation is mentioned in Table 3, Table 7 and line 111 - 115.	Please add a definition of forced degradation to the Glossary section.
EFPIA	112	112	3,3	Line 112 – please adjust 'a combination of challenges should be performed' to ‘challenges can be performed’	To demonstrate specificity/selectivity of a stability-indicating test, challenges can be performed with
EFPIA	113	116	3.3	Replace "exposed to various physical and chemical stress conditions" by "exposed to relevant stress conditions, as appropriate".	"These can include: the use of samples spiked with target analytes and all known interferences; samples that have been exposed to relevant stress conditions, as appropriate; and actual product samples that are either aged or have been stored at higher temperature and/or humidity."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gilead	114	115	3,3	Based on the dosage form all physical and chemical stress conditions may not be appropriate. For example, solution forced degradation studies of solid dosage form may not be relevant. See paper by Campbell et al J Pharm Sci. 2022 Feb;111(2):298-305 for more information. Proposed change aligns with Table 3.	Change to "Samples that have been exposed to various appropriate physical and chemical stress conditions"
GE Healthcare, Oslo	117	118	3,3	Spacing between header and text above is different from surrounding headers.	Remove blank line 117.
EFPIA	118	132	3,4	It is unclear if the validation is performed on data known to the model or on independant data	Please clarify. Suggests to align wording with the FDA guidance, "Developing and Submitting Near-Infrared Analytical Procedures for Industry" (Aug. 2021)
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	118	144	3,4	ISPE appreciates the addition of multivariate analytical procedures to ICHQ(R2). The information in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144) is well organized in its focus on the specific considerations for these types of procedures. However, other aspects of multivariate analytical procedures are included in sections of ICHQ2(R2) that focus on elements applicable to traditional analytical methods. In those sections, it is not entirely clear which elements are also appliable to multivariate methods. Therefore, ISPE recommends grouping the disparate information for multivariate analytical procedures all together in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144). The source of all relocated lines related to multivariate analytical procedures is provided in the collated recommended edits. Further, ISPE recommends the inclusion of information on how to properly establish detection limits for multivariate analytical procedures as none of the typical approaches utilized with traditional methods are ideal for these methods. It is also important to address how these limits are established for multivariate calibrations as these parameters cannot be extrapolated and defined based on approaches used for univariate calibrations. ISPE suggests the following reference published in Analytical Chemistry ("Anal. Chem. 2014, 86, 15, 7858–7866") addresses this topic well and provides the statistical reasoning for defining this important figure of merit for multivariate analytical procedures.	<u>Current Section 3.4.1. Considerations for multivariate analytical procedures (lines 133-135)</u> " • In the second phase, model validation, an independent validation data set with independent samples is used for validation of the model. 3.4.1. Reference analytical procedure(s) " And <u>Current (lines 258 – 265)</u> "4.2.1.3 Multivariate calibration Algorithms used for construction of multivariate calibration models can be linear or non-linear, as long as the model is appropriate for establishing the relationship between the signal and the quality attribute of interest. The accuracy of a multivariate procedure is dependent on multiple factors, such as the distribution of calibration samples across the calibration range and the reference procedure error. Linearity assessment, apart from comparison of reference and predicted results, should include information on how the analytical procedure error (residuals) changes across the calibration range. Graphical plots can be used to assess the residuals of the model prediction across the working range."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	118	144	3,4	ISPE appreciates the addition of multivariate analytical procedures to ICHQ(R2). The information in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144) is well organized in its focus on the specific considerations for these types of procedures. However, other aspects of multivariate analytical procedures are included in sections of ICHQ2(R2) that focus on elements applicable to traditional analytical methods. In those sections, it is not entirely clear which elements are also appliable to multivariate methods. Therefore, ISPE recommends grouping the disparate information for multivariate analytical procedures all together in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144). The source of all relocated lines related to multivariate analytical procedures is provided in the collated recommended edits. Further, ISPE recommends the inclusion of information on how to properly establish detection limits for multivariate analytical procedures as none of the typical approaches utilized with traditional methods are ideal for these methods. It is also important to address how these limits are established for multivariate calibrations as these parameters cannot be extrapolated and defined based on approaches used for univariate calibrations. ISPE suggests the following reference published in Analytical Chemistry ("Anal. Chem. 2014, 86, 15, 7858–7866") addresses this topic well and provides the statistical reasoning for defining this important figure of merit for multivariate analytical procedures.	Current (lines 363-368) "For quantitative applications of multivariate analytical procedures, appropriate metrics, e.g., root mean-squared error of prediction (RMSEP), should be used. If RMSEP is found to be comparable to acceptable root mean-squared error of calibration (RMSEC) then this indicates that the model is accurate enough when tested with an independent test set. Qualitative applications such as classification, misclassification rate or positive prediction rate can be used to characterize accuracy. And "Current (lines 399-400) Additionally, for multivariate analytical procedures, the routine metrics of RMSEP encompass accuracy and precision. Collated together as Section 3.4.1. Considerations for multivariate analytical procedures (lines 133-135) " • In the second phase, model validation, an independent validation data set with independent samples is used for validation of the model.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	118	144	3,4	ISPE appreciates the addition of multivariate analytical procedures to ICHQ(R2). The information in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144) is well organized in its focus on the specific considerations for these types of procedures. However, other aspects of multivariate analytical procedures are included in sections of ICHQ2(R2) that focus on elements applicable to traditional analytical methods. In those sections, it is not entirely clear which elements are also appliable to multivariate methods. Therefore, ISPE recommends grouping the disparate information for multivariate analytical procedures all together in "Section 3.4. Considerations for multivariate analytical procedures" (lines 118-144). The source of all relocated lines related to multivariate analytical procedures is provided in the collated recommended edits. Further, ISPE recommends the inclusion of information on how to properly establish detection limits for multivariate analytical procedures as none of the typical approaches utilized with traditional methods are ideal for these methods. It is also important to address how these limits are established for multivariate calibrations as these parameters cannot be extrapolated and defined based on approaches used for univariate calibrations. ISPE suggests the following reference published in Analytical Chemistry ("Anal. Chem. 2014, 86, 15, 7858–7866") addresses this topic well and provides the statistical reasoning for defining this important figure of merit for multivariate analytical procedures.	4.2.1.3 *3.4.1. Multivariate calibration* *Algorithms used for construction of multivariate calibration models can be linear or non-linear, as long as the model is appropriate for establishing the relationship between the signal and the quality attribute of interest. The accuracy of a multivariate procedure is dependent on multiple factors, such as the distribution of calibration samples across the calibration range and the reference procedure error.* *Linearity assessment, apart from comparison of reference and predicted results, should include information on how the analytical procedure error (residuals) changes across the calibration range. Graphical plots can be used to assess the residuals of the model prediction across the working range.* *Where applicable, the detection limits for multivariate analytical procedures should be established. Approaches such as partial least-squares calibration should be described. Other approaches may be justified.* (moved from lines 258-262) *For accuracy of quantitative applications of multivariate analytical procedures, appropriate metrics, e.g., root mean-squared error of prediction (RMSEP), should be used. If RMSEP is found to be comparable to acceptable root mean-squared error of calibration (RMSEC) then this indicates that the model is accurate enough when tested with an independent test set. Qualitative applications such as classification, misclassification rate or positive prediction rate can be used to characterize accuracy.* (moved from lines 363-368) *Additionally, for multivariate analytical procedures, the routine metrics of RMSEP encompass accuracy and precision.* (moved from lines 399-400) 3.4.1. *3.4.2. Reference analytical procedure(s)* "
PPTA	118	134	3,4	There is no clear description of the expectations in this paragraph.	Please provide more details on expectations.
EFPIA	121	122	3,4	A model is also possible with several inputs and more than one attribute	The multivariate calibration model relate the input data to one or more values for the property of interest (i.e., the model output).
EFPIA	121	121	3,4	Change "relate" in "The multivariate calibration model relate..." to "relates."	"The multivariate calibration model **relates** the input data to a value for the property of interest (i.e., the model output)."
GE Healthcare, Oslo	121	121	3,4	Verb conjugation.	Change "relate" to "relates".
EFPIA	129	129	3,4	"Rotational manner" may not be a known term	Suggests to add "e.g. for cross validation" after "rotational manner" as this term is frequently used for this kind of validation
APIC	133	134	3	Independent samples – should be used a representative sample (spiked with impurities if necessary) to ensure that all critical quality attributes of the method are evaluated	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	136	137	3		Where it reads "(…) procedures require should have values or categories (…)" only one verb should be considered (require or should have)
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	136	136	3.4.1	The word "require" seems to be misplaced here.	~~require~~
EFPIA	136	136	3.4.1	delete the word require	
Evolve-France	136	138	3.4.1	The sentence clarity may be improved by eliminating the word "require".	Samples used for the validation of quantitative or qualitative multivariate procedures should have values or categories assigned to each sample, typically obtained by a validated procedure or pharmacopeial reference procedure.
Gilead	136	137	3.4.1	redundant word in - 'multivariate procedures require should have…"	delete "require"
Katarzyna Piechota (Mrs.)	136	137	#######	Incomprehensible sentence. Too many verbs: "require should have".	Samples used for the validation of quantitative or qualitative multivariate procedures ~~require~~ should have values or categories assigned to each sample,…
PPTA	136	137	3.4.1	Sentence: "Samples used for the validation of quantitative or qualitative multivariate procedures **require should** have values or categories assigned to each sample.." . The wording of "require" and "should". Only 1 of these words should be present in the text.	Please use in the text either "require" or "should", but not both.
EFPIA	137	138	3.4.1	Also include reference samples as this writing is present on line 386 in the Q14 text. Additionally, we have seen cases where it is possible to make good reference samples but there is no alternate analytical procedure within reach.	Change "typically obtained by a validated procedure or pharmacopeial reference procedure" to "typically obtained by a validated procedure, pharmacopeial reference procedure, or reference samples"
GE Healthcare, Oslo	137	137	3.4.1	Repeated verbs.	Delete "should have".
ISCT	137	137	3.4.1	Typographical Error	Remove the words "should have"
EFPIA	139	140	3.4.1	It's not clear what this first sentence means. The sentence should be the other way around	Change to. "When a reference analytical procedure is used, the expected performance of the multivariate analytical procedure, should match the performance of the reference procedure"
GE Healthcare, Oslo	139	140	3.4.1	Sentence is difficult to understand	Consider reweite to the following: It is expected that the performance of the multivariate analytical procedure should to the minimum match that of the reference analytical procedure, if such a reference analytical procedure is used.
PPTA	152	152	4.1.	Biological methods focus on one analyte, therefore selectivity is not applicable or synonymous to specificity.	Please add additional detail to improve clarity for biological methods.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	157	159	4,1	test can not minimize interference but show if there is interference or not --> you cannot minimize the interference, you can only show if interference is present --> sentence is not clear	Proposed rewording: However, during the development of the procedure, the potential interference should be minimized in order to obtain a provcedure tat is fit for purpose.
Medicines for Europe	157	159	4.1.1	There is no proposition on what to do when a clean matrix can not be provided (when there is an interference).	An example of "eg1. if a clean from interference matrix cannot be provided (pesticides in wheat, plasticizers in sweage sludge) please use CRM material" and/or "eg2. if a clean from interference matrix cannot be provided (API in the placebo) please justify if the interference is considered significant or not for the purpose of the method"
EFPIA	163	166	4.1.1	Please provide additional guidance for 'other components present in the operating environment'	adjust to "or other components/active ingredients present in the operating environment"
ECA Foundation / European QP Association	164	164	4.1.1	Absence of interference can be shown or infered in acuracy/spiking studies	suggest adding "Absence of interference can be shown or infered in acuracy/spiking studies"
EFPIA	167	170	4.1.2	Text: 4.1.2 Orthogonal procedure comparison Specificity/selectivity can be verified by demonstrating that the measured result of an analyte is comparable to the measured result of a second, well-characterized analytical procedure (e.g., an orthogonal procedure). Orthogonal methods won't be necessarily well-characterized (compendial or validated, acc. current ICH Q2(R1)). The level of method validation of an orthogonal procedure depends on intended purpose of the procedure and technology inherent principles.	Replace Orthogonal and well-characterized by Independent (used in ICH Q2(R1) and more vague): 4.1.2 Independent procedure comparison Specificity/selectivity can be verified by demonstrating that the measured result of an analyte is comparable to the measured result of a second, independent analytical procedure (e.g., a well-characterized or orthogonal procedure).
Medicines for Europe	167	170		If further explanation can be added to clarify "well characterized analytical procedure (e.g., an orthogonal procedure)" written in 4.1.2 Orthogonal procedure comparison.	Addition of orthogonal procedure definition
PPTA	167	170	4.1.2	This section is unclear and is missing detail.	Please rephrase and provide more detail to improve understanding.
ECA Foundation / European QP Association	168	169	4.1.2	Without examples, it is difficult to understand how rersults are "comparable" for two different procedures. How can the second procedure demonstrate specificity of the first procedure?	suggest deleting this section, give examples or rephase
FUJIFILM Diosynth Biotechnologies Denmark	171	174	4.1.3	Thank you for including this statement about "Technology inherent justification"	
ECA Foundation / European QP Association	173	173	4.1.3	please gives examples for biological products. E.g. immunoassays	Include immunoassays in the examples
Medicines for Europe	179	185	4	The text is not clear: is it enough to justify the component identification with use of related or similar components and to declare that these components have no signal or this kind of justification is only an additive part of the validation and for justification of identification with reference material?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	180	182	5,1	The calculation of correction factors is usually carried out during development phase. It should be clear if it can be included in validation set.	Apart from robustness testing, the calculation of correction factors may be carried out during development phase. If so, there is no need for re-calculation during validation phase.
FUJIFILM Diosynth Biotechnologies Denmark	184	185	4.1.4.1	The requirement of "any interference" is too tight. The assessment should be based on knowledge and risk management. R1 has a better phrasing and it is recommended to keep the last sentence from R1.	Keep the wordings from R1
EFPIA	187	188	4.1.4.2	Should purity also be included in this sentence (in addition to content and potency)?	
EFPIA	187	187	4.1.4	Typo	change fulfil to "fulfill"
EFPIA	188	188	4.1.4.2	Assay, Purity and Impurity: Clarification is required that force degraded samples may be used to demonstrate specificity.	Add new text referencing the use of force degraded samples: This can be performed through the use of forced degradation samples, if appropriate.
EFPIA	190	190	4.1.4.2	Assay, Purity and Impurity: As written, line 190 implies that all detectable individual components must be identified and labelled. This should be applied to reportable components only.	An adjustment of line 190 from 'individual' to 'reportable' components.
EFPIA	191	194	4.1.4.2	Assay, Purity and Impurity: This section is focussed on separations techniques – additional verbiage for specificity of non-separation / biotech techniques is requested.	For separation techniques, suitable discrimination should be investigated at an appropriate level (*e.g.,* for critical separations in chromatography, specificity can be demonstrated by the resolution of the two components which elute closest to each other). Alternately, spectra of different components could be compared to assess the possibility of interference. For non-separation techniques (e.g. bioassay, ELISA, qPCR), specificity can be demonstrated through the use of well characterised materials to confirm the absence of interference in relation to the analyte. In cases where the analyte is a biological process related impurity (e.g. host cell protein, host cell DNA, other biological process residuals), specificity (non-interference) must also be confirmed against the product.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	195	198	4.14.2	recommended to add independent to additional procedure for clarity.	In case a single procedure is not considered sufficiently selective, an additional independent procedure should be used to ensure adequate specificity
EFPIA	200	208	4.1.4.3	Assay, Purity and Impurity: Additional verbiage is requested for specificity of biotech techniques where spiking is not practically applicable.	Where the drug substance or drug product cannot be easily separated from the excipients (e.g. bioetch molecules), spiking of the DS or DP may not be practical. In this case, discrimination may be determined through the use of samples containing only excipients and no active, thereby demonstrating that excipients do not generate a positive signal within the assay.
PPTA	200	213	n/a	More detail needs to be provided on expectiations with regard to acceptance. For example, is it mandatory that the reference materials is a reference materials with a certificate? Is it possible to self-qualify the reference material? If the analytical procedure is not yet validated, is it possible to qualify this in-house reference using this method. (See - chicken or the egg scenario - which comes first?)	Please clarify/ provide more detail.
APIC	201	205	4	For selectivity assessment, we demonstrate that all impurities are resolved between them and with the main peak, by spiking with appropriate levels of impurities and/or excipients. We do not compare assay values, as we understand that demonstrating resolution of all peaks is sufficient to demonstrate no impact in the results obtained.	
Medicines for Europe	201	208	4.1.4.2	For specificity test, accuracy test is often referred to prove the non-existence of interference on results by sample matrixes. Does this mean that confirmed accuracy alone can substantiate the validity of specificty? There are often discussions as to how extensively specificity parameter should be evaluated. Some say linearity should be demonstrated with tested samples (in-process samples and drug substance) by spiking them to the concentration level of the standard curve of a test method.	If different approaches are possible, validation tests other than accuracy could be included.
PPTA	201	201	4.1.4.2	Please correct "**For purity assay**, dicrimination of the analyte in the presence of impurities and/or excipients should…"	Please correct to: "**For a purity assay**, dicrimination of the analyte in the presence of impurities and/or excipients should…"
Medicines for Europe	202	203	4.1.4.2	The spiking concentration of impurities is not clear.	For assay, the appropriate levels of impurities should be evaluated at a concentration which corresponds to the worst-case scenario (e.g. upper specification limit), unless otherwise justified.
Medicines for Europe	206	208	4.1.4.2	To be more specific concerning unbiased measurements.	The unbiased measurement of the impurities could be proven with a satisfactory recovery in a matrix which contains all other components (APIs, known impurities and excipients) in the sample matrix.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	210	213	4.14.2	Rephrase the sentence to better describe what is expected from a second procedure. It should be an independent procedure, which can be either well-characterized (pharmacopeial or validated) or orthogonal (suitable method not necessarily validated, depending on characteristics of the technology)	"degradation products with a second independent procedure (e.g.,well-characterized or orthogonal procedure). Can "well characterized" be replaced by "appropriate specificity/selectivity"? (see our comments for line 167)
Medicines for Europe	210	213	4.1.4.2	If impurities are not available, it is not possible always to have a well-characterized procedure (e.g. more than one APIs in the product).	If a well-characterized procedure is not available (e.g. more than one APIs in the product), the successful results of the forced degradation study concerning mass balance and peak purity could establish the specificity of the method.
EFPIA	214	214	4,2	Working and Reportable Range: Adjust wording from 'working range' to 'range'	
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	214	218	4,2	ISPE would like to suggest that ICHQ2(R2) include mention of analytical procedures that utilize reference standard calibration curves to calculate content or concentration of analytes, and relative potency methods where reference standard and test samples are analyzed in dose response curves. Although use of ICHQ2 with these types of analytical procedures is implied, it would be beneficial for ICHQ2(R2) to provide more direct information for such methods, particularly with respect to working range and reportable range.	Current (lines 214 – 218): "4.2 Working Range Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range will lead to a specific working range. Typically, a corresponding set of sample concentrations or purity levels is presented to the analytical instrument and the respective signal responses are evaluated." Suggest edits (lines 214 – 218) (highlighted in italics): "4.2 Working Range Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range will lead to a specific working range. Typically, a corresponding set of sample concentrations or purity levels is presented to the analytical instrument and the respective signal responses are evaluated. *Certain analytical procedures include a reference standard calibration curve against which to interpolate the amount of analyte present in test samples, or utilize dose response curves of reference standard and test samples to generate relative potency values. In these methods, the working range is defined where performance parameters of the calibration or dose response curves (e.g., precision, accuracy, linear or non-linear response factors) are suitable to support the reportable range established for test samples.*
PPTA	214	214	4,2	The term "working range" is clear for chemical methods, but it leaves room for ambiguity and interpretation for biological methods where dose response curves for both reference standard and samples across the working range are routinely compared with respect to similarity (in addtion to linearity). Working range could also be understood as the difference of both dose response curves, i.e. their degree of overlap,	Please define more clearly the equirements for biological methods.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	215	218	4,2	Working and Reportable Range: Revise the text introducing the concept of range Suggested replacement text proposed, to provide greater clarity that procedures may be validated through use of a reportabel range or a working range.	The range of an analytical procedure can be validated through the assessment of reportable results (reportable range) or through the use of one or more working ranges. Typically, a working range corresponds to the lowest and the highest sample concentrations or purity levels presented to the analytical instrument, and for which that the analytical procedure provides meaningful results. Depending on the sample preparation (*e.g.,* dilutions) and the analytical procedure selected, the reportable range can lead to one or more appropriate working ranges.
Evolve-France	217	218	4.3	Information about requirements related to installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) or reference to another guidelines concerning this point may be useful here or somewhere else in the document.	
EFPIA	218	218	4,2	Working and Reportable Range: Add text to enable extrapolation where justifiable	In cases where materials of sufficient purity / impurity to validate the full range cannot be generated (e.g. 100% purity), extrapolation of the reportable range may be justified. In this case, a justification of the appropriateness of the extrapolation approach must be provided.
Guerbet	218	218	4.2	Please consider the application of the "combined approaches for accuracy and precision" to the *working range* determinatrion (not only to the *Validation of lower range limits*)	...responses are evaluated. Alternatively, the working range can be directly determined by the evaluation of the combined accuracy and precision across the range.
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	219	241	4.2.1.1	Perhaps it is meaningful to add in section 4.2.1.1 a paragraph related to the use of relative response factors for impurities and other substances with different UV response determined by comparison of linearity slopes.	Add the following: "*If the substance to be determined has a different specific UV absorbance than the substance used as reference standard in routine analysis, relative response factors should be calculated using the ratio between the linear slopes of the corresponding substances.* "
ECA Foundation / European QP Association	219	219	4.2.1	Suggest renaming to the more general term "Calibration model" as the text below describes the relatioship between concentration and response. This relationship can be fitted to alinear model or to a non-linear model. The calibration model should be established during development as it is too late to find out during validation that e.g. that the linear model does not fit the data. For this characteristic, it will be very useful to include verification of the calibration model as part of the life cycle approach as it is established during stage 1 and continuosly verified during stage 3 as an acceptance criterion for each analytical run.	Suggest renaming to the more general term "Calibration model". Response relationship can also be inferred from development of the analytical procedure and verified continuosly in each analytical run
EFPIA	219	265	4.2.1	Analytical Procedure Control Strategy: Table 1 describes the Suitability of Calibration model. Proving that the selected calibration model generates generate reliable results is part of the validation exercise. However, the "suitability" is no longer explicitly mentioned in the guideline. Suitability of a non-linear calibration model is well defined. This way to prove suitability could be applied to all situations (including linear models). It would clarify expectations in terms of 'Suitability of Calibration model'	Reorganisation and simplification of section 4.2.1, which could be renamed "Calibration model", instead of "Response" mentioning that the model could be linear or not (without separating 4.2.1.1 and 4.2.1.2) , but its suitability should be assessed by proving proportionality between obtained values to the true value across the working range - lift this text towards the beginning of section 4.2.1

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	220	241	4.2.1.1	In Q2(R1) no distinction is made between reporting range and working range. Now in Q2(R2) this distinction is introduced and it is mentioned that the linearity should be evaluated across the working range. But why is this? Why should the linearity not just be evaluated across the reporting range? In practice, all labs are performing linearity validation tests over the reporting range and not the working range.	
EFPIA	220	255	4.2.1.1.	linearity of results is missing. It is mixed with linearity of the response. While linearity of results is described in annex 2 (661)	
PPTA	220	220	4.2.1.1	Linear Response: The same holds for "linearity": Is this the linearity of the dose response curve or is it the linearity of the calculated potency against the theoretical potency which requires several sets of dose response curves with different predilutions? Or is it sufficient to show linearity of the dose response curve within an extended working range (beyond that of routine assays) This topic is addressed for non-linear, (252-255) but not for linear dose response curves	Please define more clearly the equirements for biological methods.
Medicines for Europe	221	225	4	Linear response: Does it mean that the linear relationship can be justified using drug product itself containing the component to be measured)?	
EFPIA	222	222	4.2.1.1	Working and Reportable Range: Adjust wording from 'working range' to 'range'	
EFPIA	223	223	4.2.1.1	Linear Response: As currently written, line 223 / 224 is restrictive on the sample types that may be utilized for determination of linearity	The response can be demonstrated directly on the drug substance or suitably characterised materials (e.g., by dilution of a standard stock solution).
EFPIA	223	224	4.2.1.1.	To minimize variation from the design, linearity can be demonstrated by varying the injection volume instead of varying the concentration (HPLC)	Please add varying injection volumen in the example
EFPIA	223	225	4.2.1.1	It's not clear what this last sentence means.	consider to take out "synthetic"
EFPIA	225	225	4.2.1.1	Linear Response: Allowance has been provided for techniques that are inherently specific without the need for further justification (154/155). The same allowance should be provided for techniques that are inherently linear.	In some cases, linearity may be inherently given by the underlying scientific principles of the analytical procedure.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	226	228	4.2.1.1	ISPE notes that the option for visual inspection of linear relationship is absent from ICHQ2(R2). We request that it be returned as one of the options for assessing linearity of response factors, which is an approach used with some methods for biological products. ISPE proposes to utilize the statement currently in ICHQ2(R1) on visual assessment of linearity (page 12).	Current (lines 226-228) "Initially, linearity can be evaluated with a plot of signals as a function of analyte concentration or content. Test results should be evaluated by appropriate statistical methods (e.g., by calculation of a regression line by the method of least squares)." Suggested edit (lines 226-228) (highlighted in italics) "Initially, linearity can be evaluated with a plot of signals as a function of analyte concentration or content. *For example,* test results can be evaluated by appropriate statistical methods (e.g., by calculation of a regression line by the method of least squares). *Alternatively, they may be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content."*
Andrea Gaggioli - ISS. ITA	229	234	4.2.1.1	I think that linearity here is not the best term. In fact, e.g.: If the regression line is "flat" (i.e.: with a low value for the slope) the performance of the method is bad but the degree of linearity could be good. In the same situation the correlation coefficient or coefficient of determination are not enough since they would be good but the performance would not be. What would be important here are the Confidence Intervals of the slope and the intercept which should be compared with 1 and 0 respectively. Correlation coefficient or coefficient of determination (alone) can be misleading (unless there is already a strong assumption of a good linear relationship between analyte concentration and response across the working range, but this is what we have to evaluate).	To be honest, I would call it "Accuracy of the Method along the working Range" according to the terminology of my first comment above: Accuracy = Precision + Trueness (Section number : many - raw 16) "Data derived from the regression line may help to provide mathematical estimates of the performance/accuracy. A plot of the data, the correlation coefficient or coefficient of determination, intercept and slope with their 95% Confidence Intervals of the regression line should be provided. An analysis of the deviation of the actual data points from the regression line, comparing the 95% Confidence Interavals for slope and Intercepts with 1 and 0 respectively is helpful for evaluating linearity"
FUJIFILM Diosynth Biotechnologies Denmark	229	234	4.2.1.1	Three of the performance characteristics to be reported (the correlation coefficient or coefficient of determination, intercept and slope of the regression line) do not tell about "suitability of calibration model". It is just "easy to report values". It is recommended that backfitting should be included, at least as an option. Backfitting will tell how large an impact the calibration curve has on the overall bias of the analytical procedure. Furthermore, backfitting can also be applied for non-linear responses discussed in lines 243 - 255. Backfitting can be applied whichever way the calibration curve appears. One can almost read that you are nearly recommending backfiitting in lines 253-255.	Allow for the option of applying back-fitting to assess the "suitability of calibration model"
EFPIA	231	232	4.2.1.1	In a general linear regression scenario with a large data set, we can use the residual plots to determine whether the model should account for curvature or not. However, in the method validation context that many of us deal with, we only have n = 5 data points in the linearity study. At best, it will be very challenging for a highly trained statistical analyst to assess curvature from a residual plot with only five points. Any patterns that might exhibit so-called curvature in a residual plot with five points could be solely due to random chance.	Please adjust 'is helpful' to 'may be helpful'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Moderna	234	235	4.2.1.1 Linear Response		Provide a recommendation on the evaluation of the significance of the intercept and acceptance criteria for single point calibration methods (which is assumed that the calibration is linear through zero).
EFPIA	235	235	4.2.1.1	Replace "establishment" with "validation" to clarify that routine testing does not require standard curves to have a minimum of 5 points.	Please adjust text to "For the validation of linearity, …"
Medicines for Europe	235	237	4.2.1.1	In some cases, during quantitative analysis of very low concentrations (e.g. aerodynamic particle size distribution of inhalation products) it is needed to extend the validation range to a very wide concentration range (QL-150% of assay target concentration). Linearity curves may differ between the extreme regions.	If a wide concentration range is applied due to the sort of analysis (e.g. aerodynamic particle size distribution of inhalation products), either more concentrations should be tested within the desired range or two separate linearity curves may be created, i.e. one for the lowest and one for the highest concentrations.
PPTA	235	255	4.2.1	For linear regression a minimum of 5 concentrations is recommended, but no minimum for non-linear regression	Proposal: 4-PF: min 7 concentrations, 5-PF: min 8 concentrations (number of parameters+3)
EFPIA	238	240	4.2.1.1	The paragraph is unclear; see proposal for enhanced verbiage	Proposal: "To obtain linearity, the measurements and/or the analyte concentration may be transformed (eg. log, square root). In the case where the variability of the measurements is heterogeneous along the range (heteroscedasticity), a weighted fit of the calibration line may be applied to improve estimation of the parameters of the model (intercept and slope) and get a more accurate estimation of back-calculated concentrations. Aforementioned transformation of the measurements may also be considered in case of heteroscedasticity."
EFPIA	239	234	4.2.1.1	Linearity should be evaluated by visual inspection' in R1 was removed, and suggest to include it in R2. Visual inspection is still valuable to ensure that the given statistics are sound and reflect the relationship between the analyte concentration and response.	Linearity should be evaluated by visual inspection of a plot as a function of analyte concentration or content.
EFPIA	240	240	4.2.1.1	Linear Response: The evaluation of values across a given working range for the comparison of observed vs theoretical sample values has been provided for non-linear responses (253 - 255). This approach is equally applicable to linear responses and so should be included in Section 4.2.1.1	Add text: Analytical procedure capability can also be evaluated across a given range to obtain values that are proportional to the true (known or theoretical) sample values.
EFPIA	242	246	4.2.1.2	This section is either misleading or confusing or both. A "coefficient of determination" is not an example of a nonlinear regression analysis. Moreover, coefficients of determinations (or R-squareds) are not appropriate for non-linear regression models. Unlike in linear models, where RSquared = "Explained Variation" / "Total Variation" is appropriate because "Explained Variation" and "Error Variation" add up to "Total Variation", this additivity property does not occur in nonlinear regression models. This is why statistical software such as JMP does not report an R square value from nonlinear regression analysis.	Remove 'e.g. coefficient of determination' as this is not a suitable non-linear analysis tool.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	242	242	4.2.1.2	Description of requirements of non-linear response indicates that also for biological methods it is sufficient to show that the dose response curve complies with the chosen model. This bears the risk - especially for models with many parameters (e.g.4-PF) and few observations always very good correlations will be found that do not reflect similarity between samples and reference standards	Please define more clearly the equirements for biological methods.
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	243	246	4.2.1.2	Perhaps it is meaningful to add examples for normal chemical substances. For instance, there is a universal HPLC detector (Evaporative Light Scattering Detector; ELSD) having a non-linear response.	Adding after the first sentence in line 243 the following term in parenthesis: "*(e.g. HPLC-ELSD)*"
EFPIA	243	245	4.2.1.2	The following sentence is very difficult to read: In these cases, a model or function which can describe the relationship between response of the analytical procedure and the concentration is necessary.	In these cases, a model or function is necessary which can describe the relationship between response of the analytical procedure and the concentration.
Medicines for Europe	245	246	4.2.1.2	No criteria for regression analysis is provided for non-linear response cases, nor the number of standards that should be used for this evaluation.	
EFPIA	249	249	4.2.1.2	"...constrained by upper and lower asymptotes."	suggest adding 'if possible', as some of the ELISA methods do not show an upper asymptote within the range of the detection system.
EFPIA	250	250	4.2.1.2	"four or five-parameter logistical function"	Right wording is: "four or five-parameter logistic function"
EFPIA	250	250	4.2.1.2	Add a sentence after the latter about the management of hetersocedasticity in case of a non-linear response.	Propoal: "In presence of heteroscedasticity, transformation of measurements or weighted fit may be applied to enhance estimation of model parameters and back-calculation of concentrations."
ECA Foundation / European QP Association	252	253	4.2.1.2	This can be interpreted as it is not required to validate the calibration model which is wrong. The calibration model should be established and demonstrated as for a linear model, just with different statistics. See Azadeh, et. Al, Calibration Curves in Quantitative Ligand Binding Assays: Recommendations and Best Practices for Preparation, Design, and Editing of Calibration Curves, AAPS journal (2018) 20: 22	The suitability of the model should be assessed by means of appropriate analysis (e.g. by setting acceptance criteria to the difference bewteen the nomial and the back caluclated concentrations).
ECA Foundation / European QP Association	253	255	4.2.1.2	The wording "instead" is not correct as this evaluation is not a substitute for evaluation of calibration model. The evaluation described here is performed as part of accuracy study and applies to all types of analytical procedures, not just to the ones with non-linear reponses. It is important to demonstrate that dilutions of a sample are measured accurately.	
EFPIA	253	255	4.2.1.2	Last sentence of the paragraph is misleading	Proposal: "Instead, analytical procedure capability to obtain values that are proportional to the true (known and theoretical) sample values across a given range should be evaluated."
EFPIA	254	254	4.2.1.2	Working and Reportable Range: Adjust wording from 'working range' to 'range'	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	258	265	4.2.2.3	For improved clarity throughout the guidance, ISPE recommends collating all concepts for multivariate analytical procedures into one Section, eg Section 3.4. Therefore, please relocate this information to Section 3.4. (lines 118-134) For methods used with biological products for total purity/impurities (eg chromatography or electrophoresis) the QL is typically validated directly using replicate precision of peak or band areas from serial dilutions of a single main species. In this approach there is no means of obtaining accuracy measurements. Therefore, ISPE suggests adding a comment to allow the use of precision alone, when justified by the nature of the method.	Suggested edit (lines 258-265) -Please relocate these lines to Section 3.4 (lines 118-144) and delete this section (lines 258-265) Current (lines 303 – 305) 4.2.2.3 Based on Accuracy and Precision at lower range limits Instead of using estimated values as described in the previous approaches, the QL can be directly validated by accuracy and precision measurements. Suggested edit (lines 303 – 305) (highlighted in italics) "4.2.2.3 Based on Accuracy and Precision at lower range limits Instead of using estimated values as described in the previous approaches, the QL can be directly validated by accuracy and precision measurements. *When technically justified, direct validation of QL may also be accomplished using precision alone".*
EFPIA	262	264	4.2.1	"Linearity assessment, apart from comparison of reference and predicted results, should include information on how the analytical procedure error (residuals) changes across the calibration range " --> the use of the word "Linearity" can be confusing and restrictive	Look at the homoscedasticity of normalized residuals
EFPIA	265	265	4,2,1	A text for Recommended data should be added	For all other tests a section for recommended data are included
Medicines for Europe	266	319	4	Validation of lower range limits: the whole section refers only to QL and DL, but the working range didn't include QL, only reporting threshold what is consistent also in relation to the ICH Q3B(R2). It should be clear defined that the QL for impurity tests is only for information, due to the fact that the working range (reportable range) is defined by reporting threshold until 120 % of specification limit. There is no added value to confirm the quantitation limit with a value lower than reporting threshold by additional analysis QL could be useful during development phase to study the impurity level of the product, but only for internal use. Validation of QL has to be validated only in case that impurities will be reported from there	
Medicines for Europe	266	266	4.2.2	There is no proposition on how to validate lower range limits in non-linear response models	The case in lines **290-292** using the standard deviation of the blank may be proposed as a general procerure, non related to specific model.
PPTA	266	319	4.2.2	No advice is provided for establishing the quantitation limit for biological tests. Does the whole dilution series, that may range over several orders of magnitude need to fulfill the criteria or is it allowed to use a truncated dilution series?	Please provide additional advice for biological methods.
EFPIA	267	268	4.2.2	Working and Reportable Range: Clarification that QL / DL should only be required when working close to the lower limits of the procedure	If the product quality attribute to be measured requires the range of an analytical procedure to be close to the lower range limits of the procedure, *detection limit* (DL) and *quantitation limit* (QL) can be estimated using different approaches.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	272	273	4	As per current guidelines, we do not assess the noise in appropriate baseline regions instead of blank samples. It is our understanding that this is not aligned with USP/EP current practices. We always assess the blank in the region of the peak of interest.	
APIC	272	273	4	Signals in an appropriate baseline region can be used instead of blank samples. USP requirements contradict this statement (<621>)	
EFPIA	272	273	4.2.2.1	Upcoming new USP general chapter <621> specifies blank injection should be used for noise calculation for S/N	remove "Signals in an appropriate baseline region can be used instead of blank samples"
Medicines for Europe	275	276	4.2.2.1	The width of the half-height of the baseline for the evaluation of signal/noise is not clear.	For chromatographic procedures and when blank samples are used, the signal-to-noise ratio is calculated using a baseline of 20 times the peak width at half-height and if this is not obtainable, a baseline of at least 5 times the width at half-height is permitted (Ph. Eur 2.2.46 11th Edition, July 2022).
Medicines for Europe	277	279	4.2.2.1	Addition of alternative noise region for calculation of signal-to-noise ratio	In case the latter is not possible a defined region in the same chromatogram can be used.
Katarzyna Piechota (Mrs.)	281	303	#######	Subsection "Based on visual evaluation" (line 298) does not correlate to estimation of σ, thus it should not be included in section 4.2.2.2 but it should constitute a separate section 4.2.2.3	4.2.2.3 Based on visual evaluation 4.2.2.4 Based on Accuracy and Precision at lower range limits
Medicines for Europe	281	289	4.2.2.2	There is no information if the DL/QL come out from linear response of the standard solution or from linear response of spiked sample solutions.	If the DL /QL come out from linear response of standard solutions then they refer to the instrumental system DL/QL, whereas the DL /QL that come out of linear response of spiked samples solution they refer to the method DL/QL. When there is no signal suppresion or enhacement from matrix then the instumental DL/QL are equal to method DL/QL.
EFPIA	288	288	4.2.2.2	Analyte is something being analyzed (e.g., a chemical substance), a molecule X cannot itself have a regression line (which is a line describing the response as a function of analyte concentration, for instance).	Suggest changing to '… *from a regression line describing the response as a function of analyte concentration*'.
Medicines for Europe	292	292	4.2.2.2	An example for "appropriate number of blank samples" would be nice. Also, these blank samples measurements, should be if the same analytical day or is it advisable to be representative of different analytical days?	An explanation or an example of "eg. at least 3 samples" will be helpful
Gilead	294	295	4.2.2.2	Change "A specific calibration curve should be studied using samples containing an analyte in the range of the DL and QL" to "A specific calibration curve should be studied using samples containing an analyte in the range of the DL and QL (e.g., from estimated DL to ~3x estimated QL)"	Adding specific approximate range for calibration curve - We have seen this apporach attempted many times at 100X QL which is not suitable. Good to provide more guidance to ensure correct application of the approach - estimated DL to ~3x estimated QL - or other acceptable suggested range.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	295	297	4.2.2.2	The sentence may be improved on various aspects; see proposal for enhanced verbiage	Proposal: "A specific calibration line should be evaluated using samples containing an analyte in the range of the DL and QL (see recommendations in 4.2.1.1 for the experimental design). The residual standard error of the regression line (i.e., root mean square error) or the standard error of y-intercept of the regression line can be used as the standard deviation."
APIC	298	298	4.2.2.2	I believe that "based on visual evaluation" should be one of the approaches to estimate the DL and QL	4.2.2.3 Based on visual evaluation
EFPIA	298	302	4.2.2.2	Linear Response: The option for visual assessment is currently included in the incorrect location (within sub-chapter 4.2.2.2.)	Text should be moved from line 298 to line 269 and form sub-chapter 4.2.2.1. Subsequent sub-chapters should be re-numbered accordingly.
Medicines for Europe	298	302	4.2.2.2	The description for determining the detection limit based on visual evaluation is under the sub-section 4.2.2.2 Based on the Standard Deviation of a Linear Response and a Slope in the current draft. As the visual evaluation is not used in estimating the standard deviation of the response, this description on determining the detection limit should be a separate section.	The section on visual evaluation should be a separate sub-section under the Section 4.2.2 Validation of lower range limits.
Medicines for Europe	303	319	4.2.2.3 4.2.2.4	Please confirm if this approach makes sense in relative quantitation(purity) method; If the accuracy/precision of the impurity is confirmed within the working range of the method, the reportable value at the lower range can be a QL? e.g., There is relative purity test and the working range is 1-3 mg/mL. At the lower range (1mg/mL), the reportable value is 2% (it is impurity). Then, can it be expressed as follows; the working range is 1-3mg/mL and the QL is 2%	N/A
ECA Foundation / European QP Association	304	304	4.2.2.3	Estimated values can also be obtained by testing repeated samples around the expected QL and calculating the pooled SD. The QL is obtained by dividing the pooled SD with the precision criteria at QL (e.g. 20% for most immunoassays)	
Guerbet	306	319	4.2.2.4	Please consider the addition of "recommended data" in the case of a validation of QL by accuracy and precision measurements.	
Medicines for Europe	311	321	4.2.2.4	An example for "suitable number of samples" is needed.	an example of "eg. at least 3 samples" will be helpful
EFPIA	314	315	4.2.2.4	A small complement to the sentence would help	Proposal: "If the QL was estimated, the limit should be subsequently validated by the analysis of a suitable number of samples to be near or at the QL; measurements of the accuracy and precision at the QL may be performed at that time, if needed."
Medicines for Europe	314	317	4	Please see explanation in previous row	If the QL was estimated and is used for reporting of impurities, the limit should be subsequently validated by the analysis of a suitable number of samples known to be near or at the QL. In case that QL was only estimated to the purpose of this Guideline and QL is outside of reporting threshold, QL can be accepted as validated by reporting threshold.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	314	317	4.2.2.4	In cases where the QL was estimated, the guideline states that the limit should be subsequently validated by the analysis of a suitable number of samples known to be near or at the QL. However, the guideline does not specify the suitable number of samples.	Additional information on the recommended suitable number of samples or commonly used number of samples would be greatly appreciated.
Medicines for Europe	314	315	4.2.2.4	An example for "suitable number of samples" is needed.	an example of "eg. at least 3 samples" will be helpful
EFPIA	315	317	4.2.2.4	.. The reporting limit ? …replace by : the lower specification of the test	
Medicines for Europe	315	317		Is it neccessary to determine QL when estimated QL is 10 times lower than reporting level? From our practical experience, testing QL 10 times lower does not provide relevant data. We believe testing QL when it is 5 times lower than reporting level should be low enough.	We suggest to change the recommendation from "e.g., approximately 10 times lower than" to "e.g., approximately 5 times lower than".
Medicines for Europe	315	317	4.2.2.4	It is not clear if QL needs to be determined if the signal/noise ratio is much lower than the reporting threshold.	QL confirmation could be omitted if it is much lower than the reporting threshold. For example, the reporting threshold for a method is 0.05% and at this concentration level the analyte has a signal/noise of 150.
Medicines for Europe	315	317	4.2.2.4	It would be great to contain exact example for following case; "In cases where the QL is well below (e.g., approximately 10 times lower than) the reporting limit, this confirmatory validation can be omitted with justification." Does it mean that 'if the estimated QL is below 10 times lower than the reporting limit, a confirmatory validation can be omitted?'.	"In cases where the ***estimated*** QL is well below (e.g., approximately 10 times lower than) the reporting limit, this confirmatory validation can be omitted with justification"
EFPIA	316	319	4.2.2.4	Reporting limit and reporting threshold are very similar terms. Both should be added to the glossary for clarity.	Please add definitions for reporting limit and reporting threshold
FUJIFILM Diosynth Biotechnologies Denmark	320	415	4,3	This section hardly takes into account that the development of analytical procedures are based on risk and knowledge management (Q14). Thus, the statement about designs in lines 349 - 351 and in lines 378 - 381 should be omitted. The fundamental assessments to be performed are stated in lines 359 - 360 and in lines 396 - 398.	It is recommended to state that the applicant should design the validation study so that the goals in lines 359 -360 and in lines 396 398 are fulfilled.
EFPIA	321	322	4.2.2.4	Linkage of Q2 to Q14: Ensure use consistent use of term ‘performance criteria’	Replace acceptance criteria with 'performance criteria'
Andrea Gaggioli - ISS. ITA	322	323	4.3	It should be the TAE, but it is not clear	maybe here TAE can be introduced

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	324	347	4.3.1	There is no mention in the Accuracy paragraph of Relative Accuracy to be used for example in Potency assay or assay where accuracy cannot be established via an orthogonal method (as an absolute value). This case is however illustrated in an example provided in Annex 2 - Table 3 (right column), line 661.	Proposal to add the following text: "4.3.1.4 Relative accuracy In some cases it is not possible to determine an absolute expected value to compare measured results. Examples are potency assays where the result is not solely proportionnal to content. Another example are procedures where the result is the ratio of 2 measurements (e.g.: evaluation of aggregation where the results is a ratio between the area of the peak of multimers and the area of the peak of monomer). In those cases Relative Accuracy can be used where the proportionality of the response is evaluted accross the range. The range is covered through dilution/spiking of a sample or by mixing of samples presenting different measured results (e.g. different level of aggregation). A reference/reliable value in determined for this/those sample(s) (for instance through the average of a number of measurements). That/these reference value(s) is/are used to calculate the expected values for the other samples that are obtained by dilution/spiking or mixing of reference sample(s).
EFPIA	329	330	4.3.1	Please remove ‘(e.g. small molecule API assay)’ at line 330.	
FUJIFILM Diosynth Biotechnologies Denmark	329	331	4.3.1	"In certain cases (e.g., small molecule drug substance assay), accuracy can be inferred ….". The statement is too narrow. It may be applicable for all analytical procedures depending on the availability of reference materiel, spiking material and orthogonal procedure.	Remove the e.g. part
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	329	331	4.3.1	ISPE agrees with the statement that “in certain cases accuracy can be inferred once precision, response within the working range, and specificity have been established.” However, the parenthetical example is only of small molecule drug substance assay. To enhance relevance to biological applications, ISPE suggest adding the two biological product examples that most frequently utilize this approach: total purity and relative potency	Current (lines 329-331) In certain cases (e.g., small molecule drug substance assay), accuracy can be inferred once precision, response within the working range and specificity have been established. Suggested edit (lines 329-331) In certain cases (*e.g.* , small molecule drug substance assay, *or biological product total purity or relative potency assays)* , accuracy can be inferred once precision, response within the working range and specificity have been established.
EFPIA	331	331	4.3.1	Working and Reportable Range: Adjust wording from 'working range' to 'range'	
EFPIA	331	331	4.3.1	No indication that accuracy can be assessed during the intermediate precision study	Proposal: "If an intermediate Precision study is to be performed, then accuracy can be assessed at that time, from an analysis of variance".
ECA Foundation / European QP Association	332	335	4.3.1.1	For bioassays, this approach is not possible because the same analytical procedure is used to establish the biological activity of the reference material. It cannot be used for analytical procedures were the "true" value of the reference material is obtained by the same procedure or were the result is reported as relative to the reference.	Suggest to specify when this approach can be used in view of my comment for e.g. bioassays

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	333	333	4.3.1.1	Reference standards should be of known concentration as well	Please adjust to 'known purity and concentration'
EFPIA	341	347	4.3.1.3	Recommended to replace "orthogonal procedure" and "well-characterized procedure" by "independent procedure" and use this terminology consistently across the guideline. Independent should cover a broader range of terminologies used by the companies and avoid conflict of terminologies. The content of the chapter has more specific details on what is expected from an "independent procedure" for accuracy determination	4.3.1.3 Independent Procedure comparison The results of the proposed analytical procedure are compared with those of a second independent procedure that ideally applies a different measurement principle (orthogonal procedure ~~see 1.2~~). The accuracy of this second procedure should be reported. Independent procedures can be used with quantitative impurity measurements to verify primary measurement values in cases where obtaining samples of all relevant components needed to mimic the matrix for spike recovery studies is not possible.
Medicines for Europe	342	347	4	Accuracy: orthogonal procedure comparison: Does it mean that the method comparison is not an alternative procedure for justification of accuracy and it can only be used if spike recovery is not applicable?	
Medicines for Europe	342	347	4	Accuracy: orthogonal procedure comparison: Does the same parameter have to be measured with the second well-characterised procedure as with the proposed procedure? eg. If the proposed procedure is a content determination, does the content with the second procedure have to be measured as well? Mass balance procedure (e.g) can not be applicable: content vs. 100-sum of impurities (the second procedure is an impurity test) ?	
ECA Foundation / European QP Association	344	344	4.3.1.3	"see 1.2)" - there is no chapter or section 1.2. What is it referrring to?	
EFPIA	344	344	4	Incorrect reference to section 1.2	Change to 4.1.2
PPTA	348	368	4.3.1	The accuracy of biological assays depends on the correct assignment of in-house reference standards against primary standards (e.g. WHO standards). The results versus primary standard are accurate by definition, but they may differ, depending on reagents and assay conditions used. Spiking is frequently not applicable as samples are already a highly purified preparation of the analyte. Orthogonal methods (e.g. clotting tests vs chromogenic tests) may yield large differences.	Please add additional advice/ recommendations for biological methods.
ANMV	349	351	4.3.1.4	A minimum number of determination and concentation levels should be provided for accuracy, such as defined for repeatability on section 4.3.2.1.	We propose the following sentence:"Accuracy should be assessed using an appropriate number of determinations and concentration levels covering the reportable range. It should be assessed on: a) a minimum of 9 determination; preferably at 3 concentrations on 3 replicates per level, each submitted to the full analytical procedure; or b) a minimum of 6 determinations at 100% of the test concentration.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ECA Foundation / European QP Association	349	351	4.3.1.4	When the accuracy is impacted by the conditions of the analytical run (e.g. analyst, materials used, etc) it is recommended that the determinations are repeated similar to intermediate precision evaluation. This is important e.g. in immunoassays were the sample preparation step can impact the accuracy result depending on the analyist that performs the dilutions. In this case, it is recommended that accuracy and precision are not evaluate independently	suggest to add recommendation
EFPIA	350	350	4.3.1.4	The word 'full' is redundant.	e.g., 3 concentrations/ 3 reportable results generated following the analytical procedure
APIC	352	354	4.3.1.4	it is now clearly indicated that the recovery should be reported as the MEAN percent recovery. Does this mean that the individual recoveries should not be assessed against the acceptance criterion and only the mean percent recovery should be?	
APIC	355	358	4.3.1.4	This section is new compared to Q2(R1). I can imagine that this is introduced to include some kind of clarification for what is meant by the instructions in line 354 ("together with the confidence intervals."). But it seems that it is still not clear what is the requirement for reporting the accuracy results. I have never seen a reported result for accuracy other than the recoveries and I still cannot understand how we should translate the instructions in this paragraph to the practice.	
Gilead	355	360	4.3.1.4	In a typical validation, recovery results (individual and mean) are compared to an acceptance criterion prescribed in the protocol based on method's intended use. This is sufficient for the purpose of demonstrating method accuracy. Additional statistical analyses may be performed but should not be required.	Either remove or make this optional. For example "Additional statistical analyses may be performed at appropriate confidence interval (e.g., 95%) to evaluate analytical procedure bias"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	355	358	4.3.1.4	The statement on confidence intervals seems to imply a new requirement for reporting accuracy data. ISPE agrees that when it is technically possible, utilizing a statistical confidence interval can be a rigorous approach to accuracy by percent recovery or difference in means of theoretical vs actual values. However, when it is not technically possible to obtain a purified, stable versions of analytes (particularly those associated with biological products), a statistical confidence interval cannot be used for purposes of accuracy. Therefore, ISPE requests the language should be more general to remain consistent with the spirit of this guidance, which allows for the use of sound scientific methods to demonstrate suitability of use for the analytical method.	Current (lines 355-358) "An appropriate confidence interval (e.g., 95%) for the mean percent recovery or the difference between the mean and accepted true value (as appropriate) should be compared to the acceptance criterion to evaluate analytical procedure bias. The appropriateness of the confidence interval should be justified." Suggested edit (lines 355-358) *"When utilized,* an appropriate confidence interval *(* e.g., 95%) for the mean percent recovery or the difference between the mean and accepted true value (as appropriate) should be compared to the acceptance criterion to evaluate analytical procedure bias. The appropriateness of the confidence interval should be justified. *Approaches other than the use of statistical confidence intervals to assess accuracy may be technically justified."*
EFPIA	356	356	4.3.1.4	Confidence Intervals: The comparison of confidence intervals to the acceptance criteria within the accuracy and precision sections represents a new commitment compared to ICH Q2(R1), and should be adjusted to provide additional flexibility in approach	Change "should be" to "can be" on line 356

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	357	357	4.3.1.4	Linkage of Q2 to Q14: Ensure use consistent use of term ‘performance criteria’	Replace acceptance criteria with 'performance criteria'
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	363	368	4.3.1	For improved clarity throughout the guidance, ISPE recommends collating all concepts for multivariate analytical procedures into one Section, eg Section 3.4. Therefore, please relocate this information to Section 3.4. (lines 118-134)	Suggested edit (lines 363 - 368) -Please relocate these lines to Section 3.4 (lines 118-144) and delete this section (lines 363-368)
Medicines for Europe	368	368	table 2	It should be clarified how it is demonstrated that the analytical procedure's ability to discriminate between acceptable and non acceptable results remains comparable	Examples would be helpful
EFPIA	370	375	4.3.2	As a method validation is a **demonstration** that a method is fit for purpose, replace the word "investigation" by demonstration or something similar to it. Before method validation, we already know what kind of precision the method can provide. Otherwise, the activity would be a qualification of faisability study.	Replace investigation by demonstration or a word of a similar meaning as demonstration.
EFPIA	372	375	4.3.2	The approach how to evaluate precision list the concept of artifically prepared samples twice. Text should be shortened with focus on the use of authentic samples and keeping artificially prepared samples only as alternative.	Precision should be investigated using homogenous, authentic samples. If a homogenous sample is not available, articially prepared samples (e.g. Matrix mixtures spiked with relevant amounts of the analyte in question) or a sample solution can be used.
FUJIFILM Diosynth Biotechnologies Denmark	376	389	4.3.2	Repeatablity and intermediate precison can be determined in a combined experiment like suggested by e.g. S. Kojima (Pharm Tech. Japan 18 (5) 695-704) and in a lot of other publications. Statistical software can easily make "components of variance" calculation and by this provide values for repeatability and intermediate precision	Allow for the option of combined model for the precision study

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	376	381	4.3.2.1	The ICHQ(R2) section on Repeatability is essentially unchanged from ICHQ2(R1) and provides only two options for assessment of intra-assay precision, with no options to justify alternative approaches. ISPE encourages ICHQ2(R2) to update the Repeatability section with guidance on the principles of intra-assay replication and expand the options for Repeatability to better reflect the diversity of analytical procedures used with different products. There is also an excellent link to ICHQ14 in that the replication scheme required in an analytical procedure should be based on offsetting the inherent (im)precision of the method as determined during ICHQ14 method development.	Current (lines 376-381) 4.3.2.1 Repeatability Repeatability *may* be assessed using: a) a minimum of 9 determinations covering the reportable range for the procedure (e.g., 3 concentrations/3 replicates each); or b) a minimum of 6 determinations at 100% of the test concentration. Suggested edits (lines 376-381) (highlighted in italics) 4.3.2.1 Repeatability *Intra-assay precision (repeatability) should confirm suitable performance of the replication scheme defined in the analytical procedure. One outcome of ICHQ14 method development is to establish an appropriate replication scheme to generate one reliable reportable result. Repeatability should be confirmed across the reportable range, and for methods that utilize reference or calibration curves, across their working range.* Repeatability *is typically* assessed using: a) a minimum of 9 determinations covering the reportable range for the procedure (e.g., 3 concentrations/3 replicates each); or b) a minimum of 6 determinations at 100% of the test concentration. *Other approaches for assessing repeatability may be appropriate, based on the intra-assay replication requirements of the analytical procedure. The specific approach used should be justified.*
ANMV	378	379	4.3.2.1	replace e.g. with preferably	The proposition is : " a) a minimum of 9 determinations covering the reportable range for the procedure, preferably 3 concentrations/ 3 replicates each; or b) a minimum of 6 determinations at 100% of the test concentration."
Medicines for Europe	378	381	4.3.2.1	The case of repeatability for impurities analysis and some analyses where there is not concentration target (e.g. aerodynamic particle size distribution for inhalers) should be taken into consideration	…at 100% of the test concentration or at the upper limit of impurities or c) a minimum of 6 determinations at QL (e.g. aerodynamic distribution)
GE Healthcare, Oslo	379	379	4.3.2.1	Formatting looks weird.	Add indent to lign up with text in line 378.
EFPIA	381	381	4.3.2.1	A small sentence could be added to indicate that it is possible to assess repeatability from the intermediate precision study	Proposal: "If an intermediate Precision study is to be performed, then repeatability can be assessed at that time, from an analysis of variance".
ECA Foundation / European QP Association	383	384	4.3.2.2	For procedures used in stability studies, the intermediate precision cannot be ommited. Please be more explicite in what circunstances are exceptions.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	385	386	4.3.2.2	For LC separations, the use of a different chromatographic column should be added as part of intermediate precision	In case of LC separations, part of the equipment is the use of a different chromatographic column.
EFPIA	386	386	4.3.2.2	A definition of environmental conditions is required in line 386	environmental conditions (e.g. temperature, humidity),'
Medicines for Europe	386	386		Since "Intermediate Precision" expresses effects of within-laboratory variations, where environmental conditions are controlled daily, testing of environmental condition effects on the measured value is often not possible and meaningless. This data can be obtained far more usefully and reliably from the "Reproducibility" testing.	We suggest to omit "environmental conditions" from the typical variations that are mentioned.
EFPIA	388	389	4.3.2.2	Clarification proposed for "The use of design of experiments studies is encouraged."	Proposed adaptation: "The use of design of experiments studies **to combin e the examination of several effects** is encouraged.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	388	389	4.3.2.2	ISPE agrees that for Intermediate Precision of some analytical procedures it may not be necessary assess individual operational effects. But the ability to assess individual components of variance (e.g., to determine hidden sources of operational bias) should be allowed as an option, where desired. Therefore, ISPE suggests including an option for assessing individual components of operational variance in data generated by Intermediate Precision.	Current (line 388-389) Studying these effects individually is not necessary. Suggested edit (line 388-389) (highlighted in italics) Studying these effects individually is not necessary, *although assessing components of variance may be performed to determine sources of operational bias.*
ANMV	389	389	4.3.2.2	A minimum number of determination and concentation levels should be provided, as an indication	The proposition is : " a) a minimum of 9 determinations covering the reportable range for the procedure, preferably 3 concentrations/ 3 replicates each, per condition, with at least three different conditions (e.g. days/equipments/conditions/analysts) b) a minimum of 6 determinations at 100% of the test concentration, per condition, with at least three different conditions (e.g. days/equipments/conditions/analysts)."
Moderna	389	389	4.3.2.2 Intermedia te precision		Provide guidance on experiments and recommended acceptance criteria to evaluate method intermediate precision in terms of minimum numbers of runs and replicates.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	390	394	4.3.2.3	The concept of reproducibility (which was also in ICHQ2 (R1) is stated as not being within the scope of ICHQ2. Therefore, ISPE recommends deletion of the section on Reproducibility since it is not relevant to a new application.	Suggested edit (lines 390 – 394) -Please delete section 4.3.2.3. Reproducibility (lines 390-394).
Medicines for Europe	395	398	4.3.2.4	The guideline states that the standard deviation, relative standard deviation (coefficient of variation) and confidence interval should be reported for each type of precision investigated and be compatible with the specification limits. However, the relative standard deviation should be sufficient in confirming the precision of the analytical procedure. Furthermore, method validation report contains sufficient data for calculating the standard deviation, relative standard deviation, and confidence interval. Therefore, it is considered unnecessary to report all requested values mentioned in the guideline.	Reporting only a representative value among standard deviation, relative standard deviation (coefficient of variation) and confidence interval (usually the relative standard deviation) should be sufficient in confirming precision of the analytical procedure. Additional flexibility in parameter to be reported would be be greatly appreciated.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	396	397	4.3.2.4	Confidence Intervals: The comparison of confidence intervals to the acceptance criteria within the accuracy and precision sections represents a new commitment compared to ICH Q2(R1), and should be adjusted to provide additional flexibility in approach	Remove "confidence interval" from sentence on line 396
Genepharm S.A.	396	398	4.3.2.4	The recommended data for precision is described to include SD, RSD and confidence interval. What does the confidence interval refer to? The average of the determinations in precision experiment? And why should it comply to the specification limits of the product (eg assay within 95.0-105.0)? wouldn't the standard deviation evaluation suffice as precision estimation?	Clarification of confidence interval should be provided Compliance to specification should be re-considered
Gilead	396	397	4.3.2.4	In a typical validation, precision results are compared to an acceptance criterion prescribed in the protocol which generally is driven by internal SOPs based on the method's intended purpose. This is sufficient for the purpose of demonstrating method precision. Product specifications generally continues to evolve post method validation during late phase clinical stage towards commericialization, this presents another practical challenge assessing compatibility to the specification limits at the time of method validation.	Remove "and be compatible with the specification limits".
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	396	398	4.3.2.4	While ISPE agrees that use of statistical confidence intervals to assess precision results is valuable where appropriate, the assessment of confidence intervals is not applicable to all methods. Therefore, ISPE recommends it should be noted as optional rather than mandatory	Current (lines 396-398) "The standard deviation, relative standard deviation (coefficient of variation) and confidence interval should be reported for each type of precision investigated and be compatible with the specification limits." Suggested edits (lines 396-398) (highlighted in italics) "The standard deviation, relative standard deviation (coefficient of variation) and confidence interval *(where appropriate)* should be reported for each type of precision investigated and be compatible with the specification limits."
FUJIFILM Diosynth Biotechnologies Denmark	397	398		Only values for intermediate precision should be compatible with specification limits.	This can be assessed by e.g. process capability
ECA Foundation / European QP Association	399	399	4.3.2.4	RMSEP	should be explained in a glossary in Q2
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	399	400	4.3.2.4	For improved clarity throughout the guidance, ISPE recommends collating all concepts for multivariate analytical procedures into one Section, e.g., Section 3.4. Therefore, please relocate this information to Section 3.4. (lines 118-134)	Suggested edit (lines 399 400) -Please relocate these lines to Section 3.4 (lines 118-144) and delete this section (lines 399-400)
PPTA	399	399	4.3.2.4	The explanation of the meaning of the acronym "RMSEP" is missing.	Please add "RMSEP" to the glossary and explain meaning.
FUJIFILM Diosynth Biotechnologies Denmark	401	415	4.3.3	Thank you for including this section	
APIC	402	404	4	It is not clear what is expected from a combined criteria to assess accuracy and precision separately.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PPTA	402	403	4.3.3	The sentence "An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion." describes "Combined approaches for accuracy and precision". In the Glossary - line 590 - the term "Total Analytical Error" is mentioned but is not referred to section 4.3.3. or any other section in ICH Q2(R2) but only in ICH Q14. We suggested to link it also to this section to clarify the relationship of terms "combined approaches for accuracy and precision" and "Total Analytical Error".	Please consider adding in line 403 "(Total analytical error (TAE))." i.e. "An alternative to separate evaluation of accuracy and precision is to consider their total impact (Total analytical error) by assessing against a combined performance criterion."
Guerbet	403	404	4.3.3	Please consider to link the mentionned "individual criteria" to the specification limits as described for accuracy and precision.	An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion, which should be compatible with the specification limits.
Guerbet	403	404	4.3.3	Please consider to link *Total analytical error* concept (defined in Glossary) to the "combined approaches for accuracy and precision"	An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion established for Total analytical error.
FUJIFILM Diosynth Biotechnologies Denmark	407	410		The application of prediction interval or tolerance interval should be supplemented with an evaluation of the process capability.	
EFPIA	410	410	4.3.3	Bayesian methods are ideally suited for this type of combined analysis of accuracy and precision. Recommend adding some language to suggest Bayesian methods as an example of an alternative approach that could be used here.	Change to: "Other approaches may be acceptable if justified. Bayesian methods, for example, can be used to quantify predictive probabilities for the range of future reportable values."
Guerbet	412	413	4.3.3.1	Please consider to provide examples of acceptable reporting for "combined values".	If a combined performance criterion is chosen, results should be reported as combined value to provide appropriate overall knowledge of the suitability of the analytical procedure (e.g., Total Analytical Error, accuracy* profile) *Accuracy defined in ISO 5725
EFPIA	415	416	4,3	Analytical Procedure Control Strategy: Use of replicates within analytical methods has not been sufficiently covered. Please insert new text discussing replication for both routine use and validation studies. Proposal provided.	4.3.4 Replication The results of precision must be representative of the replication format selected for the analytical procedure. It is acceptable to perform the validation using a replication format that is different to the actual format in the analytical procedure. The precision validation assessment can be used to calculate the precision corresponding to the application of the analytical procedure.
PPTA	416	423	4,4	Please update the definition of robustness to include other factors which are not "deliberate variations in parameters" but are important to consider for impacts on evaluation of test method performance. Sources of analytical variation that can be expected to occur over longer term implementation of a test method, including batch to batch differences in critical reagents, chromatography columns and in capillaries of CE method.	Please consider updating the definition of robustness to include other factors that are not deliberate variations in parameters (e.g. defined as ruggedness in other documents).
EFPIA	418	418	4,4	Linkage of Q2 to Q14: 'Duration' to be included in robustness to align with same proposal for Q14	The evaluation of the analytical procedure's suitability within the intended operational environment and duration should be considered

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	418	419	4,4	Since sometimes attempts to verify through Method validation by adding deliberate variations that were not considered in the development phase to avoid investigation of testing error are confirmed, it would be better if it is added that it is not possible to arbitrarily add things that are not considered in the development phase.	Addition of phrase that robustness (deliberate variations) not considered in the development phase shall not be arbitrarily added to the method validation phase.
ANMV	420	422	4.4	Following comment made on the line above, we would like to add that the validation of analytical methods is intended to demonstrate that the anaytical performances fulfill acceptance criteria. Validation of methods is also the time to check the suitability of SST parameters and criteria, as well as the robustness of the method. If deemed adequately studied during the development of the analytical method, the data about robustness can be reported from the development section into the validation report, wihout being repeated. We consider as important to include robustness study in the validation report, as it provides information on the performance of analytical method. It could be necessary to check method robustness during the verification of precision, on different analytical systems, or in case of changes and partial re-validation in order to check that the changes do not impact the robustness of the method.	We propose the following modification: " The robustness evaluation should be submitted in the validation report and data can be reported from development data for an analytical procedure on a case-by-case basis or should be made avalilable upon request."
ECA Foundation / European QP Association	425	650	5	In the glossary there are a lot of terms and definitions not used in the Q2 bulk text. Specially the term Analytical Target Profile (ATP) should have been used throught Q2 instead of "intended use". There are very few links between Q2 and Q14 and not using the same wording does not help.	Please align wording between documents
EFPIA	425	650	5	Add definition for orthogonal procedure to the glossary.	Orthogonal procedure: an analytical procedure using a different analytical principle
EFPIA	425	425	5	Add definitions of Impurities, related substances, degradation products.	
EFPIA	425	599	5	Glossary should include a definition of replication strategy.	
EFPIA	425	650	5	Remove Q14 terms from Q2 glossary if not relevant to Q2. Q2 only and common to both	Confusing and difficult to navigate the document.
Guerbet	425	425	5	Please consider the addition in the glossary of the accuracy definition as a combination of trueness and precision according to ISO 5725	
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	425	650	5	ISPE appreciates the organization of the Glossary into two sections, one for traditional methods and one for multivariate analytical procedures. However, ISPE notes the Glossaries in ICHQ2(R2) and ICHQ14 are duplicates of each other, and it is not clear why terms and concepts that are absent from Q2 are included in its Glossary. To minimize redundancies among ICHQ2(R2) and ICHQ14, ISPE recommends removing Glossary terms not used in Q2.	Specific Glossary edits are provided for terms ISPE would suggest deleting from ICHQ2(R2) because they are included in, and more relevant to, ICHQ14.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	425	650		Glossary contains many phrases that are not used throughout the text and therefore seem excessive - such as analytical target profile (ATP), critical quality attribute (CQA), quality risk management etc. However, at the same time, glossary does not contain definition of some terms that are actually mentioned in the guideline and would benefit from explanation - such as multivariate anylitical procedure.	We suggest revision of the Glossary section.
Guerbet	426	426	5	According to ISO 5725, the definition corresponds to the term of Trueness and not accuracy.	
EFPIA	430	525	5	Some terms in glossary are missing acronyms	Please include (AP) after analytical procedure (DL) after detection limit, (QL) for quantitation limit. Also check for others
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	434	437	5	Term: Analytical Procedure Attribute Included in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	438	438	5	Avoid term "analytical Procedure Control Strategy"	ICHQ10 defines control strategy and it includes the analytical procedures/control systems/etc. New terms like this should be avoided. Instead, analytical methods/procedures should be actively managed as part of an overall analytical method lifecycle management program and applicable quality management systems. This would include making method improvements over the lifecycle of the method, introducing innovative analytical technology, advanced process control technologies/methods that are demonstrated to be superior in the intended application of the method, method robustness, sustainability and/or efficiency of execution.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	438	440	5	Term: Analytical Procedure Control Strategy Included in ICHQ14	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	441	443	5	Term: Analytical Procedure Parameter Included in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	442	442	5	Including reagent quality in the definition of Analytical Procedure Parameter may be too broad. "Quality" may imply more than just 95% pure to include impurities in the reagent.	Any factor (including reagent **~~quality~~ grade**) or analytical procedure operational step that can be varied continuously (e.g., flow rate) or specified at controllable, unique levels

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	444	449	5	Term: Analytical Procedure Validation Strategy Included in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	445	447	5	Analytical procedure validation strategy should include not only the selection of the analytical procedure performance characteristics for validation, but also how to assess them.	Suggest include … the selection of the analytical procedure performance characteristics for validation, and the design strategy for how to evaluate these performance characteristics.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	450	452	5	Term: Analytical Target Profile Included in ICHQ14	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	453	455	5	Term: Calibration Model Should be moved to Glossary for Multivariate Analytical Procedures	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	457	462	5	Term: Control Strategy Included in ICHQ10	Please delete this term from ICHQ2 Glossary
EFPIA	463	467	5	The definition of co-validation is not in alignment with the definition provided in USP chapter 1224 on Transfer of Analytical Procedures. In this USP chapter, co-validation is defined as follows: the transferring unit can involve the receiving unit in an interlaboratory covalidation, including them as part of the validation team at the transferring unit and thereby obtaining data for the assessment of reproducibility. Thus, the USP definition focuses on the assessment of reproducibility. I propose to align the definition in ICH Q2 with that of USP chapter 1224.	Thus, the USP definition focuses on the assessment of reproducibility. Suggest to coinsder to align the definition in ICH Q2 with that of USP chapter 1224.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	463	467	5	Term: Co-Validation ISPE recommends moving to in ICHQ14	Please delete this term from ICHQ2 Glossary

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	463	467	5	The possibility of readjusting system suitability or sample acceptance criteria needs to be considered because the actual assay variability can be assessed from the collective data pool generated from several laboratories. The pre-defined system suitability or sample acceptance criteria is derived from the statistical evlauation of limited data pool generated at the method development stage, and for this reason, the pre-defined accetpance criteria do not represent the actual assay variability. Therefore, if the comparability of test results generated from the several laboratories can be confirmed under the assay variability identified from the proper statistical evaluation of the collective data pool, it would be considered that the pre-defined system suitability/sample acceptance criteria can be re-adjusted for routine testing.	Addition of guideline or consideration of the possibility of re-adjustment of system suitability or sample acceptance criteria based on the collective data pool generated from the co-validation strategy.
EFPIA	466	466	5	In the definition of Co-validation, please replace 'revalidation' with validation.	Please replace 'revalidation' with 'validation'.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	468	471	5	Term: Critical Quality Attribute Included in ICHQ8	Please delete this term from ICHQ2 Glossary
EFPIA	472	474	5	Replace "Demonstration that two or more analytical procedures meet the same predefined performance criteria and can therefore be used for the same intended purpose." with "Cross-validation is a well established method for internal testing within multivariate modelling where segments of the calibration data set are set aside in successive steps to provide internal test sets, commonly done until all parts of the calibration data have been used as internal test set."	It will be highly confusing for machine learning experts, chemometricians and other multivariate modelling practitioners to not even mention the most common meaning of this term in the glossary. The current definition in lines 473-474 could be kept in the glossary but with a different title, e.g. Comparability Validation.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	472	474	5	Term: Cross-Validation Included in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	475	475	5	Add DL to Detection Limit	Add DL in brackets
EFPIA	479	480	5	the definition should also apply to routine use of analytical procedure	change to " single sample preparation as per the validation protocol or analytical procedure".
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	481	484	5	Term: Established Conditions Included in ICHQ12	Please delete this term from ICHQ2 Glossary
EFPIA	484	485	5	Add definition of impurity (and related substance and degradation products) and consider aligning terms.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	488	488	5	How are environmental conditions defined? Are these sample contact environment (e.g., reagent prep, columns, consumables), or external environment (e.g., temperature, humidity), or both depending on the method? For example, it may make sense to pay attention to external humidity for hygroscopic samples on a humid day vs a dry day for residual moisture determination.	Suggest providing a definition of Environmental Conditions as: "Conditions that could impact the method based on method type. This could be sample contact environment (e.g., reagent prep, columns, consumables), or external environment (e.g., temperature, humidity)."
GE Healthcare, Oslo	488	488	5	Header is on one page while text is on following page	Add page break prior to header for "Knowledge management" to move it above corresponding text.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	489	491	5	Term: Knowledge Management Included in ICHQ10	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	492	494	5	Term: Method Operable design Region Included in ICHQ14	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	495	497	5	Term: Ongoing Monitoring Included in ICHQ14	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	502	504	5	Term: Performance Criterion Included in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	510	510	5	Please adjust the definition of platform procedures to clarify that compendial methods are out of scope.	A platform analytical procedure can be defined as a multi-product (non-compendial) method suitable to test quality attributes of different products without significant change to its operational conditions, system suitability and reporting structure. This type of method would apply to molecules that are sufficiently alike with respect to the attributes that the platform method is intended to measure. Compendial methods are out of scope of this guideline, and should be addressed as per compendial requirements for method verification. (ICH Q2)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	514	515	5	Term: Precision The definition contains precision at 3 levels, but only 2 are within the Scope of ICHQ2.	Current (lines 514-515) "Precision can be considered at three levels: repeatability, intermediate precision and reproducibility." Suggested edit (lines 514-515) "Precision can be considered at three levels: repeatability, and intermediate precision" and reproducibility."
EFPIA	516	517	5	Recommendations on Precision expression in Section 5 are not fully aligned with those in 4.3.2.4 (line 396): variance, SD or CV vs SD, RSD(CV) and Confidence interval	Align recommendations in the two sections
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	518	521	5	Term: Proven Acceptable Range for Analytical Procedures Included in ICHQ14	Please delete this term from ICHQ2 Glossary
GE Healthcare, Oslo	522	522	5	Header is on one page while text is on following page	Add page break prior to header for "Knowledge management" to move it above corresponding text.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	522	524	5	Term: Quality Risk Management Included in ICHQ9	Please delete this term from ICHQ2 Glossary
EFPIA	525	525	5	Add QL to Quantitation Limit	Add QL in brackets
EFPIA	526	527	5	suggest replacing word determined with demonstrated	True LOQ is typically much lower than validated LOQ
Medicines for Europe	526	534	10,1	It should be clarified in which part of the dossier the analytical development report/summary should be included	It should be clarified in which part of the dossier the analytical development report/summary should be included
EFPIA	528	528	5	It is not clear what is meant by "reporting threshold"	Suggest to add a definition in the glossary
APIC	531	543		The differentiation of reportable range and working range is not given in any case. In many cases the reportable range and the working range are the same. The working range is validated with the characteristics accuracy and linearity and therefore covers the reportable range.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	531	543	5	Working and Reportable Range: Revision of range definitions	**RANGE** The range of an analytical procedure is the interval between the lowest and the highest results in which the analytical procedure has a suitable level of precision, accuracy and response. (ICH Q2) **REPORTABLE RANGE** The reportable range of an analytical procedure includes all values from the lowest to the highest reportable result for which there is a suitable level of precision and accuracy. Typically, the reportable range is given in the same unit as the specification. (ICH Q2) **WORKING RANGE** Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range willcan lead to anone or more appropriate working ranges. Typically, a working range a correspondings to the lowest and the highest set of sample concentrations or purity levels is presented to the analytical instrument, for which and that the analytical procedure provides meaningful resultsthe respective signal responses are evaluated.
Medicines for Europe	531	534	5	The range is defined as the interval between the lowest and highest reportable results in which the analytical procedure has a suitable level of precision, accuracy, and response. "Response" is not mentioned in the other sections of the guideline that discusses analytical procedure performance characteristics required for the confirmation of reportable range.	The analytical procedure performance characteristics required for the confirmation of reportable range should be consistent through the guideline.
Medicines for Europe	535	537	5	Analytical procedure performance characteristics required for the confirmation of reportable range is not aligned with the requirement listed in other section of the guideline. Line 98-103: Accuracy, precision, and specificity Line 535-537: Precision and accuracy	The analytical procedure performance characteristics required for the confirmation of reportable range should be consistent throughout the guideline.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	544	556	5	Term: Real Time Release Testing Included in ICHQ8	Please delete this term from ICHQ2 Glossary
ANMV	551	551	5	It is worth defining the term replicate	Add the definition of the term "replicate"
EFPIA	554	554	5	Clarification of what a replicate is as this can be interpreted in many ways. 'Replicate' is used in many places throughout the document, and could lead to confusion if not properly defined. There is also confusion between use of the terms 'replicate' and 'analytical procedure' or 'full analytical procedure'. Please ensure clarity throughout the document as regards the differentiation between these terms and the use thereof.	Add the definition of replicate to the glossary. Definition: Replicates are independent preparations, not repeat measures of same sample in the instrument. Additionally, if duplicates are performed and averaged then the number of duplicates equals one value (eg. repeatability would require the analysis of 6 duplicate measurements) Please ensure clarity throughout the document as regards the differentiation between the terms replicate and analytical procedure / full analytical procedure, and the use thereof.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	558	560	5	The use of the word signal here may imply raw signal and could be confused with "signal" in the "signal-to-ratio", which generally is evaluated as raw signal.	Replace "signal" with "value" as follows: "The response of an analytical procedure is its ability (within a given range) to obtain a signal value which is effectively related to the concentration (amount) of analyte in the sample by some known mathematical function"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	561	564	5	Term: Reproducibility While the use of Reproducibility is outside of the scope of ICHQ2 it may be useful to retain the definition in the Glossary, with clarification that it is not in scope.	Current (lines 554-556) "Reproducibility expresses the precision between laboratories (e.g., inter-laboratory studies, usually applied to standardization of methodology). (ICH Q2). Suggested edit (lines 554-556) "Reproducibility expresses the precision between laboratories (e.g., inter-laboratory studies, usually applied to standardization of methodology). *Reproducibility is outside of the Scope of ICH Q2.*
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	561	564	5	Term: Revalidation ISPE recommends moving to in ICHQ14	Please delete this term from ICHQ2 Glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	561	564	5	Term: Robustness It is in ICHQ2 and ICHQ14	Current (lines 561-564) "The robustness of an analytical procedure is a measure of its capacity to meet the expected performance requirements during normal use. Robustness is tested by deliberate variations of analytical procedure parameters. (ICH Q14)" Suggested edits (lines 561-564) "The robustness of an analytical procedure is a measure of its capacity to meet the expected performance requirements during normal use. Robustness is tested by deliberate variations of analytical procedure parameters. (*ICH Q2 an* d ICH Q14)"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	569	576	5	Term: Sample Suitability Assessment It is in ICHQ14	Please delete this term from ICHQ2 Glossary
EFPIA	571	571	5	Linkage of Q2 to Q14: Ensure use consistent use of term 'performance criteria'	Replace acceptance criteria with 'performance criteria'
APIC	577	577			SELECTIVTY to be replaced by SELECTIVITY

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	585	588	5	Term: System Suitability Test It is in ICHQ14	Please delete this term from ICHQ2 Glossary
GE Healthcare, Oslo	588	588	5	Missing a period at the end of the sentence.	Add a period at the end of the sentence.
Andrea Gaggioli - ISS. ITA	590	593	5	TAE never appears in the text of ICH Q2(R2) (only in the Glossary) and the same definition can be applied to the so-called "Uncertainty of Measurement" when calculated by the bottom up approach using data from validation studies.	Consider the option to revise terminology and include the term "uncertainty of Measurement from validation studies"
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	590	593	5	Term: Total Analytical Error It is in ICHQ14	Please delete this term from ICHQ2 Glossary
FUJIFILM Diosynth Biotechnologies Denmark	594	599		You have "validation study" and "validation test" included in the glossary. However, reading the entire draft guideline it does net seem to be implemented consistently and unambiguously. This goes both for the guideline and the tables in Annex 2.	Make sure the same terms are used consistenly and unambigiously everywhere in the guideline
EFPIA	600	600	5	no definition of the term "multivariate" in the glossary	please add into the glossary
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	603	604	5	Term: Calibration Model This term should be relocated from the Glossary (lines 453 – 455) to the Multivariate Analytical Procedure Glossary (lines 603-604)	Current lines 453-455 CALIBRATION MODEL A model based on analytical measurements of known samples that relates the input data to a value for the property of interest (i.e., the model output). (ICH Q2) Suggested edit: Relocate the term and its definition to lines 603-604
EFPIA	605	605	5	The word 'assume' is incorrect	Please replace the word 'assume' with 'achieve'
EFPIA	619	619	5	Align "Internal testing sets" with terminology from EMEA/CHMP/CVMP/QWP/17760/2009 Rev2 uses "Calibration test set"or FDA Development and Submission of Near Infrared Analytical Procedures considers "internal validation set". Consider avoiding creating new terms for supporting harmonization.	Reword using "internal validation set" or "Calibration test set"
Medicines for Europe	638	641	N/A	Is the meaning of "Co-validation" also include "Co-development"? For example, duirng method development, analyst from recieving laboratory participate the testing to get understanding the analytical method. Through this, development can include variability from different analyst, and tech. transfer may obmit the analyst training for validation at the receiving laboratory.	Please make clear the meaning of "co-validation" whether it includes "co-development" or not. If not, how about add "co-development"?
EFPIA	652	654	6	Add references to Q3, Q8, Q9 and Q10	All these documents are referred to in the text. (Not Q3, but this is one of my earlier comments)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	655	658	7	Figure 2 has created confusion in interpretation and requires clarification that it is an example and not considered to be fully comprehensive. Additional emphasis regarding this figure in the training material is requested.	
EFPIA	655	660	7	Figure suggests that Orthogonal Procedures for accuracy and specificity are always required - they are not	Insert footnote to explain that orthogonal procedures are not always required
ECA Foundation / European QP Association	656	657	7	Figure 2 Range is not aligned with bulk text in section 4.2.1 as the title is "response" and not "Calibration model"	Suggest to align wording between sections and according to previous comment on section 4.2.1
Medicines for Europe	656	657	7	The "Table 1: Typical performance characteristics and related validation tests for measured product attributes" uses the terminology "Suitability of Calibration Model" while the "Figure 2: Selection of validation tests based on the objective of the analytical procedure" uses the terminology "Validation of Calibration Model". Both terms seem to denote the same meaning, thus, should be aligned throughout the guideline to avoid confusion. (Or additional clarification should be provided if those two terms were used to carry different meanings)	The terminology for the calibration model should be consistent throughout the guideline (Or additional clarification should be provided if those terms were used to carry different meanings)
PPTA	656	658	7	Figure 2: "Selection of validation tests based on the objective of the analytical procedure" summarizes expectations for the most common purposes of analytical procedures. For Limit Tests of Impurities "Does the procedure confirm impurities are below a given limit?" the Performance Characteristics "Specificity" and "Range" are marked and under "Validation Tests" "Validation of Range Limits" is quoted. A combined line for Range, which covers not only range but also a calibration model, DL and QL is confusing as in this context it suggests for Limit tests a sort of need for determination of a Range (i.e. upper and lower limit of range as well as DL and QL).	Please consider to separate the Performance Characteristics "Range" into two columns: -Range/Suitability of Calibration model -Quantitation & Detection Limit so that the relevant performance characteristics parameters can be clearly described, i.e. Detection Limit applicable but Working Range/Suitability of Calibration model & Quantitation Limit not applicable
APIC	657	657	7	Is the expectation in specificity to always have an orthogonal procedure and is not aligned with table in page 28 line 661; For some analytical procedures it is clear that all validation tests are necessary (e.g precision), but for specificity having mandatory orthogonal procedure is an excess.	
APIC	657	657		The figure 2 does not show the performance characteristics for DL, QL and linearity. Only the range is listed. Especially for limit tests (blue box) naming the range as performance characteristics might lead to missunderstandings. The range is described as reportable range and working range. In case of a limit test both are not meaningfull. Only the DL would be meaningfull here, because the reportable result is less than or more than the limit resp. less than the DL.	
EFPIA	657	657	7	It is described that reproducability is done "if >1 laboratory", which might be missleading. In previous section (4.3.2.3, line 391-394), it is described that "reporducability is ususally not required for regulatory submission but should be considered in case of standardizatio of an analytical procedure, for instance, for inclusion of analytical prodcedures in pharmacopoeias."	Change Figure 2 to "if >1 laboratory and in case of standardization of an analytical procedure, for instance, for inclusion of prodcedures in pharmacopoeias."
EFPIA	657	657	7	In Table 1 (Line 58-59), for assay content/potency, no lower range limit verification is required. In Figure 2, the yellow path for content/potency goes to range without note/footnote that validation of range limits is not required This could be explained by a footnote in the same way as the footnote for calibration model "* may not be needed for limit test"	Add footnote ** to "Validation of range limits": "** may not be needed for assay/content/potency testing.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	657	657	7	specify that the second objective refers to "limit test"	add "limit test" in the second lozange
EFPIA	657	657	7	need to clarify that "range limits" are not refering to QL/DL	add a note to "validation of range limits" cross refering to Table 2.
EFPIA	657	657	7	The text also mentions for accuracy "inferred once precision, response and specificity have been established"	Add a parallelogram with "possibly from precision, response and specificity".
EFPIA	657	657	7	In Figure 2, for a limits test there is no asterisk in the box for Validation of Range Limits. Why is this necessary for a limit test? The validation would focus on the ability to differentiate between those samples that are at or below the limit and those that are over. No need to show ability to differentiate values below the limit.	place an asterisk in the box Validation of Range Limits, or remove Figure 2.
ProPharma Group, Liesbeth van Rooijen	657	658	7	I think in practice "Validation of Range Limits" in this figure means something different for each of the 3 analytical procedure types for which determining "Range" seems to be is relevant according to this figure. If it refers to DL/QL determination: that is not is not a typical performance characteristic for assay methods according to Table 1. That is currently not clarified with for instance a footnote.	Please consider clarification of the figure and/or improve alignment with Table 1 with regard to "Range".
EFPIA	660	687	8	None of the examples is using the combined approach for accuracy and precision / total analytical error	Add at leastr one example using combined approaches for accuracy and precision / Total analytical error
EFPIA	660	661	8	Analytical technique by UV/VIS is commonly used for quantitative determination for protein products.	Recommendation: to add an example of quantitative determination by UV/VIS for product concentration
EFPIA	660	660	8	Consider adding a 'Typical types of change encountered during the procedure lifecycle' row at the bottom of the Illustrative examples tables?	The non-binding example section provide opportunity to exemplify the typical changes and signpost 'points to consider' for change category assignment? In particular if these examples are ultimately in a separate document and can be expanded.
EFPIA	660	660	8	Consider adding an example for cleaning method validaiton.	
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	660	600	8 Annex 2	Please consider adding an example of validation of flow cytometry for biological products. It is a major method for cell therapy products; the field would greatly benefit from guidance on an appropriate ICHQ2 validation strategy.	ISPE would be happy to provide SMEs to generate an example of method validation for flow cytometry methods to further enhance the value of ICHQ2(R2) Annex for biological products.
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	660	660	8 Annex 2	Please consider adding an example of validation of UV/VIS is commonly used for quantitative determination for protein products. It is a major method for biological products; the field would greatly benefit from guidance on an appropriate ICHQ2 validation strategy.	ISPE would be happy to provide SMEs to generate an example of method validation for UV/VIS methods to further enhance the value of ICHQ2(R2) Annex for biological products.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	660	661	Table 3	Among performance characteristic, Range is expressed as Reportable range. Is it default suggestion? If our company determined to using Working range as a default value, is it acceptable? It may depends on methodology and justification within the minimum requirement in guideline. But since the range is divided into two concept, needs to be clarified.	N/A
PPTA	660	660	8	SEC-MALS is a common and useful technique for evaluating molecular weight distribution for large molecules and particle size distribution for nanoparticles including liposomal formulations. Annex 2 does not include an example for evaluation of validation parameters.	Please consider adding examples in Annex 2 for SEC-MALS and newer multivariant analytical procedures (e.g. Near Infrared (NIR), Raman, Nuclear Magnetic Resonance, and Mass Spectroscopy) and hybrid techniques (e.g. LC-MS).
EFPIA	661	688	8	Annex 2: Either, additional clarity should be provided emphasizing that Annex Tables 3 – 11 are examples only, or consideration should be given to moving the tables from the main guideline and into the training materials.	
EFPIA	661	688	8	Annex 2: In some cases, the details are more restrictive than e.g. USP requirements, and so revision of the details should be considered.	
EFPIA	661	688	8	Annex 2: Where multiple examples are provided for assessing a performance characteristic, it needs to be clarified that these are options and that not all are required.	Ensure that 'and/or' is detailed where multiple example approaches are provided.
EFPIA	661	662	8	Annex 2: Table 3 also requires greater clarity regarding the difference between the two columns provided.	Simplify Techniques to 'Quantitative Impurity / Assay' and 'Relative Area Quantitation'.
EFPIA	661	661	8	Accuracy: the information of the recommended data (3 concentrations / 3 replicates)	Accuracy: the information of the recommended data could be included as it is done for other criteria such as repeatability; for coherence purpose
EFPIA	661	661	8	Reportable range: validation of lower range limits QL, DL: add the possibility to define / validate based on standard deviation /slope (4.2.2.2) & on accuracy/precision at lower range limits (4.2.2.3)	include the also other possibilities; else this suggests that these other possibilities are less suitable
EFPIA	661	662	8	There is not statement about inference of accuracy for the left column (separation techniques for impurities or assay)	Add the statement about inference of accuracy from precision, etc in the left column of Table 3.
EFPIA	661	661	8	In Table 3 in the row for 'Specificity/Selectivity', stabililty indicating properties re mentioned, but there is nothing in the main body of the guidance on this.	Update relevant section in the guidance
EFPIA	661	661	8	On Page 25, Table 3, Reportable Range, Right Column: Should it be "Section 4.2", instead of "Section 5.2"	Should it be "Section 4.2", instead of "Section 5.2"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	661	663	8 Table 3	While ISPE appreciates the inclusion of a validation example for Separation assays in ICHQ2(R2), we note the examples are missing some elements of quantitative separation method for biological products for purity/impurities; we also have other editorial and technical comments Please consider updating the example to include quantitative separation method for purity/impurities of biological product (eg SEC)	ISPE would be happy to provide SMEs to generate example of method validation for SEC to further enhance the value of ICHQ2(R2) Annex for biological products.
Medicines for Europe	661	662	8	table 3: "Reportable Range": reportable range for impurity testing according to page 5 table 2 is defined by reporting threshold - 120 % of specification limit. The information provided in Annex 2 is not congruent with this table and includes for reportable range Qantitation Limit. That is also in contrast to the definition in ICH Q3B(R2): the reporting threshold for impurities is defined by maximum daily intake	Maybe it would make sense to distinguish between impurities according to ICH Q3B(R2) measured by separation techniques (HPLC/UPLC, GC, CE): and for this to define only validation of reportable range (reporting threshold - 120 % of specification limit) and estimation of quantitation limit to confirm that QL is equal or lower to reporting threshold and for quantitative LC/MS to define reportable range with quantitation limit - 120 % of specification limit
Medicines for Europe	661	662	8	As separation techniques are stated: HPLC, GC, CE. In the meantime UPLC or Hybrid systems are more and more introduced. It should be stated like LC/MS: in generell LC techniques	Separation techniques (LC, GC, CE)
Medicines for Europe	661	661		In the example for Quantitative separation techniques (Table 3) the second column does not clearly demonstrate/define which options should be evaluated. For example - "Specificity" / "Selectivity" - among which options is the choice? "Spiking with known impurities / excipients" and "By comparison of impurity profiles by a secondary method" or is it among "With DS, DP, buffer, or appropriate matrix, and between individual peaks of interest. Spiking with known impurities / excipients" and "By comparison of impurity profiles by a secondary method. Demonstration of stability-indicating properties through approprate FD samples, if necessary."	Please, define more clearly.
Medicines for Europe	661	661		Please, define in more detail what you mean by "accuracy can be inferred once precision, linearity and specificity have been established".	Please, define more clearly (although already included in the current version of ICHQ2(R1).
Medicines for Europe	661	661		In the example for Quantitative separation techniques (Table 3) - validation test "Reportable range" in the third column it is not clear why measured relative result versus theoretically expected relative result should be presented.	Please, define more clearly or delete.
Medicines for Europe	661	661		Since "Reporting Level" is relevant data for all applications of the analytical procedure that is to be validated, it should be stated that linearity and accuracy are performed in the range from Reporting Level to upper working range.	Please, define the proposed range in more detail (e.g from reporting level to upper working range).
Medicines for Europe	661	661	Table 3	Validation of lower range limits: QL (and DL) through selected methodology from Section 5.2 (e.g., signal-to-noise determination). -> Section 5.2 is typo.	Correct typo to Section 4.2.2
EFPIA	662	662		Reportable range: Validation of the reportable range	The wording "validation of calibration model across range" is confusing. Indeed the purpose of the method validation is not only to validate the calibration model. As exemple, the precision is not directly related to the calibration model.
EFPIA	664	664	8	In the right column, for reportable range the text says "Validation of calibration model across the range". In this case it is not a calibration model (because result is a ratio without the use of a calibration standard). Proposal to adapt the text	Proposed adaptation: "Validation of **quantification** model across the range"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	664	665	8	Up to now, robustness testing was not required for elemental impurity methods by ICP-OES or ICP-MS and this was well accepted by all health authorities. Therefore, I strongly recommend not to introduce it now. In addition, the content of Table 4 is not aligned with USP chapter 233 on elemental impurities. This chapter states that linearity, range and QL are addressed by the corresponding accuracy experiments at 50%, 100% and 150% level. We should align ICH Q2 text with the requirements as per USP and not go beyond.	Please consider removing requriement
EFPIA	665	665	8	Confusion between working range and reportable range	Clarification needed
EFPIA	668	669	8	Specificity / selectivity for a dissolution procedure addresses the specificity / selectivity of the quantitation method, but not the specificity of the dissolution test procedure. The discrimatory power of the dissolution test procedure needs to be justified in the method development report and is part of the method design / development, but is not addressed as part of method validation. Please also refer to USP chapter 1092 on The dissolution procedure: Development and validation.	Please consider removing requriement
FUJIFILM Diosynth Biotechnologies Denmark	668	671	Table 5	Table 5 should be aligned with USP <711> and USP <1092>	
Medicines for Europe	668	669	8	Table 5: Reportable range: up to 120 or 130%? (see Line 107, Table 2: High end of reportable range is 130%. In this Table 5. up to 120%)	
EFPIA	669	669	8	Quantitation instead of quantification to make the wording alligned in the overall document	Replace quantification by quantitation
EFPIA	669	669	8	Precision and Intermediate Precision: Demonstration with a homogeneous sample from one dissolved tablet, e.g., several samples drawn from the same vessel, after analyte in sample has been fully ~~solubilized~~	Precision and Intermediate Precision: Demonstration with a homogeneous sample from one dissolved tablet, e.g., several samples drawn from the same vessel, after analyte in sample has been fully **dissolved**
EFPIA	669	669	8	Reportable range: Q-45% up to 120% of label content inconsistent with Table 2 (line 107) where reportable range is described as Q-45% upt ot 130% of declared content .	
EFPIA	669	670	8	For Specificity/Selectivity under Discriminatory power - this example implies that there are batches made that are unacceptable. In many cases no unacceptable batches are made during process optimization or design space mapping.	Suggest adding ", if applicable" after ".....versus non-acceptable batches"
EFPIA	669	669	8	Precision under validation testing methodology - this is demonstrating the sampling precision by analyst or autosampler, not the method as it should be run	Precision should be looked at across vessels, not within a vessel.
Genepharm S.A.	669	669	8 Table 5	In the precision determination of testing methodology the analysis of replicate samples from the same vessel/ solution is described. Isn't this equivalent to system precision? Can it be replaced by replicate injections of a standard solution?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	669	670	8 Table 5	While ISPE appreciates the inclusion of a validation example for dissolution assays in ICHQ2(R2), we note in Table 2 that the reportable ranges for common uses of analytical procedures (lines 107-108) states upper limit for dissolution on 130% of declared content of dosage form. However, this conflicts with the Tablet 5 example of dissolution test validation states up to 120% Please harmonize these two values for upper dissolution limit	Current (table 5 column 3 row 5 Reportable Range) "Linearity: Demonstrate linearity from sample concentrations (as presented to quantitative measurement) in the range of Q-45% up to 120% of the content stated on the label, for immediate-release solid dosage forms." Suggested edit (table 5 column 3 row 5 Reportable Range) "Linearity: Demonstrate linearity from sample concentrations (as presented to quantitative measurement) in the range of Q-45% up *to 130%* of the content stated on the label, for immediate-release solid dosage forms."
ECA Foundation / European QP Association	673	674	table 7	Specificity can be inherently given by the underlying scientific principles of binding assays. Ligand binding assays uses the unique ability of the ligand to bind its target receptor, or antibody binding to antigen.	Suggest to add that specificity can be justified inherently
ECA Foundation / European QP Association	673	674	table 7	Recommendation to evaluate precision and accuracy combined as it is not possible to obtain a reference material or a "true" value/sample to assess accuracy alone.	Recommend combined precision and accuracy. E.g. 5 levels in 3 replicates over multiple days/analysts/preparations (normal laboratory variation)
ECA Foundation / European QP Association	673	674	table 7	There is no evaluation of the calibration model. See previous comment to 4.2.1.2	
EFPIA	673	673	8	example for biological assays, robustness: impact of sample degradation should not be in Robustness section but in specificity/selectivity	remove "impact of sample degradation" from robustness part of the table
EFPIA	673	673	8	Table 7 states that accuracy must be studied at minium 5 levels. There is no scientific rationale for 5 levels should be needed for binding and cell-based assays, whereas 3 are aufficient for other technologies.	Reduce the number of levels to 3 or add rationale for using 5.
EFPIA	673	674	8	Table 7: Specificity/Selectivity: No response from "cell line only" is only true for cell-based assays, but this concept should cover all types of assays.	change to: "No dose-response in the absence of sample."
EFPIA	673	674	8	Table 7: Accuracy: Does it need to be reference material? Can it be any appropriate sample (e.g., RM)?	Rewrite text to allow for the use of an appropriately characterized material (e.g. GMP lot) in addition to the reference standard
Gilead	673	674	Table 7	Example in Annex 2 (Table 7) for a binding/cell-based assay list example validation method approaches for repeatability and accuracy is inconsistent with the guidance. Example states NLT 5 levels but ICH Q2 states 3 levels for repeatability (line 378) and accuracy (line 350)	To align the example in Annex with the guidance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	673	673	8 Table 7	While ISPE appreciates the inclusion of a validation example for in vitro potency assays in ICHQ2(R2), we note that only the USP <1033> element are given in the example. Numerous ICHQ2 elements of in vitro potency method validation are missing from the example here. We also note that ICHQ14 presents a very lengthy Annex on in vitro potency assay lifecycle which includes an outline for validation. To avoid duplications between guidance documents, ISPE recommends removing the potency assay validation elements from ICHQ14 and referencing ICHQ2 for the validation example.	ISPE would be happy to provide SMEs to update the ICHQ2 validation elements that are missing in the in vitro bioassay examples in ICHQ2. Please remove the duplicated method validation example from ICHQ14 section on method lifecycle. Also, ISPE recommends summarizing the extensive in vitro potency QbD example in ICHQ14 then publishing the full details separately as detailed ICH training materials.
Medicines for Europe	673	673	8	Table 7:Bioassay: It would be appreciated to make it clear whether the measurement procedure and evaluation of performance characteristics have to be referred to the single values or reportable values ?	
Medicines for Europe	673	673	8	Table 7: Bioassay: Repeatability: Why is it required to measure with 3 replicates at 5 levels? Generally a bioassay can not be measured within a short interval of time so the intermediate precision can be the relevant performance characteristic for the evaluation of a bioassay precision using different concentration levels with replicates. So is the repeatability necessary?	Repeatability: at the nominal concentration with 6 replicates or NLT 3 levels with NLT 3 replicates /level. Intermediate precision: at multiply levels (NLT 5 levels with NLT 3 replicates /level))
Medicines for Europe	673	673	8	Table 7: Bioassay: Robustness: Impact of sample degradation: Does it mean the degradation during sample preparation?	
PPTA	673	673	Table 7	Table 7 as example for biological assays is very helpful, however, some ambiguities remain: Repeatability: NLT 3 replicates at not less than 5 levels. Does this need to be done, even when the routine method is carried out with 2 replicates at 4 levels? The result does not reflect the routine method then. Or does it mean that the samples are to be prediluted with 5 different factors and this is to be repeated three times resulting in 2x4x5x3=120 measurements for repeatability? For intermediate precision, which usually reflects better method variation, no such requirements are provided. Accuracy: The in-house reference standard is typically calibrated against the primary reference standard in 6-12 independent runs (3 runs would not be precise enough). However, it is not clear why this has to be done at 5 different concentrations, if in a routine assay the reference standard is always used at the same concentration? Reportable Range: Please confirm that this is not the range given by the dose response curve but a deliberate different range compared to the reference standard (e.g. 80%, 90% , 100%, 110% and 120%) of the reference standard.	Please provide more details/ clarify as per the examples in the comment.
EFPIA	676	676	8	Technique is referred to as Gel Electrophoresis for the separation and analysis of macromolecules.	Specificity/ Selectivity Orthogonal Procedure Comparison: Test reaction specificity by **gel** electrophoresis ~~gel~~, melting profile or DNA
EFPIA	676	677	8	"Intermediate precision Comparison of measurements using the same procedure performed by another analyst on a different day." The word COMPARISON is not appropriate. What is assessed is variability	Adapt vocabulary to ICH Q2 definition

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	676	676	8	Currently says "…range should cover 5 to 6 log…". While qPCR is capable of a very broad linear range, 3 to 4 logs is usually sufficent for practical use. Suggest changing "should" to "may" and "at least" to "or more".	…range may cover 5 to 6 log…or more
EFPIA	676	676	8	Would it be worthwhile providing an example of the approach to be undertaken for a limit test as well?	Add a column to Table 8 for qPCR limit test.
EFPIA	676	677	8	Table 8: Precision: Repeatability: This doesn't seem clear - how is the sd derived?	Rewrite text to provide clarity how the SD is derived
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	676	677	8 Table 8	While ISPE appreciated the inclusion of a residual DNA method validation in ICHQ2(R2), the example is missing ICHQ2 validation of DNA calibration curve; other technical edits and editorial changes to the example ISPE recommends updating the example with the DNA calibration curve requirements	ISPE would be happy to provide SMEs to update the DNA method example with ICHQ2 validation of DNA calibration curve
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	678	681	8 Table 9	While ISPE appreciates the inclusion of a Light Scattering method validation, in ICHQ2(R2) we note that the validation requirements are different between LD and DLS in some instances. ISPE is concerned this may create substantial confusion on validation strategies appropriate for the two different methods.	ISPE suggest splitting the table into two columns, one for light diffraction and the other for DLS. Alternative, there could be two separate tables, one for each.
Medicines for Europe	678	679	8 Annex 2	It is not clear which parameters should be evaluated for specificity of laser diffraction	The number of particles/detection number could be an indication of the blank sample
APIC	679	679	8	In particle size measurements, we do not assess specificity/selectivity nor we assess the reportable range. We do not analyze a blank before standard or sample measurements (we analyze the background before measuring a sample and that must meet an acceptance criterion defined in the analytical method/validation protocol). We analyze the samples and assess precision of the results, taking into consideration that the method was developed for the particle size range defined in the product specification. Can the reportable range be clarified?	
EFPIA	679	680	8	Annex 2: Technology description is unclear in Table 9	Clarification that it is not describing particle measurement for biologics is required
EFPIA	679	679	8	Validation requirements are different between LD and DLS in some instances. This may add to confusion and labs force fitting testing that is irrelevant or unnedded depending on technique.	Split table into two columns, one for light diffration and the other for DLS. Or, have two separate tables for each.
EFPIA	679	679	8	Specificity and Selectivity is not appropropriate for these techniques as the techniques can not distinguish between individual or types of particles.	Add text: Typically not applicable but, {then original text}
Medicines for Europe	679	679	Table 9/ Accuracy	"appropriate instrument qualification" for showing system accuracy is quite general.	Please explain how qualifying a system in a general range provides
PPTA	679	680	8	Electron microscopy is a common and useful technique for evaluating particle size and morphology. Particularly, cryo-electron microscopy is a technique that can provide 3D density maps at near-atomic resolution. It is important to update the performance characteristics for particle size measurement with electron microscopy requirements.	Please consider to include electron microscopy performance characteristics for particle size measurement with electron microscopy.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	682	685	8 Table 10	While ISPE appreciates inclusion of an NIR method validation in ICHQ2(R2), we would like to request a slight clarification on measures for accuracy to include 'mean bias'.	Current (Table 10, column 2, row 3) Accuracy is typically reported as the standard error of prediction (SEP or RMSEP) Suggested edits (Table 10, column 2, row 3) (highlighted in italics) Accuracy is typically reported as the standard error of prediction (SEP or RMSEP) *and mean bias."*
Orion Corporation	682	684		Table 10 is a NIR method validation example for core tablet assay. Same validation testing methodology can be used also for Raman Assay.	Table 10 Title NIR to be changed to NIR/Raman. Technique: NIR/Raman method validation example for core tablet assay Robustness: Chemical and physical factors that can impact NIR/Raman spectrum Note: NIR/Raman measurements are sensitive to changes in tablets composition and properties outside variation present in the calibration set.
EFPIA	683	683	8	This provides the analyst more flexibility. The regression coefficient, especially with models with > 1 latent variable, is the more critical metric relating which variables are more impactful to the model.	Performance characteristic –Specificity/Selectivity) Absence of interference: Comparison of API spectrum and the loadings plots **and/or regression coefficient** of the model
EFPIA	683	684	8	Accuracy: After "...(RMSEP or SEP)", please add "and mean bias".	Clarification of measures for accuracy.
EFPIA	683	684	8	Specificity/Selectivity: Rejection of outliers (e.g., excipient, analogues) not covered by the multivariate procedure. Proposed change: Rejection of outliers (e.g., excipient, analogues) not covered by the validation procedure.	The refection of outliers is covered during the internal testing according to lines 614-615, so it is covered by the multivariate procedure.
EFPIA	683	684	8	Table 10. NIR, confirm that"well-defined secondary procedure" can be other than the reference procedure	
EFPIA	683	684	8	Additional clarification on Repeatability shall be added regarding the precision is done by analyzing the same tablet multiple times with tablet reposition OR by analyzing different tablets from the same batch.	Add clarification on Repeatability regarding the precision is done by analyzing the same tablet multiple times with tablet reposition OR by analyzing different tablets from the same batch.
APIC	686	686	8	For DL, responses should not be taken in consideration for calculations, as this level is below the QL. We apply a criterion of s/n not less than 3 with two different preparations (one injection each). The statistical variation at DL level does not seem relevant, as DL is below a quantifiable level and is not used for range definition.	
Dr. Uwe Lipke as Member of EDQM Group of Experts 7	686	686	8, Table 11	Row "specificity / selectivity" – Absence of interference: The potential for ion suppression during ionisation resulting in non-detection of peaks of interest should be explicitly mentioned here.	Add under the heading "*Absence of interference*" the following: "*no ion suppression for the peak of interest.*"
EFPIA	686	686	8	Under intermediate precision, it is stated "Comparision of measurements of the same samples made in different laboratories." This is in contradiction to the definition of intermediate precision ("within-laboratory variation").Nevertheless, it is appreciated that different labs should be allowed, considering that number of LC-MS instruments within a lab can be limited.	List this option under reproducability and allow to use reproducability instead of intermediate precision.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	686	687	8	"Measurements of the same samples performed in the same laboratory but under varying conditions (e.g., different LC/MS systems, different analysts, different days). ' instead of 'Comparison of measurements of the same samples performed in the same laboratory but under varying conditions (e.g., different LC/MS systems, different analysts, different days). " The word COMPARISON is not appropriate. What is assessed is variability	Adapt vocabulary to ICH Q2 definition
EFPIA	686	686	8	Confusion between working range and reportable range	Clarification needed
EFPIA	686	687	8	Replace "MS drying/ desolvation temperature, MS gas flow" with "optimise ion source parameters, which may include MS drying/ desolvation temperature, MS gas flow, ion transmission (fragmentor/cone) voltages"	Only a limited number of specific ion source parameters have been highlighted and there are more that should be considered.
EFPIA	686	686	8	Consider the 'Technology Inherent Justification' approach in the Accuracy of LCMS. If the instrument is perfoming within qualified parameters, the measured mass should be very close to the 'accepted true value' i.e. the theoretical mass	
GE Healthcare, Oslo	686	686	8 (Table 11)	Inconsistent use of LOQ for quantitation limit. The abreviation QL is used throughout except in this table.	Change LOQ to QL
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	686	688	8 Table 11	While ISPE appreciates the inclusion of quantitative LC/MS validation in ICHQ2(R2), we have suggestions to expand the example to cover numerous additional ion source parameters.	ISPE would be happy to provide SMEs to update the LC/MS method parameters to improve the value of the example by expanding the application for other ion source parameters.
Medicines for Europe	686	686		Regarding the example for Quantitative LC/MS (Table 11) - validation test "Precision" - "Repeatability": we do not find the measurement of at least three replicates at each of at least three spiking levels necessary. For example, if we prove that the analytical procedure is repeatable at QL, it will also be repeatable at the specification limit.	We suggest to change the recommendation to measuring at least six replicates at QL or at the Reporting Level or at least add this as another possibility.
Medicines for Europe	686	686		Regarding the example for Quantitative LC/MS (Table 11) - validation test "Reportable Range": we do not believe validation of DL and QL using LC/MS makes sense and gives any additional value to the validation. The sensitivity of the instrument is highly dependent on its cleanliness (the efficiency of ionization in the ionic source and the efficiency of ion transmission to the detector) and can vary greatly from day to day.	We suggest to remove the requirement for DL and QL determination or state it in a similar way as in the Table 3 (QL, DL through one selected methodology, e.g., signal-to-noise determination).
Medicines for Europe	686	686		Regarding the example for Quantitative LC/MS (Table 11) - validation test "Robustness": given the very powerful and specific nature of the mass spectrometer, we believe that many of the recommended parameters to be deliberately varied are meaningless - especially the variation of MS parameters (gases, temperature, mass accuracy and collision energy). According to our opinion, the SST criteria, stated in the analytical procedure, should be enough and such rigorous testing is unnecessary.	We suggest to remove recommendation for variation of MS parameters.
Medicines for Europe	686	686	Table 11/ Intermediate precision	Proficiency testing (interlaboratory) is combined with intralaboratory testing and expressed as mandatory to execute both to justify intermediate precision. Please divide the inter and intra-laboratory testing and let the interlabaratory testing optional.	Reproducibility Comparison of measurements of the same samples made in different laboratories.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	686	686	Table 11/Reportable range/validation of lower range	To be more specific concerning quantitative and qualitative ions in MRM cases	e.g S/N of the Quantitative and qualitative ion in LOQ concentration should be >10 or For the Quatitative ion only the S/N at LOQ level should be more than/or equal to 10.