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Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-D-1503

Q2(R2) Validation of Analytical Procedures and Q14 Analytical Procedure Development; International Council for Harmonisation; Draft Guidances for Industry

To Whom It May Concern,

Biotechnology Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) draft guidances for industry entitled "Q2(R2) Validation of Analytical Procedures" and "Q14 Analytical Procedure Development."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

We appreciate FDA's role in the development of these guidances that will harmonize scientific approaches for analytical procedure development and include validation of a wider range of analytical techniques. BIO agrees that efforts to facilitate regulatory evaluations and potential flexibility in postapproval change management of analytical procedures will better enable our member companies to bring safe and effective products sooner to the ultimate benefit of our patients.

BIO is pleased to provide the following list of general recommendations for the Agency's consideration. These recommendations are elaborated in the tables beginning on page 3.

General Comments Regarding "Q2(R2) Validation of Analytical Procedures"

- BIO believes FDA should provide greater detail on different types of range and how they link to validation in section 4.2 to ensure clarity for industry.
- Clearer guidance on linear and non-linear models in the section 4.2.1 would be helpful for industry.
    - The concept of linearity loses continuity throughout the document. For example, in Annex 2, "Illustrative Examples for Analytical Techniques", there are several recommendations of assessing linearity as Expected (Theoretical) vs Observed (Measured) concentration. Whereas in the main body, e.g., beginning line 221, this concept is not mentioned. The different ways of assessing linearity should be clearly delineated in the text.

- Depending on the type of test method, linearity can be assessed in different ways:
  - For quantitative test methods that are direct measurements (e.g., UV/Vis using the extinction coefficient, biological activity or binding assays), linearity can be assessed with a plot of signal vs. analyte concentration. In some cases, the response will be non-linear (refer to section 4.2.1.2).
  - For quantitative test methods that use a standard curve, regardless of the model, if accuracy of the method is being assessed across the working range, then linearity can always be assessed with a plot of Expected (Theoretical) vs. Observed (Measured concentration). In these cases, the standard curve fit, be it linear, quadratic, 4-parameter etc., is usually well characterized during development and the method procedure has validity criteria around it. For these assays, the working range may be different than the standard curve range (e.g., the standard curve range may be 10 - 100 and the working range may be 50 - 250) and some samples will need to ne diluted into the curve range. This type of assessment is directly related to precision, accuracy and range and can be assessed from the same data set (e.g., a plot of expected vs. observed for 5 concentrations levels, 3 replicates, across the working range).

- We suggest that the guidance should clarify that the use of confidence intervals improves accuracy and precision rather than suggesting they should always be used.
- We note that not all terms listed in the glossary are found in the body of the general guideline, e.g., references to CQA. Some principles from the glossary should be included in the core document. Alternatively, FDA could clarify that not all terms included in the glossary are referenced in the guideline but are included for cross-referencing purposes.
  - We suggest that the guidance make reference to replication strategy in main body and glossary.
- We agree with the introduction of the platform method concept (and abbreviated validation, when justified) and emphasize that it is beneficial.
- In general, it would be helpful to 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.

General Comments Regarding "Q14 Analytical Procedure Development"

- We note that an explanation of replication strategy in the main body and glossary would be helpful.
- It is unclear whether established conditions (ECs) relate to SST and/or method parameters.
- In general, several examples and language are mostly specific to small molecules. We recommend adding more language and examples to ensure further applicability for large molecules.

Please consider the following tables outlining granular comments on specific language in each of the draft guidances.

General Comments Regarding "Q2(R2) Validation of Analytical Procedures"

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 2-8	Clarity on applicability of guidance to all modalities	Provide clear language that the guidance is applicable to all modalities
Lines 25-27	Reference materials may not always be required for a validation study in some of the elements added to Q2R2. For example, 'technology inherent justification' specificity test, and multivariate analytical procedures.	Add 'as appropriate' to sentence "Suitably characterized reference materials…should be used throughout the validation study as appropriate."
Lines 32-35	It is unclear whether SST and robustness need to be done in a GxP manner (equipment, analyst, laboratory, materials)	Please clarify the Agency's intent.
II. SCOPE		
Lines 37-39	Specifies chemical and biological/biotechnological products only without definition as this could include gene therapy/other types of products	Provide clear language that the guidance is applicable to all modalities
Lines 37-39	It is unclear whether this revision applies to only new or revised procedures for release and stability and not to method transfer and validation gap analysis (e.g., Eudralex)	Please clarify the Agency's intent.
Lines 41-42	Application of phase-appropriate manner is unclear on FDA's thinking of what is required during development	Similar to ICH Q5E, provide a section in the guidance on phase-appropriate method validation and nomenclature
III. ANALYTICAL PROCEDURE VALIDATION STUDY		
Lines 48-49	Meeting objectives alone is not the purpose of a validation study	Provide clearer language that validation study is used to assess if a method is suitable for its intended use and meets its objectives
Lines 69-71	Footnotes 3 and 4 appear to be reversed.	Reverse the order and numbering of footnotes 3 and 4.
Line 72	Reproducibility is not mentioned in the Table	Add Reproducibility in the Table as well.
Lines 74-76	Mentions documenting and justifying objective, performance characteristics, and criteria of procedure.	Consider introducing "ATP" here
Lines 77-85	This text places analytical validation in context of analytical procedure lifecycle and Q14. However, key concepts from Q14 are not mentioned.	If established conditions, PAR, or MODR concepts should be addressed as part of a validation study in the enhanced approach, Q2 should provide guidance in how to incorporate these concepts in a validation study. Please clarify the expectation on the level of quality of these documents (GxP/non-GxP) since the validation study and validation report leverage

SECTION	ISSUE	PROPOSED CHANGE
		potentially non-GxP developmental data.
Lines 92-94	The discussion of co-validation includes a statement "When transferring analytical procedures…". This statement implies that transfer and co-validation are the same activity and could cause confusion.	Revise the text to differentiate the concepts of co-validation and comparative transfer. Define the amount of labs for determination of Reproducibility as part of co-validation. Add additional term as part of co-validation: Inter-Laboratory Evaluation, in case only 2 labs are involved Consider that co-validation might also be used in the context of analytical procedure transfer: "Co-validation can be used to demonstrate that the analytical procedure meets predefined performance criteria by using data from multiple sites and can also be used for the transfer of analytical procedure."
Lines 96-97	It is unclear whether cross-validation can be used for concomitant validation of online and offline methods	Please clarify that the cross-validation could be used in the context of simultaneous validation of an on/it/atline and an offline method.
Lines 100-103	It is unclear whether lines 100-103 imply that specificity should be demonstrated at both the upper and lower end of the range or whether 100% of nominal quantity/acceptance limits sufficient to demonstrate specificity. Note that this requirement for specificity is not stipulated in chapter 4, section 4.1, as it is for accuracy and precision in section 4.3.1 and 4.3.2. Annex 2 also does not require specificity the over the reportable range. Q2 (R1) definition for range: The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.	Please clarify the Agency's intent.
Lines 107-108	Potency reportable range is expressed differently than other reportable ranges.	Consider revising potency row to align expression of reportable range

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		with other rows in table (i.e., 80% of specification limit, 120% of specification limit), or if this is not the intent of the row, clarify how "specification -20%" or "specification +20%" should be calculated.
Lines 107-108	The range suggested for dissolution method validation has changed relative to R1	Please clarify if this change in criteria is applicable exclusively to new methods rather than existing methods previously validated as per R1. This request for clarification stems from the Eudralex requirement that before the transfer of a method, the validation be assessed and remediated against current criteria. Should this new R2 criteria become effective, it would be helpful to understand whether this new criterion would be applicable to methods previously developed as per R1 before a method transfer.
Lines 108-116	Demonstration of stability indicating properties, mentions use of physical and chemical stress conditions but does not mention ICH Q1A or B.	Add reference to ICH Q1A and B. Would also need to add to line 654 if mentioned as references.
Lines 109-116	Some procedures are stability indicating per design, e.g., the quantitative measurement of a degradation product. In these cases, performing challenges does not add value as long as the procedure has been demonstrated to be accurate.	Proposal to add after the section: "In some cases, depending 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 ensure that the procedure is stability indicating."
Lines 111-113	Use of the terms 'test' and 'challenge' seem inconsistent with the terminology used throughout Q2(R2).	Align terminology. For example, "stability-indicating test" should be "stability-indicating analytical procedure" to avoid confusion with the separate term "validation test". The term "challenges" appears to refer to "validation tests" or perhaps the design of a "validation study".
Line 120	In the example of input variables it is unclear whether the components at different wavelengths are input or output variables for a spectrum.	Distinguish between the multivariate concept (e.g., PLS as mentioned in line 131) vs. multiple linear

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	Consider that these are output variables which are analyzed simultaneously, thus being classified a truly multivariate analysis.	regression used in DoE (not multivariate because may have multiple input variables but analyzed one output variable at a time), to be precise in terminology, DoE is a multifactorial analysis.
Lines 121-122	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).
Lines 136-137	Unnecessary word	"Samples used for the validation of quantitative or qualitative multivariate procedures ~~require~~ should have values or categories assigned to each sample…"
Lines 157-159	Test cannot minimize interference. It can show whether or not there is interference.	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."
IV. VALIDATION TESTS, METHODOLOGY AND EVALUATION		
Lines 209-213	Language present seemingly implies that a second orthogonal method is always required to verify specificity if impurities or related substances are not available. It does not make mention of forced degradation experiments/peak purity as a means of demonstrating specificity as noted in the current ICH-Q2(R1). Forced degradation is mentioned elsewhere in the document (e.g., Annex 2) but could be better clarified here.	"… specificity can be demonstrated by comparing the test results of samples containing typical impurities, related substances or degradation products (for example such as those obtained by stress conditions) with a second well-characterized procedure (e.g., pharmacopeial procedure or other valid orthogonal analytical procedure) or other technically justifiable approach."
Lines 210-213	Soften wording as comparison to orthogonal procedure is not always required or even possible in some cases (approach should be technically justified). For example, a screening system with orthogonal conditions may be an appropriate approach; these methods are not validated. Peak purity in LC methods is another approach. Information on peak purity determination is missing, which is included in currently effective Q2 version on page 9 (last two rows).	Change the word 'validated' to 'valid'. Add following sentence from currently effective Q2 version: "Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry)."
Line 214-218	It would be important to clarify the range categories, especially working range, and how they link to development and validation.	Proposed clarification:

SECTION	ISSUE	PROPOSED CHANGE
		"In most cases the reportable range is identical or corresponds directly (when considering the effect of dilution) to the validated working range. However, in some cases the reportable range can be wider than the corresponding validated working range. This is the case when additional alternative samples dilutions are planned to be used in a procedure and in order to accommodate the fact that some samples may fall outside of the validated working range when applying the initial sample dilution. This means that the validated working range of the procedure is too narrow when compared to the amplitude of product specification. In that case the alternative samples dilutions proposed must be validated by demonstrating that method performances are acceptable whatever the planned dilutions applied to the samples. Another case is encountered when validating purity assays and when a sample at 100% purity is not available in order to cover experimentally the higher part of the product specification range. The validated working range will cover (at least) the lower product specification but will be limited to the % purity of the sample presenting the highest purity % and which is available at the moment of the validation. In that case, and upon appropriate justification, the reportable range will be extended to 100% of purity while the validated working range will be limited to the highest % purity for which the analytical procedure has been experimentally demonstrated to have a suitable level of precision, accuracy and linearity."
Lines 219-240	This section is missing theoretical vs actual plots for establishing linearity. It is mentioned for non-linear responses, but can also be used here.	Please consider an addition.

SECTION	ISSUE	PROPOSED CHANGE
Lines 231-234	Language is unclear regarding expectations of analysis of data point deviation from the linear regression line. For example, it would be helpful to clarify whether an additional statistical treatment is required to assess nonrandom patterns in residuals.	Clarify if language entails expectations beyond the listed requirements: (A plot of the data, the correlation coefficient or coefficient of determination, y-intercept and slope of the regression line).
Line 239	Use of term “population” of data points – the generated data are just but samples from the population.	Delete “of populations”
Line 251	First two sentences of paragraph are unclear	Clarify verbiage
Line 283	Here, 3.3 is being used whereas the recommendation in line 275 is 3. This was also in the Nov 2005 version.	Please clarify
Lines 298-302	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
Lines 320-415	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. It should also explain that it is acceptable to perform the validation studies using an assay format that is different from the final replication strategy but, in that case, the results of the validation - and specifically of the precision - must be expressed (after calculation) in the final assay format corresponding to the selected final replication strategy. Replication strategy should also be addressed in ICH Q14 (and glossary).	Consider adding the following text: “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 calculated as an average of several intermediate results. It is acceptable to perform the validation using a replication format that is different from the final replication strategy which would enable further calculation of the precision corresponding to the application of the selected final replication strategy / assay format if required."
Lines 329-331	In certain cases (e.g., small molecule drug substance assay), however this is very often the case for Large Molecules as well; it would be useful to be inclusive so that it isn't interpreted as applying to only small molecule assay	Change "e.g. small molecule drug substance assay" to "e.g. assay"
Lines 349-360	The section should be clarified with regard to which paragraph applies to which type of experiment (for example lines 352 to 354 would be applicable to spike experiments; lines 349 to 351 would be applicable to method precision etc.). Clarity confidence intervals are not always required or appropriate.	The type of data collected should be appropriate for the type of study conducted (as described in the subsections Section 4.3.1). For example, for a spiking study, Accuracy should be assessed using an appropriate number of determinations and concentration levels covering the reportable range

SECTION	ISSUE	PROPOSED CHANGE
		(e.g., 3 concentrations/3 replicates each of the full analytical procedure). In this case, the Accuracy should be reported as the mean percent recovery by the assay of a 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 . For comparison to a reference material or orthogonal procedure, 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. Use of confidence intervals may not be appropriate when there is insufficient data.
Lines 363-366	Focusing only on RMSEP is too restrictive. Most of the routine samples will reside within a reasonable window around the label claim. As such, using an approach like an equivalence test with paired data offers a chance to critically evaluate how acceptable the model results are compared to the reference method results. It would be strongly preferred to have both options explicitly stated rather than just mention RMSEP. The sentence beginning with "If RMSEP is found to be comparable ..." suggests the model would not be accurate enough if RMSEP isn't comparable to RMSEC. But RMSEP is a squared difference approach. So more extreme values on the edge of that range would have more leverage in that calculation. What would be of more interest would be how the method is performing within a window where results would be more typically expected. One could still evaluate 3 reps at 3 levels across the range, but that could also be done with an equivalence testing approach.	"For quantitative applications of multivariate analytical procedures, appropriate metrics, e.g., root mean-squared error of prediction (RMSEP), and/or tests, e.g. equivalence test with paired data, 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. Alternatively, an equivalence test with paired data provides an acceptable choice for comparing model results to reference method data."
Line 364	Clear definition of RMSEP and RMSEC is needed	Include in glossary with formula

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Line 391-394	Pharmacopoeia methods are not part of the scope of Q14, and Q2 and Q14 are complementary documents. Standardization of analytical procedures is achieved through the method-transfer study conducted between the receiving and originating laboratories.	"Investigation of reproducibility is usually not required for regulatory submission but should be considered in cases of standardization of an analytical procedure, for instance, ~~for inclusion of procedures in pharmacopoeias~~ to qualify a receiving laboratory to utilize a method that originated in another (transferring) laboratory."
Lines 416-423	The robustness section does not mention sample/standard solution stability, which is commonly performed during validation studies. We should take this opportunity to clarify that sample solution stability should be included during development studies, thus does not need to be repeated during validation.	Revise sentence to state "Robustness testing should show the reliability of an analytical procedure with respect to deliberate variations in parameters **and sample and standard solution stability**."
V. GLOSSARY		
Lines 430-433	Definition of 'Analytical Procedure' should be expanded. Many sources (including IQ position paper "Method validation in the age of QbD") add that procedure is what describes how to get reportable result (may involve multiple methodologies, calculations etc.). It may also be useful to add a definition for 'method'.	Please consider expanding the definition.
Lines 464-467	Definition of "Co-validation" needs revision. Full revalidation is not co-validation. The prefix 'co-' is generally understood to mean something that is done jointly. Full revalidation is an independent activity of the receiving unit, as is partial revalidation. Co-validation would be when each lab performs parts of the validation resulting in a single validation report.	Remove "partial re-validation" and "full re-validation" from this definition.
Line 472	It is unclear how to conduct cross validation and how to evaluate it	We suggest providing some guidance for the minimum requirement for different methods
Line 516	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 these two sections
Lines 531-543	The definition of range in the document is tied to linearity responses. However, the definition makes no mention of linearity and only described range as having precision and accuracy.	Update definition to include linearity (and non-linearity where appropriate)
Line 534	Alignment of terminology within document	Consider whether "response" should be changed to "specificity" to match language earlier in guideline (e.g., line 101). Alternatively, consider "reportable range" or "linearity"

SECTION	ISSUE	PROPOSED CHANGE
Lines 535-543	Distinction between 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 levels.	Add distinguishing qualities to working range (as opposed to) reportable range and/or define "meaningful" results.
Line 605	Limits the mathematical transformation to the input variables. The input and/or output data may need transformation to meet model assumptions (e.g., normality, homoscedasticity, etc.).	Replace sentence with "Mathematical operation on input and/or output data to meet model assumptions (e.g., normality, homoscedasticity, etc.).
Line 660	Figure suggests that Orthogonal Procedures for accuracy and specificity are always required.	Insert footnote to explain that orthogonal procedures are not always required
Line 676	Technique is referred to as Gel Electrophoresis for the separation and analysis of macromolecules.	"Test reaction specificity by gel electrophoresis ~~gel~~, melting profile or DNA"
Line 676-677	"Intermediate precision: Comparison of measurements using the same procedure performed by another analyst on a different day."	Adapt vocabulary to ICH Q2 definition
Line 683	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.	"Comparison of API spectrum and the loadings plots and/or regression coefficient of the model"
Line 683	Refer to previous comment (lines 363-366) in the section on accuracy earlier in the document. A focus just on SEP or RMSEP is more restrictive. Allowing an option to see equivalency should also be allowable.	"Demonstration across the range through comparison of the predicted and reference values using an appropriate number of determinations and concentration levels (e.g., 5 concentrations, 3 replicates). Accuracy is typically reported as the standard error of prediction (SEP or RMSEP) and/or as the results of an equivalence test with paired data comparing the model predictions to the reference method values."
VI. REFERENCES		
General	Reference listing appears to be incomplete	Include ICH Q8 and ICH Q12
VII. ANNEX 1 SELECTION OF VALIDATION TESTS		
Line 668	Non-acceptable batches seem difficult to define	Suggest adding a clearer definition or providing examples, e.g., stressed samples, deliberately over-coated samples, etc.
VIII. ANNEX 2 ILLUSTRATIVE EXAMPLES FOR ANALYTICAL TECHNIQUES		
Line 661	On Page 25, Table 3, Reportable Range, Right Column: Should be "Section 4.2", instead of "Section 5.2"	Change Reportable Range, Right Column: from "Section 5.2" to "Section 4.2"

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Line 668	On Table 5, reportable range is listed as up to 120%, where earlier in the guideline (Table 2) it is listed as 130%	Align recommendations
Line 686	On Table 11, it is unclear why evaluation of LC injection volume is mandated for robustness. Other sections state "for example."	State that the factors "may" be considered, or list them as examples

Specific Comments Regarding "Q14 Analytical Procedure Development"

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 15-25	Please clarify if the enhanced approach will afford the flexibility to make changes within the design space with minimal or no post approval changes. Please comment is there are or there will be dialog with any Health Authorities to discuss this topic and a possible commitment to honor the benefits of the enhanced approach to method development.	Lines 15-25
II. SCOPE		
Line 34	Clarify what is meant by "out of scope" since a compendial method should be validated.	
Lines 28-29	Specifies chemical and biological/biotechnological products only without definition as this could include gene therapy/other types of products	Provide clear language that the guidance is applicable to all modalities
Lines 40-47	In Q14, there is mention of platform methods across products but details are lacking so it is difficult to understand when platform procedures might be appropriate, and where development/validation can be abbreviated.	Can there be more clarity, or an example, regarding application of a platform procedure to guide sponsors in terms of the risk-based approach?
Lines 41-43	Q14 - standard vs enhanced approach. We like the direct statement that the minimal approach remains acceptable; is there potential to provide either examples or further detail on when the enhanced approach may be more highly recommended?	add an example of when an enhanced approach is recommended, or include an example in section starting on line 66 and direct reader to the later section
Lines 41-42	Difference between minimal and enhanced approach is not made clear; it is also difficult to understand where in development enhanced approach becomes important (phase 1 vs. later, etc.)	Please clarify
Lines 48-50	Please clarify that if SST and robustness are now part of method development as per Q14, does this work need to be done in a GxP manner (equipment, analyst, laboratory, materials)?	It would be useful to have examples of model ATPs included in the guidance
Lines 48-50	Revised text clarifies when development data can be used as validation data during development. The current text is ambiguous.	In general, data gained during the development studies (e.g., robustness data from a design of experiments (DoE study)) can be used as validation data for the related

SECTION	ISSUE	PROPOSED CHANGE
		analytical procedure performance characteristics and does not ~~necessarily~~ need to be repeated if scientifically justified.
Lines 70-71	Suggest including discussions for both the sample variability and method variability.	Provide more guidance on evaluation of each, how to decouple them and use them to aid the risk assessment
Line 75	Context for using "multi-variate". Multivariate analyses (like principal component analysis in line 590) are used when more than one response output variables are modeled simultaneously against multiple input variables. Some multivariate techniques do not make a distinction between input and output variables. If multiple output responses are modeled one at a time against multiple variables as is done in DoE (as exemplified in lines 49 and 903 as well as cited in line 389 of Q2), that is not a multivariate analyses, rather multifactorial design analyzed using multiple linear regression. However, in line 195, the guidance classifies DoE as a multi-variate analysis.	Clarify the usage of multi-variate throughout the document. If traditional DoE is being referred to, distinguish it from the rest of multivariate examples (e.g., machine learning, neural networks, PCA, etc.).
Lines 99-100	"Reducing the amount of effort across the analytical procedure lifecycle" may not be a true advantage of the enhanced approach. The enhanced approach may lead to a greater level of effort throughout development in many cases, and this upfront investment may result in streamlined change management during the analytical procedure lifecycle.	Revise the language to focus on the post-approval change management benefit. For example: "Streamlining change management and regulatory notification requirements across the analytical procedure lifecycle."
Line 107	In Figure 1, it is unclear why some lines are solid and some are dashed Additionally, the blue box (analytical procedure development) should be depicted as a circle in itself, including another arrow from control strategy back to risk assessment. This is described in lines 153 to 155, but not reflected in the figure. Furthermore, robustness studies should be explicitly mentioned within the blue box. Having the analytical procedure control strategy within the blue box without a link back to the product control strategy is considered as not ideal.	We recommend adding a key to clarify formatting conventions. We also recommend adding an arrow from procedure control strategy to risk assessment (circle). Include robustness studies in workflow (with preceding risk assessments).
III. ANALYTICAL TARGET PROFILE (ATP)		

SECTION	ISSUE	PROPOSED CHANGE
Line 116	Consider that the ATP may prove to be irrelevant	Provide lifecycle management example
IV.	**KNOWLEDGE AND RISK MANAGEMENT IN ANALYTICAL PROCEDURE DEVELOPMENT AND CONTINUAL IMPROVEMENT**	
Line 166-166	There is no information about the methods of ongoing monitoring.	Please provide more guidance on how ongoing monitoring is supposed to be performed or make a reference to appropriate literature. If monitoring is supposed to remain as generic as written in Q14, at least a reference to Q10 should be made.
V.	**EVALUATION OF ROBUSTNESS AND PARAMETER RANGES OF ANALYTICAL PROCEDURES**	
Lines 173-189	It is unclear whether 5.1 and 5.2 are discussing the same concept.	Clarify the relationship between robustness and parameter ranges.
Lines 200-201	Inconsistent terminology	Change terminology: “variables (inputs)” to “parameters” and “outputs” to “attributes”.
Lines 189-216	PAR and MODR concepts are not clearly explained or differentiated. The text suggests that PAR and MODR are similar concepts, but PAR is univariate and MODR is multivariate. If this is a correct distinction, it can be stated more directly.	Revise the section to define and differentiate the PAR and MODR concepts more clearly.
Lines 194-197	The text says “In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multi-variate experiments (DoE). Risk assessment and prior knowledge should be used to identify parameters, attributes and appropriate associated ranges to be investigated experimentally.” It does not explain that at the end of this process the critical attributes of the procedure must be identified.	Proposed rewording: “In an enhanced approach, the ranges for the relevant parameters and their interactions can be investigated in multi-variate experiments (DoE). Risk assessment and prior knowledge should be used to identify parameters, attributes and appropriate associated ranges to be investigated experimentally. The aim of this approach is to identify critical attributes which therefore require specific control.”
VI.	**ANALYTICAL PROCEDURE CONTROL STRATEGY**	
	n/a	
VII.	**LIFECYCLE MANAGEMENT AND POST-APPROVAL CHANGES OF ANALYTICAL PROCEDURES**	
Line 326-327	Revised text clarifies that this description is for the enhanced approach.	Figure 2 summarizes how risk assessment and risk reduction measures can help identify appropriate reporting categories for ECs using the enhanced approach.

SECTION	ISSUE	PROPOSED CHANGE
Line 348-349	Add the full text for the acronym "QRM" as it is not included prior to this point in the guideline.	"When implementing changes to analytical procedures, Quality Risk Management (QRM) can be used to evaluate the impact of the changes and re-confirm that the originally agreed reporting category is still appropriate."
Line 357	If knowledge about a condition is "low" then presumably risk associated with change is an unknown, so it is unclear whether the bottom-left quadrant is applicable here (i.e., difficult to determine the risk to be high or low if knowledge is low).	Clarify table and consider if the 4-quadrant visualization tool is appropriate here
VIII.	**DEVELOPMENT OF MULTIVARIATE ANALYTICAL PROCEDURES**	
Lines 409-416	The term "calibration sets" is not defined.	Add explanation on this topic.
Lines 419-422	Unclear how variable selection should be justified	Add clarification or examples
Line 430	Robustness should be built into the model by including relevant sources, or by demonstrating that the model is robust to that variation. There are endless variations to be encountered once a product goes commercial, and the key is to demonstrate the model is robust, but that does not always mean including those samples in the model.	Suggest to change to: The robustness should be built into the model by including relevant sources of variability… or by demonstrating that variability does not affect the accuracy of model predictions.
Line 468	There is no reference made to Figure 3 in Section 8. It would be helpful to integrate this figure with the discussion of the multivariate model lifecycle as a complement to the text.	The multivariate model lifecycle (see Figure 3 above) is iterative and can be broken down into 3 major components:
Line 488-489	Additional sentence was included to make this explicit that in addition to model assessment, model development and revalidation would also be performed in the PQS.	"If an issue is identified, model development and revalidation may be needed, for example, to add samples into the calibration set and remove those that are no longer relevant. This model development and revalidation is performed within the PQS."
Line 493	Addition to clarify the reference to the figure.	"The dashed arrows in ~~the figure~~ Figure 3 illustrates reintroduction into the lifecycle flow…"
IX.	**DEVELOPMENT OF ANALYTICAL PROCEDURES FOR REAL TIME RELEASE TESTING: SPECIAL CONSIDERATIONS**	
	n/a	
X.	**SUBMISSION OF ANALYTICAL PROCEDURE RELATED INFORMATION**	
Lines 524-596	It is suggested that Established Conditions be located in a regional section (3.2.R); if different countries agree to different change notification categories, or different EC we may end up with multiple versions which will be more easily managed outside of S.4.2/P.5.2. Also, some EC	Please consider revision.

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	may not fit as easily in S.4.2/P.5.2 (e.g., column flow as an EC fits in S.4.2/P.5.2, but if a performance characteristic serves as EC, it doesn't). Finally, development/supportive information best belongs in a development section like S.2.6 or P.2 as is suggested for multivariate model development, OR in the same document with the EC in 3.2.R	
Line 531	The request that the analytical procedure should describe the steps in sufficient detail for a skilled analyst to perform the analysis introduces significant burden and pressure for post-approval management	High level and key elements of the analytical procedure should be provided, instead of all the details.
XI. GLOSSARY		
Lines 645-647	The concept of cross-validation is defined in Q14 (and Q2), but no real discussion of how cross validation may be employed within the method development lifecycle is provided. It should be made clear that demonstration of cross validation can allow application of either method if filed as equivalent methods. Including this in the example provided in the annex describing a change between Chiral CZE and Chiral HPLC may be an appropriate means of introducing this concept.	Add discussion of cross-validation applications
Line 705	Alignment with ICH Q2	Should "response" be changed to "specificity" to match language ICH Q2 guideline (e.g., line 101)? Or specificity added here as well?
Line 782	Unclear meaning	Replace “assume” with “achieve”
XII. REFERENCES		
Lines 836-1718	The annexes are difficult to read because sections and sub-sections are not visually distinct.	Reformat or restructure the annexes for ease of navigation by a naïve reader.
Line 889-890	Clarify the abbreviation “AP”, since the abbreviation “AP” is not utilized in previous or subsequent text.	“Well justified analytical procedure ~~AP~~ performance criteria cover/link to CQAs and their acceptable”
Line 907	“Peak characterization available” meaning unclear	Clarify within text
Line 928	Unclear whether impurities a-e were specified at NMT 0.1% each, or summed together must be NMT 0.1%	Clarify within text
Line 933	Accuracy text: unclear that that the recovery criteria are for imps, not DS	Clarify within text
Line 972	Alignment	Update LOQ to QL to match ICH terminology
Line 1034	Technology Specific Analytical Procedure Attributes - resolution should be spelled out instead of referred to as "R" or abbreviated as Rs. Confusing given R also used for linearity in lines below	Clarify within text

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Line 1034	The interplay of controlled factors for each SST, and what that means for this procedure, is unclear - i.e., it is unclear whether one could change anything not listed as a controlled factor for an SST, as long as the SST criteria is still met	Clarify within text
Line 1034	Undefined acronyms	Add table footnote similar to line 1500 to define PA, NL, and NM.
Line 1034	Typos	"Clear scientific relationships between pressure, capillary length and rinsing volume exist, allowing adjustments between various equipment~~1Erreur ! Signet non défini~~." "The performance over the reportable working range has been demonstrated ~~though~~ through the linearity experiments at validation."
Lines 1114-1114	Terminology: chiral describes a molecular property, but cannot describe an analytical technology	Replace "chiral" with "enantioselective"
Lines 1122-1124	Analogous to the RTRT and traditional end-product testing, the specification needs to be modified to define when the alternative method would apply in the control strategy.	"The intended change is not related to any quality issues of the product, or the established CZE procedure and the company does not intend to modify the ~~specifications~~ acceptance limits for the chiral impurities"
Line 1144	The specification will need to be updated to change the listed test from CZE to HPLC and/or delineate when the alternative technique is applied. However, the acceptance criteria will remain unchanged.	"…the ~~specifications~~ acceptance limits for the chiral impurities remain unchanged."
Lines 1219-1220	Might the inclusion of USP references as justification in the example lead to false assumption that EU/Japan will accept USP rationale? Options: include similar EP/JP reference	Include similar EP/JP reference in footnote
Line 1284	Remove unnecessary beginning parenthesis.	"The cell line and its performance (viability, cultivation conditions, cell density…"
Lines 1602-1603	Revise text for clarity.	"The change from ELISA to a cell-based assay is outside of the selected technology of the specification and a potential impact on the specification acceptance criteria cannot be excluded."
Lines 1677-1716	The discussion of MODR expectations may reflect a significant decrease in operational freedom. Annex B implies that full validation is required at the extremes of method variables to allow parameter	Please consider whether establishing this standard within the ICH example is warranted.

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	adjustments within an MDR. This is not consistent with our historical application of robustness data. Chromatographic robustness data (wherein system suitability criteria are demonstrated within a given parameter's PAR) have been judged sufficient evidence of freedom to operate within that PAR. Instructions here imply that additional validation would be expected to move from the center target condition. Some of the examples given (e.g., repeatability/intermediate precision validation across the MODR) seem unwarranted given the other controls in place (Precision SSR during method execution).	
Lines 1677-1716	While PARs are introduced in the glossary, their application for operational flexibility of a method is not clearly established.	This could be clarified in the Annex B example.
Lines 1682-1684	Revise text for clarity.	"The extent of validation activities and the respective operational flexibility ~~associated~~ needed should ~~requires to~~ be assessed and justified on a case-by-case basis."
Line 1717	Multivariate model example does not seem to be as comprehensive as other 2 examples.	Suggest including introductory / additional explanatory text
Line 1717	Additional text added to make more explicit regarding what is meant by change management. This maximizes the flexibility for the analyst.	"Change Management (model assessment/monitoring, maintenance, redevelopment, and revalidation) per PQS"

Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's draft guidances for industry entitled "Q2(R2) Validation of Analytical Procedures" and "Q14 Analytical Procedure Development." As FDA continues to consider these topics, we would welcome future opportunities to discuss our comments.

Sincerely,

/s/

Alex May, M.S.
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Biotechnology Innovation Organization