July 19th, 2021

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

Re: Docket No. FDA-2021-D-0166: International Council for Harmonisation Q12: Implementation Considerations for Food and Drug Administration-Regulated Products

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Draft Guidance: *International Council for Harmonisation Q12: Implementation Considerations for Food and Drug Administration-Regulated Products* (Draft Guidance).

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.

BIO appreciates FDA's commitment to harmonization of regulatory concepts across regional Health Authorities through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Harmonization of critical regulatory concepts is an important part of ensuring a consistent and predictable regulatory environment and gives sponsors confidence that their drug development program will be generally accepted within different regions. BIO believes that the concepts in Q12 are important and warrant broad recognition across the globe. Even though implementation of Q12 is voluntary, this Draft Guidance explains FDA's expectations on implementation of Q12 (e.g., format, eCTD locations for information) if an applicant so chooses to implement Q12 and thus is a helpful document.

We appreciate the significant information provided in Section C. Established Conditions; however, we note the following overarching comments to this section:

- It is not clear whether this document should be read in conjunction with the FDA's May 2015 Draft Guidance "*Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products*" and/or whether that guideline has been withdrawn? FDA made it clear in the 2015 Draft Guidance and again here that ECs exist in all dossiers, and in this Draft Guidance that the application of Q12 to call out specific ECs and their reporting categories is voluntary. We note however, that FDA only provided clarity on which elements of the CTD are considered ECs in the 2015 ECs Draft Guidance which is not referenced here. Should companies continue to use the 2015 guidance to define what FDA *"typically considers to be EC*s" (per line 81)?

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- We note that FDA have introduced terms "specific ECs" (line 101) which closely mirrors the term "*explicit ECs*" proposed in the Step 1 drafts of ICHQ12. We support this but note the need to refer to the 2015 guidance to determine what are "*non specified ECs*".
- We welcome the general principles of applying ECs to information on Drug Device Combinations (DDCs) in Section 4, but note it is important that requirements for ECs are aligned globally and we urge FDA to ensure this section is aligned with the principles and examples under development by the ICH Q12 IWG. Additionally, as noted in the chart we are concerned about the potential introduction of new terms which are not internationally aligned (e.g., the term "primary characteristic"). It is not clear also how the terms in this section relate to terminology in ICHQ8-11 (e.g., how "criticality" links to ECs?). For example, which elements of the device are considered input materials CQAs for the drug product?

BIO appreciates this opportunity to comment on the Draft Guidance: *International Council for Harmonisation Q12: Implementation Considerations for Food and Drug Administration-Regulated Products*. 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/
Victoria A. Dohnal, RAC
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS:

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. CONSIDERATIONS FOR IMPLEMENTATION		
A. Introduction		
B. Categorization of Postapproval CMC Changes		
Lines 58-64:	We appreciate that the Guidance confirms notification categories and that changes to non-ECs can be made under the PQS with no regulatory action (e.g., no requirement to supply information on changes to non-ECs within the annual report).	BIO suggests making this more explicit by including a sentence such as: "As indicated in ICH Q12, the lowest risk changes are managed and documented within the pharmaceutical quality system (PQS) applying the principles of ICH Q10 and ICH Q9 and do not need to be reported."
C. Established Conditions		
Lines 73-74:	The Draft Guidance states "In addition, existing FDA guidance documents describe a broad set of postapproval changes and make recommendations for how they should be reported". The purpose of ICH Q12 is to allow for the Sponsor to use a reporting category that is appropriate for their product based on ICH Q12 science and risk-based principles with justification, even if not in alignment with current expectations.	BIO suggests editing the text to read: "In addition, existing FDA guidance documents describe a broad set of postapproval changes and make recommendations for how they should be reported. Use of ICH Q12 principles may allow for use of different reporting categories than recommended in current guidance or current expectations."
Lines 84-86:	The Draft Guidance states "If specific ECs are not proposed, ECs would be those that FDA typically considers to be ECs based on the risk-based paradigm set forth in the regulations and the recommendations contained in guidance regarding postapproval changes."	BIO suggests editing the text to read: "If specific ECs are not proposed, changes to information in the dossier should be handled according to ~~ECs would be those that FDA typically considers to be ECs based on~~ the risk-based paradigm set forth in the regulations and the

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	It appears that this sentence describes "implicit ECs". However, in Q12 it was decided to not include implicit and explicit ECs. This may be confusing if there are still ECs even though Q12 is not applied. In the lines 71-72 it also stated that other regulations do not specify ECs.	recommendations contained in guidance regarding postapproval changes." Alternatively, lines 84-86 could be deleted.
Lines 103-104:	The Draft Guidance provides "Specific ECs are not proposed; postapproval changes will follow the regulations and the recommendations in guidance" as one of the options for the cover letter.	BIO suggests that this stipulation should be removed from the Draft Guidance, since following regulations and guidance is already implied when a Sponsor decides not to implement Q12 and define specific ECs.
Lines 106-138	BIO believes that the information regarding whether or not specific ECs are being proposed could be captured more clearly in the form of a checklist to be submitted by the applicant.	FDA may wish to consider appending a template checklist to the Guidance for this purpose. We provide the following example of a proposed checklist: ¨ Specific ECs are proposed ¨ Specific reporting categories are proposed for ALL ECs ¨ Specific reporting categories are proposed for limited set of ECs ¨ Specific ECs are proposed BUT specific reporting categories are not proposed ¨ Specific ECs are not proposed (¨ = checkbox; applicant to check the relevant checkbox)

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Line 106:	The Draft Guidance states "Include one of the following statements in eCTD section 3.2.R of the application:" In order to have greatest flexibility it should be possible to submit ECs with no diverging reporting categories and at the same ECs with diverging reporting categories based on justification and broader risk understanding and knowledge of such ECs. It is not necessary to apply ECs to all parts of the Module, thus there should be a possibility to have specified ECs for certain sections and no defined ECs for other sections.	BIO suggests editing the text to read: "Include at least one of the following statements in eCTD section 3.2.R of the application…"
Lines 115-116:	The Draft Guidance provides "Specific ECs are not proposed; postapproval changes will follow the regulations and the recommendations in guidance" as one of the options for the cover letter.	BIO suggests that this stipulation should be removed from the Draft Guidance, since following regulations and guidance is already implied when a Sponsor decides not to implement Q12 and define specific ECs.
Lines 122:	The Draft Guidance states "Include one of the following statements in eCTD section 3.2.R of the application:" In order to have greatest flexibility it should be possible to submit ECs with no diverging reporting categories and at the same ECs with diverging reporting categories based on justification and broader risk understanding and knowledge of such ECs. It is not necessary to apply ECs to all parts of Module, thus there should be a possibility to have specified ECs for certain sections and no defined ECs for other sections.	BIO suggests editing the text to read: "Include at least one of the following statements in eCTD section 3.2.R of the application…"

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Lines 148-151:	The Draft Guidance states "When proposing specific ECs, applicants should include a scientific justification for their selection in the relevant parts of module 3 of the application. In this justification, applicants should address both the identification of particular parameters or attributes as ECs and the proposed reporting categories (if applicable)." It is important to ensure that guidance regarding CTD location doesn't prevent companies from submitting the same dossier all over the world (including countries that do not accept EC).	BIO recommends clarification of "relevant parts" of module 3. For example, does "relevant parts" include 3.2.R, where a comprehensive summary document containing a justification based on information and data located in multiple other module 3 sections could reasonably reside?
Lines 155-171:	The Draft Guidance discusses the parameters and attributes identified as ECs. BIO notes that in order to meet the suggestion in the text there would be a lengthy explanation for the general process/tools used for identifying ECs and determining reporting categories, where applicable. In addition, more specific details would need to be provided for each parameter. BIO assumes that the Agency does not want a complete description of the general risk assessment process at the point of discussion for each parameter or unit operation. In addition, with respect to information/data used to justify the parameters, "relevant parts of module 3" could include multiple locations for each parameter or unit operation.	BIO recommends the Guidance include an option to include all risk assessment process/tool explanation and EC/reporting category justifications in a comprehensive summary document located, for example, in 3.2.R.
Lines 160 – 163:	The Draft Guidance states "A description of the applicant's risk assessment process (including tools)	BIO suggests editing the text to read:

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	used to identify particular parameters or attributes as ECs, the criticality assessment conducted to determine the level of impact of each parameter on product quality…" An overview of the applicant's risk assessment process is typically provided in the introduction to the Drug Substance Manufacturing Process Development and Drug Product Pharmaceutical Development sections. This statement in the Draft Guidance is very broad and is open to interpretation as to how much detail on the risk assessment process is expected by FDA. The output of the risk assessment should be provided, not the approach that was taken to develop the risk assessment.	"A description of the applicant's risk assessment process (including tools) used to identify particular parameters or attributes as ECs, the results of the applicant's criticality assessment conducted to determine the level of impact of each parameter on product quality…"
Lines 190-191:	The Draft Guidance states "…their associated reporting categories can be specified in and approved as part of the application." BIO notes that the DMF holder may not be willing to share proprietary manufacturing information with the applicant, so the applicant may not have access to this information.	BIO suggests editing the text to read: "…their associated reporting categories can be specified in and approved as part of the application. Alternatively, eCTD section 3.2.R should include the statement 'specific ECs are not proposed for DMF [reference number]."
Lines 208-210:	The Draft Guidance states "One approach is to assess the "characteristics of the product that are essential for its safe and proper use" (primary characteristics) relating to the device constituent part and to identify the associated ECs." FDA should use consistent terminology for characteristics pertaining to the device constituent of	BIO believes that consistent and known terminology should be used throughout the Guidance. Where a new term is being introduced, it is important to clearly define and discuss how it is different from existing terminology.

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	a combination product. The term "primary characteristics" has not been previously used by FDA, and it is unclear how "primary characteristics" compare to Essential Performance Requirements (EPRs). If these terms are equivalent, the Draft Guidance should use consistent terminology. If "primary characteristics" do not refer to EPRs, the Guidance should clarify how they differ. This comment applies throughout the Draft Guidance document, including within Appendices A and B.	
Lines 244-245:	The Draft Guidance states "As indicated in ICH Q12, applicants may propose to add, eliminate, or make changes to approved ECs or revisions to their associated reporting categories through:" It is unclear what is meant with "changes to ECs". ECs could be changed according to their pre-agreed reporting category. Thus, it may be confusing if stated in line 253 that all other changes need to be submitted as PAS (besides addition of an EC with guideline reporting category).	BIO suggests the Agency provide clarity which changes to ECs are meant in the context here or "or make changes to approved" is removed from the text.
Lines 249-251:	The Draft Guidance states "Addition of an EC that provides increased assurance of the quality of the drug substance or product with a reporting category provided for in the regulations or recommended in guidance should be submitted as a CBE-0 (see § 314.70(c)(6))." A parameter initially identified as low risk (non-EC) could subsequently be identified as an EC based on	BIO suggests editing the text to read: "Addition or reclassification of a non-EC to an EC that provides increased assurance of the quality of the drug substance or product with a reporting category provided for in the regulations or recommended in guidance should be submitted as a CBE-0 (see § 314.70(c)(6)).

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	manufacturing experience. This change would provide additional clarity in the Guidance.	
Lines 272-276:	The Draft Guidance states "To ensure that FDA has access to up-to-date analytical procedures, applicants should include in the annual report a copy of all analytical procedures that have been appropriately modified during the reporting period without a submission (i.e., managed only through the PQS as changes did not relate to ECs)."	BIO requests that this expectation be removed from the Guidance, since it essentially makes any change to an analytical method at least a notification, thereby eliminating the management of appropriate changes via an effective PQS as permitted by Q12. Further, there are other ways to share the most up-to-date analytical procedures with FDA, e.g., upon request in case required for testing by a state laboratory.
D. Postapproval Change Management Protocol		
E. Product Lifecycle Management Document		
		BIO requests that the Agency clarify that PLCM document should not always be required (for example when there are no specified ECs). We also request further clarification on timing of the initial PLCM document submission and if it could be submitted with either the initial marketing application or at the stage of post approval variations.
Lines 300-315:	Facility establishment identifier (FEI) is mentioned as being preferred information in the PLCM. BIO believes that Facility / FEI number is above and beyond the information specified in ICH Q12.	We suggest that guidance can be given for the Sponsor to indicate, where applicable, any facility-specific differences in EC.
Lines 302-305:	The Draft Guidance states "FDA recommends that the PLCM document be provided in tabular format in	We believe that the eCTD section reference should be sufficient for identification of location. As such, BIO

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	eCTD section 3.2.R, with specific references to the submission sequence, eCTD section number, and page number where each EC's scientific justification can be found."	suggests removing the text referring to the page number as this could be challenging when preparing an application.
Line 306, Footnote 15:	The Draft Guidance mentions manufacturing sites where an EC will be implemented with the Footnote discussing facilities responsible for design control for a combination product.	BIO requests that FDA provide additional clarification on the relevance of Footnote 15. A design control site would generate the data that justifies the EC, but not likely to implement the EC.
Lines 318-319:	The Draft Guidance states "If no specific ECs are proposed, submission of a PLCM document is not necessary." It is not clear that a PLCM document is only needed when specified ECs are proposed. As written, this seems linked to the lifecycle maintenance of the PLCM.	BIO suggests adding the following text after this sentence: "Where specific ECs are proposed, a complete list of specific proposed ECs, their reporting categories (if proposed), and the eCTD locations for…"
F. Pharmaceutical Quality System and Change Management		
Line 337:	The Draft Guidance discusses that "reassessment of the relevant ECs" should be included in supplements that propose a new site. Where the same company PQS is in play, one would expect that the ECs and reporting conditions should remain the same provided the manufacturing process and the principles of operation for equipment does not change.	BIO suggests that the Draft Guidance should include additional details to clarify what this reassessment entails when adding a new site. For example, manufacturing process ECs (parameter PARs, in-process controls) would generally apply to the new site as long as the equipment is same operating principle and scale-down models used to originally establish PARs remain applicable.
Lines 342-343:	The Draft Guidance states "FDA will also consider information included in a supplement that supports a	BIO believes that the Draft Guidance should state what information should be included in the supplement to support the GMP standing and PQS

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	determination that the new site deserves the same level of regulatory flexibility…"	effectiveness of the new site to enable this flexibility and how this information differs from the information that FDA generates from PAI and compliance inspections to make that determination.
Lines 345-348:	The Draft Guidance states "The determination of PQS capability will consider factors such as whether the new site is operated under the same PQS as the original…" BIO notes that different sites may have differences in their PQS, important is the PQS capability and not the sameness of the PQS.	BIO suggests editing the text to read: "The determination of PQS capability will consider factors such as whether the new site is operated under ~~the~~ ~~same~~ an equivalent PQS as the original…"
G. Relationship between Regulatory Assessment and Inspection		
H. Structured Approaches for Frequent CMC Postapproval Changes and Stability Data Approaches to Support the Evaluation of CMC Changes		
APPENDIX A. ESTABLISHED CONDITIONS FOR COMBINATION PRODUCTS WITH DEVICE CONSTITUENT PARTS		
Lines 392-393:	Appendix A includes a list of items that are generally considered ECs for the device constituent including "Manufacturers: Name, address, and responsibilities for sites that perform assembly, packaging, and testing of the device constituent part." BIO notes that assembly, packaging, and testing typically pertain to the overall combination product.	BIO suggests editing the text to read: "Manufacturers: Name, address, and responsibilities for sites that perform assembly, packaging, and testing of the ~~device constituent part~~ combination product."
APPENDIX B. DECISION TREE FOR IDENTIFYING ESTABLISHED CONDITIONS AND REPORTING CATEGORIES FOR DEVICE CONSTITUENT PARTS		
	The decision tree box stating "design features that are primary characteristics".	BIO recommends clarifying if these are the same as what FDA has been referring to as "Essential Performance Requirements (EPR)".

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		The decision tree should be updated to better align with ICH terminology. In particular, the criteria for determining the reporting category for changes to ECs ("What is the level of potential risk associated with the proposed change?") should be updated to align with the decision tree in Figure 1 of ICH Q12 ("Considering the output of the criticality assessment and the control strategy, what is the risk to product quality if the parameter is changed")
Decision Point "CBE-30 or CBE-0":		BIO suggests adding a reference to the Annual Report as a notification mechanism for Low-Risk changes.
APPENDIX C. PRODUCT LIFECYCLE MANAGEMENT DOCUMENT EXAMPLE		
Lines 407-412:	The Draft Guidance provides one example for a small molecule.	It would be beneficial to provide examples of biologic and analytical established conditions. These examples would provide clarity to Sponsors of how to follow the Agency's recommendations for a change to an established condition. This clarification should reduce ambiguity, minimize the number of questions received from Sponsors, and thereby reduce potential delays in drug development.
Lines 409-411:	The Draft Guidance states "In this example, where the applicant proposes to follow FDA regulations and the recommendations in guidance for a change to a particular established condition, the reporting category has been left blank."	This table does not include references to the eCTD sections where ECs and filing categories are justified. The text calls for provision of those references in the PLCM. Additionally, some of the rows in the table with the specified category should change and be left blank since they reflect current regulations and/or guidance.

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Row: Seq 0004…	The example suggests that all process parameters included in the Design Space (DSp) for blending would be ECs.	It would be beneficial to understand the general expectations. Namely, are only selected process parameters within a DSp classified as ECs or is the entire DSp an EC? If the latter is the case, then it can limit utilization of knowledge generated during development for streamlined post-approval management. A DSp can be represented by a mathematical expression, or by ranges for material attributes and process parameters. For the latter case, it would be helpful if only selected parameters (and their associated ranges) are classified as ECs. Otherwise, the following challenges associated can be anticipated: 1. A DSp will invariably consist of CPPs and non-CPPs, and by the virtue of the entire DSp being an EC, even the non-CPPs in the manufacturing process will become ECs. This might somewhat negate the value of ICH Q12. 2. A DSp will consist of material attributes and process parameters that do not have interdependencies. This knowledge is available during development, and by claiming a DSp as an EC, the ability to change a single parameter within a DSp might be limited, especially in a case where such a parameter might be a non-CPP and therefore, in principle, a non-EC.

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		In general, DSp should be a development tool, and not used as a regulatory tool for post-approval management. In case a DSp is represented by a mathematical expression, a potential approach would be to classify such a DSp as a high, medium, or low impact model. For example, a DSp with low impact can be classified as a non-EC.