Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	1. Introduction	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.						
	1. Introduction	32	32	1	Its not 'the' SST	change 'the' to 'a'						
	3. Analytical Procedure Validation Study	69	69	3	(3) in the table is related to specificity. In the explanation it refers to accuracy and precision	Correct the reference with (4)						
	3. Analytical Procedure Validation Study	70	71	3	(4) in the table is related to accuracy and precision. In the explanation it refers to specificity	Correct the reference with (3)						
	3. Analytical Procedure Validation Study	72	72	3	The table does not mention reproducibility and the footnote is an explanation that the approach of testing reproducibility and intermediate precision can be made as a single experiment. Therefore, it should rather be described in section 4.3.2.3 Reproducibility than in a table footnote.	Move Footnote to section "Reproducibilty"						
	3 ANALYTICAL PROCEDURE VALIDATION STUDY	84	85	Fig. 1	The term “platform knowledge” is more broad and more suitable to Fig 1 than “platform method/analytical procedure” as encompasses analytical procedures, analytical technologies and prior knowledge. ICH Q2(R2) and ICH Q14 recognizes the use of platform analytical procedures and technology. However platform knowledge is not present in figure 1. “Platform knowledge” refers to prior knowledge of platform methods or platform technologies that can be applied to multiple products. It is commonly used for biologicals, but not	Suggestion to add "platform knowledge" as a bullet point on the left that can inform Validation protocol design.						
	3.1 Validation during the lifecycle of an analytical procedure	95	95	3,1	No reference to the term bridging studies	Please clarify if the cross validation concept includes the bridging studies. Bridging is a common term used for the comparison of different analytical procedures (new with old)						
	3.1 Validation during the lifecycle of an analytical procedure	96	97	3,1	cross validation is not examplified. Can we use it for concomittant validation of online and offline methods?	The cross validation could be used in the context of simultaneous validation of an on/in/atline and an offline method. The glossary definition of cross validation must include the multivariate methodologies.						
	3.2 Reportable Range	107	107	Table 2	For dissolution testing, the follow range are considered in the ICH Q2(R2): Low end of reportable range: Q-45% (immediate release) of the dosage form strength first measurement timepoint or QL (modified release) High end of reportable range: 130% of declared content of the dosage form	For dissolution testing, it is proposed to change the ranges to: Low end of reportable range: -20% rel of first measurement timepoint or QL. High end of reportable range: +20% of declared content of the dosage form. Justification: Immediate release forms can be classified as rapid and/or very rapid dissolution and in some cases the range fall in within the example provided of Q-45%. But this is not always true and dissolution range is product formulation dependent. Stated as it is, the information can be mislead and for all immediate release products to be used as general rule Q-45%. Proposal is in line with majority of the guideline in the subject. High end was also updated from 130% to 120%,						

Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	3.3 Demonstration os stability indicating properties	109	116	3,3	Some procedures are stability indicating per design ex: the quantitative measurement of a degradation product. In that case performing challenges (degradation,…) does not add value as long as the procedure has been demonstrated to be accurate.	Proposal to add after the section: "In some cases, and depeding on proper justification as well as validation of other parameters, the demonstration of the stability indicating capacity of a procedure is not necessary. For instance the demonstration of specificity, accuracy, precision, and linearity of a procedure used for the quantitative determination of an impurity can be sufficient to						
	3.3 Demonstration os stability indicating properties	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						
	3.4.1 Reference analytical procedure(s)	136	136	3.4.1	delete the word require							
	4.1 Specificity / Selectivity	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 procedure that is fit for purpose.						
	4.2.1.1 Linear Response	226	228	4.2.1.1	I'm missing the visual assessment of the data prior to linear regression analysis. ICH Q2(R1) requires visual assessment of the data as prerequisite for linear regression analysis. This requirement is very meaningful, as data from linear regression analysis, especially correlation coefficient, do often not show that linear relationship is missing. Therefore, I propose to add the corresponding sentence from ICH Q2(R1). If visual assessment is no longer required, the statistical assessment of any non-random pattern should be changed to mandatory, not 'helpful' as currently stated.	Initially, linearity can be evaluated visually with a plot of singals as a function of analyte concentration. If there is a linear relationship, test results should be evaluated by appropriate statistical methods.						
	4.2.1.1 Linear Response	237	237	4.2.1.1	Note clear what is meany by 'Other approaches shoud be justified' on line 237	remove 'Other approaches should be justified' from line 237						
	4.2.1.1 Linear Response	238	246	4.2.1.1	The mention of the weighting factor in the reviewed guideline makes the options of mathematical transformation more strict than the current version. “ICH Q2(R1): In some cases, to obtain linearity between assays and sample concentrations, the test data may need to be subjected to a mathematical transformation prior to the regression analysis. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity.” “ICH Q2(R2): To obtain linearity, the measurements can be transformed, and a weighting factor applied to the regression analysis (i.e., in case of populations of data points with different variability (heteroscedasticity), including log or square root). Other approaches should be justified.”	Proposed to keep the wording of current ICH Q1(R1) for the mathematical transformation, and add the weighting factor application to heteroscedastic data as example. This would allow for more flexibility in the use of mathematical transformations. “To obtain linearity, the measurements may need to be subjected to a mathematical transformation prior to the regression analysis. E.g. when data set presents unequal variability (heteroscedasticity), a weighting factor can applied to the regression analysis, including log or square root.”						
	4.2.1.2 Non-linear Response	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.						
	4.2.1 Response	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	Propose: 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						

Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	4.2.2.1 Based on signal-to-noise	269	269	4.2.2.1	Maybe we could provide guidance how the baseline amplitude is defined.							
	4.2.2.2 Based on the Standard Deviation of a Linear Response and a Slope	292	292	4.2.2	DL/QL determincation based on the Standard Deviation of the Blank Measurement of the magnitude of background response is performed by analysing an appropriate number of blank samples and calculating the standard deviation of the responses Explaination is needed on use of this approach. (Stuart W - what it should say here is that this approach is only feasible when there is a measureable background signal in the blank which is at least 10 times the noise, for example measuring Ca by ICP when there is always a background of Ca. For empty blanks in chromatography it cannot be used.)	It is recommended that scope of determing the DL/QL with this method shall be explained in brief. There is no clarity how this approach is used to calculate DL/QL. It is not very popular in the industry and perhaps not being used.						
	4.2.2.2 Based on the Standard Deviation of a Linear Response and a Slope	298	298	4.2.2	Based on visual evaluation should be marked as an independent sub-chapter in analogy to "4.2.2.1 Based on signal-to-noise"							
	4.2.2.2 Based on the Standard Deviation of a Linear Response and a Slope	298	302	4.2.2.2	DL and QL estimation based on visual evaluation should be one chapter level up. Seems to have been put under chapter 4.2.2.2 by mistake	"Based on visual evaluation" should be on same sub-chapter level as 4.2.2.1, 4.2.2.2 and 4.2.2.3						
	4.3 Accuracy and Precision	320	415	4.3	There is no reference to replication strategy / assay format and the link with procedure performance (specifically with precision). This section should express the requirement to evaluate precision data in the assay format corresponding to the replication strategy selected for the procedure.	Proposal to add the following text: "4.3.4 Replication strategy The results of Precision must be representative of the replication strategy / assay format selected for the procedure as the final result of a procedure can be						
	4.3.1 Accuracy	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).						
	4.3.1.4 Recommended Data	355	360	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	Proposed: Change "should be" to "can be" on line 356 to provide additional flexibility in approach						

Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	4.3.1.4 Recommended Data	355	358	4.3.1.4	The proposed statistical evaluation for accuracy contradicts the recommended sample size in row 349 to 351, as the risk of inflating the confidence interval based on low sample size is high, and would not enable correct evaluation of the method characteristics. Therefore, we should keep flexibility in choosing an appropriate approach for accuracy evaluation.	Accuracy should be reported as mean percent recovery by the assay of the known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals. An appropriate confidence interval 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. Alternatively, direct comparison of the mean percent recovery or the difference between the mean and accepted true value against the acceptance criterion may be applied.						
	4.3.1.4 Recommended Data	362	362	4.3.1.4	Definition of "major analyte" not given							
	4.3.2 Precision	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	Replace investigation by demonstration or a word of a similar meaning as demonstration.						
	4.3.2 Precision	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.						
	4.3.2.2 Intermediate Precision	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 combine the examination of several effects** is encouraged.						
	4.3.2.2 Intermediate Precision	389	389	4.3.2.2	Intermediate Precision The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the	In precision test -new evalaution factor, environmental condition have been included. It is recommanded to explain what is expected under this condtions. Usually in lab temperature is controlled between 15 to 25 degree. However there would not be 100 % controll						
	4.3.2.3 Reproducibility	391	391	4.3.2.3	Is this co-validation?							
	4.3.2.3 Reproducibility	392	392	4.3.2.3	Is reproducibility not a relevant aspect during co-validation that is submission relevant?							
	4.3.2.4 Recommended Data	396	398	4.3.2.4	Ambiguous reference to a confidence interval under recommended data for Precision	Add clarity to what confidence is requested or remove confidence interval as a recommended result/data						
	4.3.2.4 Recommended Data	396	398	4.3.2.4	Recommended data for Precision requires the upper CI for the CV. There is an impact on the n° of replicates to be performed in order to obtain a reasonable upper CI.	To better clarify the use of CI						

Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	4.3.2.4 Recommended Data	399	400	4.3.2.4	"Additionally, for multivariate analytical procedures, the routine metrics of RMSEP encompass accuracy and precision". RMSEP = standard error of prediction. More details needed to understand what it is and also more details or examples of multivariate procedures.							
	5. Glossary	425	599	5	Glossary should include a definition of replication strategy.							
	5. Glossary	425	650	5	Add definition for orthogonal procedure to the glossary.	~~Orthogonal procedure: an analytical procedure using a different analytical principle~~						
	5. Glossary	425	0	5	The glossary lists several terms which are not explicitly mentioned in ICH Q2, but only in ICH Q14. I recommend to limit the glossary to these terms which are used in ICH Q2.							
	5. Glossary	434	650	5	There is no requirement to include in a glossary the explanation of terms that are not used anywhere else in this guideline - superfluous and makes the document longer than it needs to be and more challenging to find terms that are actually included. If they are important deifintions for terms used in other guidances then they should be included in the glossary of those.	Remove definitions of the following: ANALYTICAL PROCEDURE ATTRIBUTE ANALYTICAL PROCEDURE CONTROL STRATEGY ANALYTICAL PROCEDURE PARAMETER ANALYTICAL PROCEDURE VALIDATION STRATEGY ANALYTICAL TARGET PROFILE (ATP) CRITICAL QUALITY ATTRIBUTE (CQA) ESTABLISHED CONDITIONS (ECs)						
	5. Glossary	457	462		The definition of "analytical control strategy" is missing - here only reference to ICHQ10 is given.	Add reference to Q14						

Submitted to (for ICH admin use ONLY - add relevant ICH Member)	Part of Guide	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale - Justificativa (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) - Proposta de alteração	Comment Category	Theme	Cross-reference	Current Status	ICH Comment	ICH Disposition
	5. Glossary	463	467	5	co-validation should also include the notion of "initial" validation, not only a "re-validation"							
	5. Glossary	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							
	5. Glossary	475	475	5	Add DL to Detection Limit	Add DL in brackets						
	5. Glossary	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						
	5. Glossary	525	525	5	Add QL to Quantitation Limit	Add QL in brackets						
	5. Glossary	535	543	5	Distinction betwen working range and reportable range is not very precise, where working range produces "meaningful" results. The examples often include "linearity" in working range. Examples for reportable range include detailing results that exceed specs but are accurate and precise at those	Add distinguishing qualities to working range (as opposed to) reportable range and/or define "meaningful" results.						
	5. Glossary	541	543	5	"sample working range" and "instrument working range" should be better explained / defined							