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An agency of the European Union

27 July 2022

Submission of comments on ICH guideline Q2(R2) on validation of analytical / ICH guideline Q2(R2) on validation of analytical EMA/CHMP/ICH/82072/2006 / EMA/CHMP/ICH/195040/2022

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
ICH@ema.europa.eu
All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
For more details on how to use this template please refer to the tab "Manual for commenter".

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)
ECA Foundation / European QP Association				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
			Q2(R2)	ICH Q2 does not integrate with ICHQ14 - Figure 2 is too simplistic	Integrate ICH Q2 with Q14
			Q2(R2)	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
			Q2(R2)	No mention of analytical procedure life cycle	A lifecycle diagram showing the three stages: development, validation and use
			Q2(R2)	The Analytical Target Profile does not feature in Q2(R2) apart from the glossary	
			Q2(R2)	There is no complete analytical procedure life cycle described in either Q2 or Q14	
			Q2 (R2) and Q14	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
			Q2 (R2) and Q14	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
	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)
	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
	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.

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	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
	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.
	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?
	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.
	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
	102	102	03. Feb	clear wording should be chosen	replace reporting limit by reporting threshold
	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
	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"
	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
	173	173	4.1.3	please gives examples for biological products. E.g. immunoassays	Include immunoassays in the examples
	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
	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).
	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.	
	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)	
	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

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	344	344	4.3.1.3	"see 1.2)" - there is no chapter or section 1.2. What is it referrring to?	
	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
	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.	
	399	399	4.3.2.4	RMSEP	should be explained in a glossary in Q2
	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
	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
	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
	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)
	673	674	table 7	There is no evaluation of the calibration model. See previous comment to 4.2.1.2	