Biotechnology Industry Organization

May 20th, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-0103: Draft Guidance for Industry on Analytical Procedures and Methods Validation for Drugs and Biologics

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Analytical Procedures and Methods Validation for Drugs and Biologics."

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO commends FDA for releasing this revision of the 2000 Draft Guidance for Industry entitled "Analytical Procedures and Methods Validation" with its strong focus on regulatory science and modernization. We note that the emphasis on the use of risk-based decisions is consistent with recent international harmonization efforts, especially with International Conference on Harmonisation (ICH) guidelines Q8, Q9, Q10, and Q11. One additional area where quality risk management can be applied is in platform-based manufacturing and testing. Manufacturers that have several products of the same type often use similar manufacturing and analytical methods. We believe that additional guidance around the use of analytical development and validation data from a similar product to support the approval of a new application would be helpful to Sponsors.

Further, we support the introduction of the concept of the analytical target profile (ATP) to guide method development. It would also be helpful to allow options in this Draft Guidance that align with the concepts of analytical quality-by-design (QbD) and risk management.

Additionally, we find that the Draft Guidance provides ample examples for methods related to procedures and validation of small molecule products. We believe it would be helpful to Sponsors if the Draft Guidance provided additional examples and guidance on physiochemical procedures for biological products.

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While we appreciate the progressive nature of this Draft Guidance, we note that it lacks some specific detail that was in the 2000 "Draft Guidance for Industry on Analytical Procedures and Methods Validation.[1]" We believe it would be helpful to reference the specific validation criteria required for assessment by type of analytical method as discussed in ICH Q2(R1).

Finally, in general, it appears that the amount of information requested in the New Drug Application/Biologics License Application (NDA/BLA) under the proposed guidelines has increased substantially over the current standards, and consequently, the level of detail requested in the Draft Guidance is not consistent with a risk-based approach to review and approval. Specifically, we find that Section IV on Content of Analytical Procedures seems to be quite prescriptive and believe that it will increase the post-approval change burden if it does not allow for appropriate flexibility.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Analytical Procedures and Methods Validation for Drugs and Biologics." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

[1] "Guidance for Industry Analytical Procedures and Methods Validation" http://www.fda.gov/ohrms/dockets/98fr/001424gl.pdf July 2000

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 37-41	This section refers Sponsors to other guidances for phase one studies.	We ask that FDA provide additional guidance for phase-specific studies beyond phase one to facilitate Sponsor understanding of expectations during development.
II. BACKGROUND		
Lines 81-82:	This line references the ICH M2 eCTD: Electronic Common Technical Document Specification.	We ask that FDA changes this reference as ICH M2 eCTD is specific for electronic common technical document (CTD) set up. We suggest the following: "Analytical procedures and validation data should be submitted in the corresponding sections of the application in the ~~ICH M2 eCTD: Electronic Common Technical Document Specification~~ ICH *M4Q(R1): Quality Overall Summary of Module 2 and Module 3: Quality*"
Lines 85-88:	This section discusses FDA recognized sources for analytical procedures.	Only one example is given as an FDA recognized source. As manufacturing is now a global endeavor, it would be helpful to have a list of FDA recognized sources as opposed to only the US-based one.
III. ANALYTICAL METHODS DEVELOPMENT		
Lines 95-100:	The Draft Guidance discusses parameters that may be evaluated including specificity, linearity, limits of detection (LOD) and quantitation limits (LOQ), range, accuracy, and precision.	We suggest that the use of the analytical QbD approach and the concept of the ATP as an integral part of the method development-qualification lifecycle be considered. Please add the following sentence at the end of the paragraph:

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		"The concept of a pre-defined Analytical Target Profile (ATP) can be used for both initial method development to define the intended use as well as for further method evolution during development." We also suggest that the analytical procedures in this Draft Guidance also apply to the process analytics used for process decisions.
Lines 102-103:	The Draft Guidance discusses that the robustness of methods should be evaluated to help decide which method to submit for approval.	The Draft Guidance seems prescriptive and needs to allow for the use of analytical QbD during analytical method lifecycle management. Please edit as follows: "During early stages of method development, the robustness of methods should be evaluated because this characteristic can help you decide which method you will submit for approval. These method robustness studies may include analytical QbD principles throughout the analytical method lifecycle." We also ask the Agency to clarify expectations for robustness to be included in analytical validation protocols using a defined sample set and acceptance criteria as opposed to performing robustness studies only during early development without defined criteria for development of method parameters.

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Lines 106-109:	The sentence "You should submit development data within MV section if they support the validation of the method" is located at the end of paragraph on early stages of method development. However, this sentence appears to be more applicable to the paragraph from lines 110-117 regarding systematic approach for method robustness studies.	We recommend moving this sentence to the end of line 117.
Lines 110-112:	The Draft Guidance discusses fully understanding the effect of changes in method parameters. However, this understanding is intended for later development stages.	To ensure clarity that this statement applies to later development stages, we recommend editing the statement as follows: "Later in development, to ~~To~~ fully understand the effect of changes in method parameters on an analytical procedure, you should adopt a systematic approach for method robustness study (*e.g.*, a design of experiments with method parameters).
Lines 112-113:	The Draft Guidance discusses understanding method robustness; we note that platform knowledge may also be applied to gain this understanding.	Please edit text to read: "You should begin with an initial risk assessment, including use of platform knowledge, and follow with multivariate experiments."
IV. CONTENT OF ANALYTICAL PRODCEDURES		
Lines 120-213:	Much of this section pertains to instrumental analysis.	Please add additional examples of information to be provided for wet chemical and cell-based assay methods as we believe that Sponsors would find these examples

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		helpful.
Lines 120-213:	This section discusses the content of analytical procedures, but is lacking a section on acceptance criteria.	We believe it would be helpful to include a section on the need for establishing criteria for accepting the data for each sample (sample acceptance) by comparing data output with the working reference standard profile.
Lines 122-123:	This section discusses acceptance criteria, however the term is unclear.	We ask the Agency to clarify its use of "acceptance criteria" as System Suitability Criteria to distinguish from product acceptance criteria (*i.e.* specifications).
Lines 124-127:	The Draft Guidance discusses analytical procedures from FDA recognized sources. We believe that the Agency should consider adding the European Pharmacopoeia (EP) to the list.	Please consider adding the European Pharmacopoeia (EP) to the list of FDA recognized sources in addition to the United States Pharmacopeia and The National Formulary (USP/NF) and the Association of Analytical Communities (AOAC) International.
A. PRINCIPLE/SCOPE		
B. APPARATUS/EQUIPMENT		
C. OPERATING PARAMATERS		
Lines 145-146:	The Draft Guidance discusses "experimental configuration", however, it is unclear what this term means.	Please clarify, modify, or include an example for the term "experimental configuration" (*e.g.,* sample sequence, etc ...).
D. REAGENETS/STANDARDS		

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Lines 148-160:	This section covers reagents/standards, but should only apply to critical reagents and reference standards.	General laboratory chemicals, salts, and solvents should not require specific description in the regulatory dossier. Safety information (MSDS) for general laboratory chemicals should be stored in the laboratory in which they are used and are vendor-specific, therefore safety information should only be required for reference material or custom/in-house reagents. The mechanism for qualification of new lots of critical reagents should be provided. In the case of reference standards, the unique identifier may also be provided.
Lines 152-154:	This section includes grade of chemical as an item to be listed regarding regents/standards. However, chemical grade should only be listed if the grade is critical to the method performance.	Please revise the statement to read: "If the chemical grade is critical, then it should be listed. ~~Grade of chemical~~ (e.g., USP/NF, American Chemical Society, High Performance or Pressure Liquid Chromatography, or Gas Chromatography and preservative free)." We also ask FDA to allow for substitution of reagent grades by evaluation of performance equivalency in cases where the reagent is no longer supplied by the manufacturer.
Line 157:	The section on reagents/standards states that "standard potencies (purity correction factors" should be listed.	Including standard potencies (purity correction factors) would cause sponsors to have to revise/update their method every time a new standard is issued. Standard potencies should already be reported in the reference standard sections of the regulatory dossier. As such, we ask that this be removed from the list.

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Line 160:	"Validated or useable shelf life" is listed as a requirement under reagents/standards, however, this term may not apply to the specific case for reagents.	Please revise to read: "~~Validated~~ Defined or useable shelf life, or retest strategy."
Lines 162-163:	It is unclear if the requirement is that full qualification procedure be included in the test method or if a detailed procedure can be referenced (*i.e.*, qualification of new batches must be performed as described in SOP-XXXX). If the reagent qualification procedure is extensive, it would seem to add opportunity for confusion for an analyst attempting to perform a routine experiment.	We also ask the Agency to clarify that the qualification of new batches of biological reagents, such as monoclonal antibodies, polyclonal antisera, or cells, should be referenced in the Analytical Procedures section used locally. To this end, we recommend editing the statement as follows: "New batches of biological reagents, such as monoclonal antibodies, polyclonal antisera, or cells, may need ~~extensive~~ qualification procedures included or cross-referenced as part of the analytical procedure."
E. SAMPLE PREPERATION		
Lines 169-171:	The Draft Guidance states that "A single preparation for qualitative and replicate preparations for quantitative tests with appropriate units of concentrations for working solutions (*e.g.*, µg/ml or mg/ml) and information on stability of solutions and storage conditions."	For test methods shown to have high precision and the precision is well within the material specification limits, single preparation should suffice even for quantitative tests. Further, we do not feel that replicate preparations for quantitative tests should be mandated. To this end, please edit the statement to read: "A single preparation for qualitative ~~and replicate preparations for quantitative~~ tests with appropriate units of concentrations for working solutions (*e.g.*, µg/ml or mg/ml)

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		and information on stability of solutions and storage conditions. The number of replicates for quantitative methods should be determined based on the precision of the analytical method."
F. STANDARDS CONTROL SOLUTION PREPERATION		
Lines 175-177:	This section appears to require data to support the stability (*e.g.,* expiry) of all standards. However, at times initial expiry is not supported by data but is based on historical information.	We ask the Agency to allow for flexibility in determining the stability for the solutions mentioned here based on nature of the chemical and also the manufacturer or historical information.
G. PROCEDURE		
Lines 181-184:	This section discusses a step-by-step description of the method and allowable operating ranges and adjustments if applicable and includes "sensitivity solution", however, we find this term to need clarification.	We ask the Agency to consider providing clarification of "sensitivity solution" (*e.g.,* solution used to confirm resolution of closely eluting peaks vs solution used to confirm system performance at Quantitation Limit) in this section. We suggest the following revision: "A step-by-step description of the method (*e.g.*, equilibration times, and scan/injection sequence with blanks, placebos, samples, controls, sensitivity solution (~~for~~ quantitation limit of impurity method) and standards to maintain validity of the system suitability during the span of analysis) and allowable operating ranges and adjustments if applicable."

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H. SYSTEM SUITABILITY		
I. CALCULATIONS		
J. DATA REPORTING		
Lines 206-213:	The Draft Guidance states "A presentation of numeric data that is consistent with instrumental capabilities and acceptance criteria." It is unclear whether "consistent with instrumental capabilities" means to instrument's full capabilities? For example, if a method has precision capabilities to report to one decimal place, but specification is to integer value, is that a mismatch?	Acceptance criteria could be presented at a lower number of significant figures than instrumental capabilities. As such, we suggest editing the statement to read: "A presentation of numeric data that is consistent with ~~instrumental capabilities and acceptance criteria~~ acceptance criteria and not beyond instrumental capabilities."
Lines 210-213:	The Draft Guidance discusses the inclusion of retention times (RTs) for chromatographic methods, however the use of RT may not be applicable for biologics. A comparison of the chromatograms is more useful for relative purity methods.	We ask the Agency to make the retention time criteria necessary based on the nature of the method (*e.g.,* RT is needed for identity methods but not for relative purity methods).

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V. REFERENCE STANDARDS AND MATERIALS		
Lines 216-223:	The terminology around "reference standards" and "reference materials" is confusing since they are not consistent between ICH Q6 and ICH Q7. Q6B differentiates between reference standard (international or national standards) and reference material (primary and secondary in-house reference made by the manufacturer). Q7 does not mention reference material, but allows primary reference standard to be either in-house or from an officially recognized source. Q6A does not define any distinction between reference standard and reference material.	We recommend changing the statement as follows to align with the terminology in Q6B as none of the guidance mention primary and secondary reference standards: "Primary and secondary reference materials and reference standards ~~and materials~~ are defined and discussed in the following ICH guidances…"
Lines 224-226:	The Draft Guidance discusses avoiding added impurities and inaccurate analysis, however, it is unclear what is intended. Is the term "to avoid added impurities" intended to mean "to avoid degradation"?	We ask the Agency to clarify what is intended by the term "to avoid added impurities". If it is intended to mean "to avoid degradation" we recommend the following edit: "You should strictly follow storage, usage conditions, and handling instructions for reference standards to avoid added impurities, degradation, and inaccurate analysis."
Lines 238-239:	The Draft Guidance cites "reference materials from other sources", however, it is unclear what is meant by this.	We ask the Agency to clarify whether "reference materials" in this context means the same as "reference standards."
Lines 245-249:	The Draft Guidance recommends a two-tiered approach to qualifying new	While we appreciate and welcome the recommendation of a two-tiered approach we note that even using a two-tiered

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	reference standards.	reference standard approach, analytical drift can be an issue with long-term storage of the primary reference batch. This can be accounted for by ensuring the primary reference standard has not changed over the use-time of the secondary reference standard by including the primary standard and old secondary standard in the qualification of the new secondary standard. We also believe it would be helpful to have additional guidance on qualification required for primary versus reference standard. We ask the Agency to clarify whether the extended characterization proposed in the Draft Guidance apply to only primary or to both primary and working standards.
VI. ANALYTICAL METHOD VALIDATION FOR NDA, ANDAs, BLAs, AND DMFs		
A. NONCOMPENDIAL ANALYTICAL PROCEDURES		
Lines 260-264:	The section requires a description of methodology of each characteristic test and predetermined and justified acceptance criteria.	We request the Agency consider replacing the term "characteristic test" with "validation characteristic" in order to be consistent with section VI B of the Draft Guidance and ICH Q2R1 terminology.
B. VALIDATION CHARACTERISTICS		
Lines 271-300:	The Draft Guidance requires the demonstration of sample stability through the time required to complete the analysis.	We recommend evaluating the stability also of the reference materials, controls, and reagents used in the assay. A non-protocol driven study of column lifetime and storage is also recommended.

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Lines 267-268:	The Draft Guidance states that "ICH Q2(R1) is considered the primary reference for recommendations and definitions on validation characteristics for analytical procedures." This statement is positioned in section A under Noncompendial Analytical Procedures. Where it is a reference for validation characteristics, it should be moved to section B.	We recommend this statement be moved to Section B for Validation Characteristics after the section heading.
Lines 284-286:	The Draft Guidance discusses detection of changes in quality attributes and stability indicating assays.	We ask FDA to clarify that assays selected for use in the stability program should be demonstrated to be stability indicating.
Lines 284-290:	The Draft Guidance discusses demonstrating specificity of a stability-indicating assay. We recommend adding a clarifying sentence to the paragraph.	Please add the following sentence: "Verification of the stability indicating properties of the method may be performed and documented during method development."
Lines 292-296:	This section lists the requirements for accuracy and reliability; however these should not be difference from the performance characteristics required for method validation which are specified in lines 276-282.	Please edit the statement to be in alignment with lines 276-282: "As the holder of the NDA, ANDA, or BLA, you must: (1) submit the data used to establish that the analytical procedures used in testing meet ~~proper standards of accuracy and reliability~~ validation characteristics, and (2) notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application, including

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		changes to analytical procedures and other established controls."
Lines 294-296:	The Draft Guidance states that the application holder must notify the FDA about each change in condition in an approved application beyond the variations already in the application.	We recommend that this should be a risk-based assessment of changes, just as one would do for process changes. Risk-based assessment would allow for decreased level of detail required in the dossier, easing life-cycle maintenance.
Lines 298-300:	The Draft Guidance requires the inclusion of robustness data in the method validation package. However, it seems that this would be too much detail to be part of such a submission.	We recommend editing the statement to read: "The submitted data ~~should~~ may include the results from the robustness evaluation of the method, which is typically conducted during method development or as part of a planned validation study."
Lines 298-300:	The ability to utilize platform knowledge for robustness should be included (if justified). This would enable faster method development lifecycle for platform methods.	We recommend adding the following to the end of the paragraph: "Robustness of methods can utilize data from other products if it can be scientifically justified (for example, some method classes may perform the same independent of the product, and other method classes may perform the same within a product modality, *i.e.*, for all IgG1 molecules)."
C. COMPENDIAL ANALYTICAL PROCEDURES		
Lines 304-322:	The section discusses that results should be generated under a verification protocol.	The verification of a compendial method includes running the method with current material to determine if the method is suitable for use. Validation is not performed and thus a protocol is not required. Results are recorded in a

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		laboratory notebook, worksheet or other controlled test record. Further, the validation of the method is performed by the Sponsor/submitter of the method to USP. The predetermined acceptance criteria are essentially the compendial specification. Predetermined acceptance criteria are used when validating a method and should be omitted from this section. The information included under (2) (details of the methodology) is recorded in a laboratory notebook and does not require a protocol. Overall, we find this section is too prescriptive and should be revised to better reflect the minimum steps necessary to demonstrate the method is suited for use.
Lines 317-221:	The section discusses considerations that may influence what characteristic tests should be in the protocol.	We request that the Agency consider replacing the term "characteristic test" with "validation characteristic" in order to be consistent with section VI B and ICH Q2R1 terminology.
VII. STATISTICAL ANALYSIS AND MODELS		
A. STATISTICS		
Lines 329-336:	The Draft Guidance provides limited insights into elements of comparative analysis for lab to lab transfer purposes.	We believe more insight into and/or expectations around level of precision and accuracy needed for lab to lab transfer, including need for early and late stage programs, would be helpful to Sponsors.

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Lines 332-334:	The section discusses that reportable statistics should be provided with justification.	We find the phrase "should be provided with justification" needs further clarification. We suggest the following edit: "Reportable statistics of linear regression analysis R (correlation coefficient), R square (coefficient of determination), slope, least square, analysis of variance (ANOVA), confidence intervals, etc., should be provided ~~with justification~~ based on the intended use of the method."
B. MODELS		
Line 340:	The section on models references the use of chemometric and/or multivariate models.	We find the use of the term "chemometric" to be unclear. We ask the Agency to provide a footnote on reference to chemometrics to clarify what approaches can be used.
VIII. LIFE CYCLE MANAGEMENT OF ANALYTICAL PRODCEDURES		
Lines 349-351:	The Draft Guidance discusses trend analysis intervals to evaluate the need to optimize or reevaluate the analytical procedure.	We believe a qualifying statement would be helpful as trend analysis of analytical data is easily confounded by changes in reference standard or changes in manufacturing process.
Lines 365-367:	The Draft Guidance states that archived samples should include "samples that represent pivotal clinical trial material and marketed product."	We note that there can be challenges with demonstrating how representative retention samples remain after long-term storage. We request that the FDA provide guidance for demonstrating that samples have not been impacted by long-term storage before use in justifying analytical method life-cycle.

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A. REVALIDATION		
Lines 387-388:	The Draft Guidance states that "The degree of revalidation depends on the nature of the change."	We believe it would be helpful to Sponsors to include an example of when a partial revalidation could be warranted.
B. ANALYTICAL METHOD COMPARABILITY STUDIES		
Lines 418-420:	The use of an alternative procedure should not necessarily require full validation as it depends on the nature of the change. As an example, demonstration of comparable accuracy and precision, and limit of quantification/quantification limit (LOQ) where applicable between the two methods, should suffice.	We suggest editing the statement as follows: "You should identify the use of the alternative analytical procedure (*e.g.*, release, stability testing) and provide a rationale for its inclusion, validation data, and comparative data to the FDA approved analytical procedure. If the original FDA approved method is updated (for example, new equipment model), comparative data should be provided to the FDA dependent on the nature of the change."
Lines 440-441:	The number of batches analyzed for comparison should be statistically relevant and justified for a pre-established confidence interval.	Equivalence, non-inferiority, or superiority studies should be performed with appropriate statistical methods to demonstrate that the new or revised method performance is comparable or better than the original method. As such we recommend the following revision: "The number of batches analyzed for comparison ~~should be statistically relevant and justified for a~~ and the pre-established confidence intervals should be appropriately justified."

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Lines 450-462:	In this section, the concept of co-validation involving multiple testing sites as a way of showing comparability among these sites should be discussed. Co-validation may be performed as a part of intermediate precision study during method validation and this would be done in lieu of conducting method transfer studies.	We suggest editing the section as follows: "…The comparative studies are performed to evaluate accuracy and precision, especially with regard to assessment of interlaboratory variability. Comparability of multiple laboratories or sites may be shown by designing co-validation, participation of multiple laboratories or sites into method validation…"
Lines 452-462:	This section discusses analytical transfer studies. There are times that waiving such protocols are scientifically justified.	We recommend adding the following: "In limited situations, method transfers may be waived if scientifically justified and documented (for example, some method classes may perform the same independent of the product, and other method classes may perform the same within a product modality, *i.e.*, for all IgG1 molecules)."
C. REPORTING POSTMARKETING CHANGES TO AN APPROVED NDA, ANDA, OR BLA		
IX. FDA METHODS VERIFICATION		
Lines 486-488:	The Draft Guidance states "For certain biological products, samples representative of the product for licensure along with summaries of results of tests performed on the lots represented by these samples should be submitted with the BLA."	We believe it would be helpful if the Agency share the risk-based selection criteria used to determine products/analytical methods selected for testing during registration and routine batch release.