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Submission of comments on ICH guideline Q2(R2) on validation of analytical procedures, Step 2b EMA/CHMP/ICH/82072/2006

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
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Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
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.
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."

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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.”*
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.

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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.	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." 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-

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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." 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***
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."*

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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."*
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."
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."*

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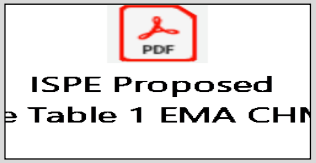
International Society for Pharmaceutical Engineering (ISPE) Transparency Register 316626227774-56	58	72	Table 1	ISPE is concerned that Table 1 remains heavily biased towards chemical products in the terms used in the header for product attributes. Although Table 1 is very efficient, it is challenging 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: 
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
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"

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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."
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"*

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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 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. 3.4.1. Reference analytical procedure(s) " And Current (lines 258 – 265) "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." And 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
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."*

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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.*
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".*
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.

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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."*
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)
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.*
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.*

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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).
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."
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)
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.
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
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

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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
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
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
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
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
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

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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
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.”~~
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
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
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

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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
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
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
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

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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.
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.
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."
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.
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

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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.
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."*
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.