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September 1, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–D–0436: International Conference on Harmonisation; Draft Guidance on Q11 Development and Manufacture of Drug Substances

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "International Conference on Harmonisation (ICH); Draft Guidance on Q11 Development and Manufacture of Drug Substances." We appreciate the efforts of FDA and other ICH parties to harmonize the scientific and technical principles relating to the description and justification of the development and manufacturing process in the Common Technical Document (CTD) to enable a consistent approach for providing and evaluating this information across the three international regions. Overall, BIO agrees with and supports the Draft Guidance, which is consistent with Quality-by-Design (QbD) principles and provides enough flexibility to establish a risked-based approach with a variety of project circumstances. We have provided the following general comments and specific line-by-line changes to enhance the value of the document to biopharmaceutical manufacturers.

BIO represents more than 1,100 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.

I. Positive Changes and Useful Examples in the Guidance to be Retained

The Draft Guidance makes several positive recommendations that make significant progress towards a more science and risk-based approach, which should be retained in the final document. These recommendations, such as approaches to starting material selection and justification and appropriate use of data from smaller-scale studies to support process validation, are discussed in greater detail in our specific comments.

The Draft Guidance provides useful examples that compare the traditional approaches to the enhanced approaches. BIO also appreciates the inclusion of examples and sections that address the specific concerns for biotechnological/biological entities. For example:

- Section 3, Manufacturing Process Development, serves as a good roadmap for developing a strategy for manufacturing process development and defining the critical aspects that need to be investigated. The subsection outlining the information that should be included in a submission is also informative.

- Illustrative Example 2, Use of Quality "Risk Management to Support Lifecycle Management of Process Parameters, provides a very useful approach on how process parameters can be categorized using Quality Risk management, and most importantly provides a potential regulatory mechanism on how future changes to such parameters can be handled post-approval at an ICH level, which can help in driving for global harmonization for post-approval changes.

- Illustrative example 4, Selecting an Appropriate Starting Material, is a good example of how to consider all general principles in conjunction, rather that applying each general principle in isolation.

Case studies and mock-ups developed for ICH Q8, such as Sakura tablets by the Japanese National Institute of Health Sciences (NIHS) and "Examplain" hydrochloride by the European Federation of Pharmaceutical Industries and Associations *(*EFPIA*)*, were very helpful. Please consider developing similar mock-ups or case studies for this guideline.

II. Flexible Regulatory Approaches to QbD

The Draft Guidance states that "a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation. (Lines 82-84) BIO agrees that the application of flexible regulatory approaches, especially as it applies to post approval change management, is an important concept that should be retained in the final document.

III. Critical Process Parameters and Consolidation of ICH Guidelines:

There is no mention in the Draft Guidance of Critical Process Parameters associated with drug substance. The definition of parameter criticality is a challenge for many companies, and general approaches to defining criticality should be described. Equally the link between critical process parameters and design space have not been addressed in this guidance as well as in Q8, thus leaving a significant gap in driving for global harmonization of "What constitutes a design space". We hope that the ICH Q11 Expert Working Group (EWG) will take this under consideration and provide additional guidance in this area.

Overall it may make sense after finalizing Q11 to consider consolidating Q8 and Q11 into one ICH guideline on Pharmaceutical development with the following parts. By doing this it may be possible to eliminate some of the redundant text in Q11.

1. General development approaches (ICH Q8 (R2)-Part II)
2. DP specifics (ICH Q8 (R2)-Part I)
3. API specifics (ICH Q11 core)
4. Examples (ICH Q11 examples)

CONCLUSION:

BIO appreciates this opportunity to comment on the "International Conference on Harmonisation; Draft Guidance on Q11 Development and Manufacture of Drug Substances." Specific, detailed comments are included in the following chart. 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)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 67-70:	In addition to the ICH Q8, Q9, and Q10 guidances, there is important implementation information approved by the ICH-Steering Committee (SC) which includes ICH Quality Implementation Work Group (Q-IWG) Question & Answers (Q&A), points to consider documents, and training materials.	Please add: …pertain to the development and manufacture of drug substance**.** For implementation of these principles, support is available (see Q&As, 'points to consider' and training/workshop material by ICH Q-IWG).
Line 72:	Maintaining the validity of the traditional approach to development is a positive message that should be retained in the final document.	Please retain.
Lines 76-80:	Design space is integral to the enhanced approach, but variations in the use of the design space may be appropriate. This aligns with the text later in the document, stating that "An applicant can choose either a traditional approach or an enhanced approach to drug substance development, or a combination of both. (lines 153-155)	Please edit statement to read: In an enhanced approach, risk management and more extensive scientific knowledge are used to ~~select~~ identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish ~~any~~ potential design space(s) and develop appropriate control strategies applicable over the lifecycle of the drug substance**.**
Lines 80-82:	Annex I of Q8 provides the key principles of QbD for drug product and the Q8 core documents link to the P2 part of the CTD.	Please add: As discussed in ICH Q8 Part II for drug product…

III. MANUFACTURING PROCESS DEVELOPMENT		
Lines 104-108:	Please clarify that design and performance are relevant characteristics.	For clarity, please edit statement to read: The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development, design, and performance of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form).
Line110:	Knowledge and understanding of the CQAs can be acquired from experience from data generated for closely related products.	Please edit statement to read: Knowledge and understanding of the CQAs can evolve during the course of development or can be acquired from experience from data generated for closely related products.
Lines 120-122:	Acknowledgement of the value of informal risk assessment approaches is important.	Please incorporate
Lines125-126:	Clarify that prior knowledge includes knowledge taken from the literature.	Please add: Prior knowledge can include established biological, chemical and engineering principles, taken, *e.g.*, from literature, and applied manufacturing experience.
Lines 127-129:	Acknowledgement of prior knowledge including platform manufacturing is valuable to retain.	Please incorporate
Lines 139-140:	"Studied" implies the expectation for	Please edit first bullet to read:

	experimental work when a number of other sources of knowledge can be used.	Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on product quality can be ~~studied~~ evaluated and controlled;
Lines 153-155:	Please provide additional options for control associated with real time release testing (RTRT) approaches	Please edit statement to read: …..which can, for example include a proposal for a design space, release based on parametric control, and/or real time release testing (RTRT).
Lines 160-164:	The clarity provided by the guidance that CQAs are only associated with the drug substance should be retained.	Please retain
Lines 184-192:	We recommend that the risk of biological product CQAs, particularly for impurities, be assessed based on their potential to elicit immunogenicity.	Please edit statement to read: "Biotechnological/biological products, for example, typically possess such a large number of quality attributes that it might not be possible to fully evaluate the impact on safety and efficacy of each one. For biological products, CQAs, particularly for impurities, should be assessed based on their potential risk to elicit immunogenicity. Risk assessments…"
Lines 198-200:	This section provides clear linkage between material attributes and process parameters and the associated CQAs. However, material attributes and process parameters that have an impact on drug substance quality are critical, not just important.	Please replace "important" with "critical" so the sentence reads: Those material attributes and process parameters that are found to be ~~important~~ critical to drug substance quality should be addressed by the control strategy

Lines 201-203:	Risk assessment is only one side of the coin. If a control strategy is defined, risk control and risk communication have to be used.	Please add: Risk assessment as part of a Quality Risk Management approach to define the control strategy of materials upstream from the drug substance can include an assessment of manufacturing process capability, attribute detectability, and severity of impact as they relate to drug substance quality.
Lines 220-222:	If quality risk management (QRM) is applied, risk review should lead to a review of the risk assessment.	Please add: Further risk assessments, *e.g.*, as follow-up of a risk review can be used to focus development…
Lines 235:	Acknowledgement of the value of small scale models to process development should be retained.	Please retain
Lines 237-239:	To provide clarity around what would be considered a "scientifically justified model," we recommend adding an example. We also suggest additional clarifying language.	Please edit the statement to read: A scientifically justified model (*e.g.*, the utilization of linear velocity of the edge of a mixing propeller, rather than rotation speed, to evaluate the scale effect of the mixer, granulator, etc.) can enable a prediction of product quality and can be used to ~~support the extrapolation of~~ predict a set of operating conditions across multiple scales and equipment.
Lines 247-249:	In order to leverage the use of platform data in support of limited validation studies, there should be a stronger link of the text in this part of the document to chapter 7.2	Please add: Irrespective of whether the manufacturing process of a product has been developed using prior knowledge the manufacturing process should be appropriately validated, *i.e.*, a limited number of validation studies may need to be repeated, as appropriate. (see Process Validation/Evaluation Section 7)"

Lines 250-257:	With the first paragraph in the section describing the uses and objectives for a design space the second part of the section could speak to approaches for the development of a design space. Additionally, due to the complex nature of products and complex interaction of CQAs that can affect them (*e.g.*, impact of cell culture parameters on glycosylation, various post-translational modifications), we recommend that considerations specific for biological entity design space be added.	Add the following language and edits: The development of a design space is often iterative starting with general links between the QTPP, Drug product and drug substance CQAs and each respective process. The approach to and the design space(s) will evolve along with the factors listed above. Design spaces can be developed narrowly, by focussing on a single unit operation, or more broadly, across several unit operations. For chemical entity ~~design space~~ development, a major focus is ~~knowledge~~ control of ~~formation, fate, and purge~~ impurities (formation, fate, and purge)...All steps (or unit operations) should be evaluated to establish their potential to effect impurity levels and establish appropriate ~~acceptance criteria~~ control for impurities as they progress through multiple process operations. Design space considerations for biological products will be particularly intricate due to the complex nature of the products themselves and the complex interactions that can affect them, (*e.g.*, the design space for cell culture must assess the wide variety of parameters that can affect glycosylation, various post-translational modifications and disulphide scrambling in the final drug substance.
Lines 265-268:	Bring Q11 into agreement with already established guidance	Please edit statement to read: The significance of a drug substance manufacturing change during development should be assessed by evaluating its potential to impact the quality of the intermediate ~~drug substance~~ nearest the change (and/or intermediate, if necessary ~~appropriate~~).
Lines 313-314:	It is not clear how extensive the development comparability discussion will need to be. It should not be expected to restate too much of the detailed information provided in earlier	Please edit the statement to read: A summary discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

	submissions (CTAs, IND amendments).	
Lines 320-323:	QRM is more than only risk assessment in this case.	Please add: The studies and risk assessments / controls used to establish important aspects of the commercial manufacturing process…
Lines 320-323:	Setting the expectation that studies be listed in a table format is overly prescriptive and may not make sense in many cases. The subsequent paragraph provides sufficient detail to understand what is meant by "appropriately described".	Please edit the statement to read: The studies and risk assessments used to establish important aspects of the commercial manufacturing process and control strategy cited in the application should be appropriately described ~~listed (e.g., in tabular form).~~
Lines 335:	The use of small scale models should be linked to the development of the commercial manufacturing process not necessarily to development studies.	Please edit to read: Small-scale models use to support ~~process development studies~~ the development of the manufacturing process should be described
IV. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS		
Lines 348-351:	A description of comparability plans to address different types of post-approval changes (*e.g.*, changes that are not likely to require comparability studies, changes that will require biochemical comparability studies, changes requiring additional nonclinical studies, etc.) should be included. This can be done in tabular format, with a brief rationale for each plan.	Please edit the statement to read: To facilitate the approval of a design space for a complex product, such as a biotechnological/biological product, an applicant can choose to provide information on how movements within the design space will be managed post approval. This may include a description of comparability plans to address different types of changes (*e.g.*, changes that are not likely to require comparability studies, changes that will likely require biochemical comparability, changes that will likely require nonclinical studies in addition to biochemical comparability) presented in tabular format. This could help the reviewer understand how residual risk will be managed."

V. SELECTION OF STARTING MATERIALS AND SOURCE MATERIALS		
Lines 357-463:	General principles approach to starting material selection and justification represent significant progress toward a more science and risk-based approach to starting material selection and should be retained.	Please retain.
Lines 412-415:	Including the option to propose an isolated intermediate from a semi-synthetic drug substance manufacturing process (with appropriate justification) is also a step toward science and risk based regulation and should be retained.	Please retain.
After 438	Please provide guidance regarding changes in the manufacturing process of a regulatory starting material.	Please add: A change to the manufacturing process for a registered starting material should be managed with the overall quality system. The potential change should include an evaluation of its' potential to impact the drug substance impurity profile, an assessment of whether the current analytical methods and specifications continue to be appropriate and the impact, if any, on the overall control strategy.
Line 443:	Material derived from a non-pharmaceutical market often requires more, not less, scrutiny than custom-synthesized materials. Also, as is the case with excipients the pharmaceutical market might not be large enough.	Please delete "non-pharmaceutical market" so the sentence reads: A commercially available chemical is usually one that is sold as a commodity in a pre-existing, ~~non-pharmaceutical~~ market in addition to its proposed use as starting material.

VI. CONTROL STRATEGY		
Line 477:	An important purpose of the control strategy is control of the critical process parameters.	Please add "especially control of critical" to the third bullet: In-process controls (including in-process tests and especially control of critical process parameters)
Lines 483-485:	The description of traditional approach to development is not accurate.	Please edit to state: In a traditional approach to developing a manufacturing process and control strategy, set points and operating ranges are typically set ~~narrowly~~ based on the observed data to ensure consistency of manufacture.
Lines 489-491:	Please edit the statement to have a more accurate description of traditional versus enhanced approaches to development:	Please edit to state: An enhanced approach to manufacturing process development may generate~~s~~ more comprehensive process and product understanding than the traditional approach, so sources of variability can be identified in a more systemic way.
Lines 498-500:	Control strategy options should include testing the product, in-process testing up-stream of the product, procedural or parameter controls.	Please edit to include the following: In either the traditional or enhanced approach, the control strategy can include an in-process determination (in-process testing or parametric control) that a CQA is within an appropriate limit, range, or distribution in lieu of testing the final drug substance.
Line 519:	Additional guidance about real time release testing would add value to the document. The end of section 6.1.2 would be an appropriate place to introduce the topic.	At the end of section 6.1.2 please add: In either the traditional or enhanced approach, the control strategy can include robust controls designed into the process such that an

		attribute is assured of being within its appropriate limit, range, or distribution without testing the final drug substance. For example in a synthetic process that uses dichloromethane in an early step, removal of the solvent could be demonstrated at that step and therefore testing for the solvent would not be included in the final drug substance specification. For biotechnology/biological product, testing for adventitious agents is an important in-process control that is normally done in the unprocessed bulk instead of in the final drug substance. In Real Time Release Testing (RTRT), in-process testing and/or monitoring directly impact the decision for batch release and are performed in lieu of testing on the final drug substance. Use of RTRT should provide no less assurance of conformance to the drug substance specification than if testing on the finished drug substance were performed. For example, when considering the use of RTRT, applicants should determine how factors downstream from the point at which RTRT will be employed impact the quality of the drug substance, such as temperature changes, oxidative conditions, light, ionic strength, or shear. Once these factors are understood RTRT specifications can be established that will ensure that the drug substance, if tested, will meets its' specifications. For a drug substance the RTRT specification does not necessarily need to be identical, or tighter, than the corresponding drug substance specification. Also when RTRT is proposed for d rug substance CQA, the drug substance specification should include a suitable analytical procedure and associated acceptance criteria to enable independent testing and, if appropriate stability testing. RTRT can replace release testing on the finished rug substance, but does not replace the review and quality control steps called for under GMP to release the batch.

Lines 522-525:	We suggest the following grammatical clarifications	Please improve clarity by editing to read: The summary of the overall control strategy can be presented in either a tabular format or in a diagrammatic format.
VII. PROCESS VALIDATION/EVALUATION		
Line 541:	Additional guidance about the expectations for validation of a design space should be provided.	Please add the following sentence after line 412: There is no *a priori* requirement that the outer limits of a design space need to be confirmed at commercial scale if sufficient data can be provided that demonstrate the process (unit operation) is not scale or equipment dependent.
Line 546:	This needs to specify this sentence applies to synthetic non-sterile processes otherwise it contradicts the previous section on biotech.	Please edit to read: For non-sterile drug substance synthetic processes ….
Lines 563-573:	Support for the appropriate use of data from smaller-scale studies to support process validation is consistent with movement toward a science and risk-based approach to development and should be retained in the guidance.	Please retain
Lines 582-584:	The following statement is very high level: "When platform manufacturing experience is utilised, the suitability of the control strategy should be demonstrated and the drug substance manufacturing process should be appropriately validated at the time of marketing authorisation application".	An example would help readers to understand how suitability can be shown and what this means in the end for validation.

VIII. SUBMISSION OF MANUFACTURING PROCESS DEVELOPMENT AND RELATED INFORMATION IN COMMON TECHNICAL (CTD) FORMAT		
Sections 8 & 9:	With regard to sections 8 and 9, we suggest that either or both of these sections contain some text indicating which section in CTD format should be used to address lifecycle management *e.g.* "Lifecycle management can be summarized in Section 3.2.S.2.6 or 3.2.S.2.2."	Please clarify
Line 601:	Analysis is only one part of risk assessment.	Please edit statement to read: The assessments used to guide and justify development decisions (*e.g.*, risk assessment ~~analyses~~ and functional relationships linking material attributes and process parameters to drug substance CQAs) can be summarized in section 3.2.S.2.6.
Lines 626-628:	Because S.4.5 is the drug substance specification justification section, this is not necessary a good place to address the control strategy since that would lead to inappropriate emphasis on testing.	Please remove "good" so the sentence reads: The section of the application that includes the justification of the drug substance specification (3.2.S.4.5) is a ~~good~~ place to summarize the overall drug substance control strategy.
IX. LIFECYCLE MANAGEMENT		
Lines 663-669:	Chemical equivalence and comparability should be addressed in the lifecycle section.	Please replace the existing paragraph with the following: Proposed changes to the manufacturing process must be evaluated for their impact on drug substance CQAs. Evaluation should be as close as possible to the point in the process at which the change is made (*i.e.*, by showing equivalence at the compound just after the change).

		For example, for small molecules equivalence may be judged by comparison of the pre and post-change impurity profiles. A compound can be considered equivalent if there are no new impurities (at the ICH Q3 qualification level) and no increase in known impurities at the specification level. For biotechnology products the concept of equivalence is replaced by the concept of comparability (ICH Q5E).
X. ILLUSTRATIVE EXAMPLES		
Examples	As discussed in our general comments, the examples provide valuable additional clarification and should be retained.	Please retain.
Lines 699:	Process parameters that have an impact on drug substance quality are critical.	Please replace "important" with "critical" so the sentence reads: Time of reflux and water concentration were identified as the most ~~important~~ critical parameters affecting the hydrolysis of intermediate F.
Line 833: Example 5	Example should illustrate as many possible CQA control strategy approaches as possible. One option that is missing would involve design space control of the attribute without confirmation testing.	Please change the last column response from Yes/Yes to No/Yes for Impurity X