Biotechnology Industry Organization

July 31, 2015

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

Re: Docket No. FDA-2015-D-1659: Draft Guidance on Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance on Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" ("Draft Guidance").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 members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

A. General Comments

Generally, BIO would like to highlight the following three points:

1) The Draft Guidance is one positive step forward on reporting chemistry, manufacturing, and controls (CMC) changes for approved drug and biologic products;

2) Many changes to an approved drug and biologic product can be managed by the Pharmaceutical Quality System (PQS); and

3) We encourage FDA to work with the International Conference on Harmonization (ICH), specifically the Q12 working group, on a global approach for these types of changes.

BIO agrees with the guidance's recommendation that not only can a drug be managed over its lifecycle via the CMC process, but also under current good manufacturing practices (cGMPs) per 21 CFR 210 and 211, and ICH Q7. Indeed, many products are successfully managed in this way. The guidance also calls on the PQS to manage the process over the product lifecycle, which BIO believes is appropriate.

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We acknowledge that the table included in the Draft Guidance is intended as a guide to assist in identifying established conditions and that relevant information would still be considered an established condition even if it is not located in one of the specified sections. BIO believes that the converse concept should also hold true; that all information in common technical document (CTD) sections marked as established conditions may not always be established conditions, based on the knowledge and experience of a manufacturer for a particular application. As such, manufacturers have the flexibility to make an argument that such information is not an established condition. For example, the Draft Guidance generally recognizes process validation to not be an established condition; however, this is somewhat in conflict with the equipment settings and ranges that are highlighted as established conditions. It should be noted that topics such as machine settings—unless critical to quality (*e.g.,* sterilization parameters)—should generally not be established conditions and instead treated as supportive information in an application.

B. Clarity Improvements

The Draft Guidance provides more granularity around which sections of the CTD contain information that would be considered an established condition. However, we recommend that the Draft Guidance contain adequate descriptions of the flexibility afforded to manufacturers to make the case that particular information may or may not be an established condition based on the knowledge and experience for a particular application. It is also important that the guidance recognize and encourage continuous process improvement and the ability of the PQS to manage certain changes. Further, information supporting established conditions will likely change over the course of the product's lifecycle and manufacturers should have the opportunity to update the established conditions in a particular application as they gain more knowledge and experience. Finally, it is important that the guidance recognize that because of the differences between large- and small-molecules, established conditions could vary depending on whether the submission is for a new drug application (NDA) or biologics license application (BLA).

Although flexibility identifying established conditions is desired, there are some sections of the guidance that might benefit from greater clarity. For example, the Draft Guidance states that "sufficient detail" should be given to assure process performance and quality of the approved product; however, it is unclear what would qualify as sufficient detail. To provide better clarity on this point, BIO recommends that examples which depict the extent of detail expected in specific CTD sections to demonstrate process performance and quality of the approved product be added to the Guidance, either in an Appendix or a supplemental Q&A document.

Finally, there are many footnotes to the Draft Guidance that contain requirements or other important information. For example, footnote 12 points to a different section of the CFR for additional expected content. BIO believes that important details of this nature should be integrated into the text of the document for ease of use and clarity.

C. Combination Products

The Draft Guidance includes information on submission content for small molecules and biologics, but does not address information that is provided in BLA or NDA submissions for integrated drug delivery combination products, nor does it exclude them. BIO asks FDA to state clearly in the introduction whether such device constituent parts of combination products are within the scope of this guidance (*e.g.,* design verification data, design validation data, or the design history file).

CONCLUSION:

In conclusion, we would like to reiterate the following three points: 1) we believe the Draft Guidance to be one positive step forward on reporting CMC changes for approved drug and biologic products; 2) many changes to an approved drug and biologic product can be managed by the PQS; and 3) we encourage FDA to work with ICH, specifically the Q12 working group, on a global approach for these types of changes.

We provide additional specific, detailed comments to improve the clarity of the Draft Guidance 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 23-25:	The Draft Guidance states, "For those changes that do require reporting, a better understanding of the established conditions could allow for a more effective post-approval submission strategy by the regulated industry."	To improve the clarity of this statement, BIO suggests editing the text to read: "~~For those changes that do require reporting, a~~ A better understanding of the established conditions could allow for a more effective post-approval submission strategy ~~by the regulated industry~~ for those changes that do require reporting."
II. BACKGROUND		
Lines 111-114:	The Draft Guidance states, "…could rely upon one or more robust PQSs to assess, validate, and implement many post-approval changes appropriately, resulting in a more systematic reduction in or elimination of certain reporting requirements"	BIO believes it would be helpful to define "one or more robust PQSs." To this end we suggest following the ICH Q10 definition. BIO suggests following modification: "…could rely upon one or more robust PQSs in compliance with ICH Q10 to assess, validate, and implement many post-approval changes appropriately, resulting in a more systematic reduction in or elimination of certain reporting requirements"
III. ESTABLISHED CONDITIONS		
A. DEFINITION OF ESTABLISHED CONDITION		
Lines 128-129:	The Draft Guidance states, "Sufficient detail should be provided in the application regarding the proposed established conditions to assure process performance and quality of the approved product."	BIO notes that the wording ("sufficient detail") is subjective and does not provide guidance to the reader. BIO recommends that examples which depict the extent of detail expected in specific CTD sections to demonstrate process performance and quality of the approved product be added to the Guidance, either in an Appendix or a supplemental Q&A document.

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B. ELEMENTS OF A CONTROL STRAGETY THAT MAY BE CONSIDERED ESTABLISHED CONDITIONS		
Lines 140-144:	The Draft Guidance states, "The controls can include parameters and attributes related to drug substance (DS), excipients, in-process materials, inclusive of small and large molecule products, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring, sampling, testing, and control, etc."	In order to ensure consistency between this Draft Guidance and ICH Q10, BIO suggests editing the statement to read: "The controls can include parameters and attributes related to drug substance (DS) and drug product materials and components, facility and equipment operating conditions~~, excipients, in-process materials, inclusive of small and large molecule products, facility and equipment operating conditions~~, in-process controls, finished product specifications, and the associated methods and frequency of monitoring, ~~sampling, testing,~~ and control~~, etc.~~" This proposed wording agrees with the wording in ICH Q10. Additionally, BIO suggests using the topics listed in line 140-144 as the headers for the examples listed in the bulleted list in lines 154-166. Finally, BIO believes that changes to the frequency of monitoring and sampling should be conditions that can be changed within a PQS that complies with ICH Q10. As such, the frequency of monitoring and sampling should not be part of established conditions.
Lines 154-166:	The Draft Guidance discusses control strategy elements that could be established conditions.	For consistency with the list in lines 140-144 mentioned above, BIO suggests using these (drug substance, drug product materials etc.) as the topic headings in the bulleted list in lines 154-166.
Line 156:	The Draft Guidance states, "Source of and specifications for starting materials for biological	BIO suggests further specifying the meaning of and providing examples for the term "source" of starting materials for small

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	products."	molecule drugs.
Lines 161-162:	The Draft Guidance states, "Specifications including the tests, analytical procedures and acceptance criteria; including specifications for the DS, other components, in-process materials, and the DP."	BIO suggests clarifying this bullet point to include release and stability tests: "Specifications including the tests (release and stability), analytical procedures and acceptance criteria; including specifications for the DS, other components, in-process materials, and the DP."
Line 166:	The Draft Guidance states, "Maintenance strategy for chemometric and/or multivariate models (e.g., for models that may have a high impact on product quality).	BIO believes that a maintenance strategy for a model should be regarded as maintenance to any system or equipment used to manufacture a substance or product. Chemometric and/or multivariate models may be used to optimize the manufacture of a substance or product within an established range (an agreed operating range described in the application). Maintenance of a model is part of continuous quality improvement, and therefore changes to the model maintenance strategy (when maintenance is performed, what is included as part of maintenance) should not require submission to the Agency. The only exception is when a change in the model results in a change to established process range.
Lines 168-169: (figure)		For additional clarity BIO suggests amending the outer box of the figure to read: "Control Strategy (Managed under PQS)"
Lines 174-175:	The Draft Guidance states, "In these cases, FDA will consider these aspects when assigning allowable variations within the established	It is unclear what is meant by "allowable variations within the established conditions." As such, BIO asks FDA to provide clarity regarding this term, as well as examples.

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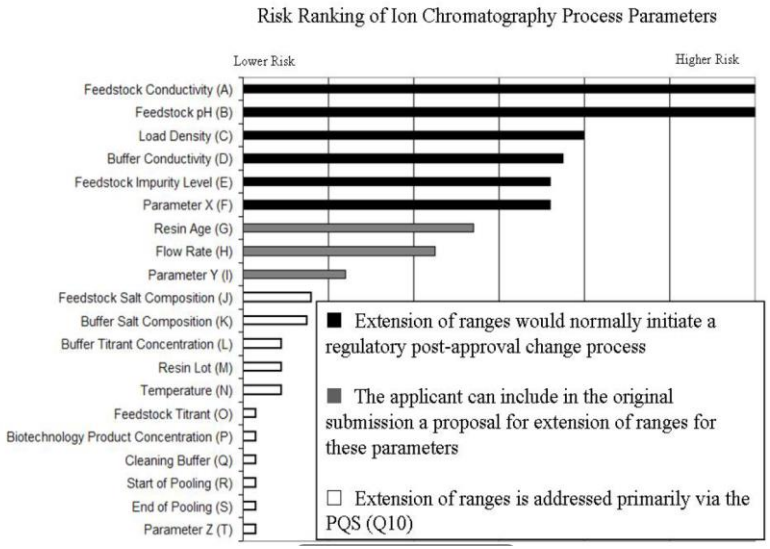
	conditions in the application."	
Line 183 – 190:	Although a control strategy is generally supported and verified by elements listed below, these elements are not generally considered established conditions: "**Batch records[13]**" "[13] The batch record should reflect the current manufacturing process and the associated in-process parameters and controls needed to ensure product quality and performance. It is not expected that all changes to a batch record would be reported to FDA, but if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory submission. Refer to 314.50(d)(1)(ii)(c) and 314.94(a)(9) for associated regulations about batch record submission."	All the details are captured in the batch record or master batch record description, BIO agrees with FDA that batch records are not part of established conditions. Additionally, the low risk parameters should not be part of established conditions, as stated in the example in ICH Q11 (see below figure). The low risk parameters and changes to these should be addressed primarily via the PQS. 

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Lines 183-195:	The Draft Guidance lists elements of an application that are not generally considered established conditions.	BIO asks FDA for clarification on what the expectation is for updating the application with additional validation data that is not generated to support or lead to a change in an established condition (*e.g.,* continuous process verification).
Line 186; footnote 13	The footnote states, "The batch record should reflect the current manufacturing process and the associated in-process parameters and controls needed to ensure product quality and performance. It is not expected that all changes to a batch record would be reported to FDA, but if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory submission."	BIO notes that "process parameter" is an ICH term, "in-process parameter" is not, and the usage may confuse readers between process parameters and in-process controls, which are two distinct categories of process inputs (controlled parameters) and process outputs (tests) respectively. As such, we recommend editing the statement to read: "The batch record should reflect the current manufacturing process and the associated ~~in-~~process parameters and in-process controls needed to ensure product quality and performance."
IV. PRINCIPLES FOR ESTABLISHED CONDITIONS IN APPLICATIONS		
A. SECTIONS OF CTD THAT TYPICALLY CONTAIN ESTABLISHED CONDITIONS		
Line 206:		BIO suggests adding a line preceding the table stating that CTD content should be consistent with current ICH regulations/guidance. Additionally, we suggest FDA provide examples of data in other Module 3 sections not listed in the table that may be considered an "Established Condition."
Line 208; pages 7-11	This section lists out the sections of the Common Technical Document (CTD) that often contain established conditions.	BIO requests FDA remove the column "Examples of Established Conditions" in the table. BIO instead recommends that examples are added to the

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		guidance, either an Appendix or a supplemental Q&A document, which depicts the extent of detail expected in specific CTD sections to demonstrate process performance and quality of the approved product.
Line 208; page 7:	CTD section 3.2.S.1.2 Structure is included as an established condition.	BIO suggests that structure should be eliminated as an Established Condition as this section is a summary of information provided in S3.1 Elucidation of Structure. Changes that would impact the structure would be a part of the control strategy or manufacturing process and starting materials that are a part of the Established Conditions and indicated in 3.2S2.3 Control of Materials and 3.2S.2 Manufacturing Process and Process Controls.
Line 208; Page 7:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	In CTD section 3.2.S.2.2 (Description of Manufacturing Process and Process Controls), the operating conditions are investigated in process characterization studies and thus the claimed process parameter ranges should be considered as part of the established conditions and not the target settings. Thus, BIO recommends the following changes: "Sequential procedural narrative, including certain information in the control strategy that assures process performance and drug substance quality, such as: identification of steps, process controls and parameters ~~(with ranges)~~, equipment and operating conditions ~~(including target settings)~~, input materials, and intermediates."
Line 208; Footnote 16:		BIO recommends incorporating the content of this footnote on process validation activities a part of the main text rather than a footnote. This is a core element that the guidance is intending to clarify.

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Line 208; page 8:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	BIO suggests indicating that CTD section 3.2.S.2.4 (Controls of Critical Steps and Intermediates) applies only to intermediates if part of the overall control strategy.
Line 208; pages 8, 11:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	In CTD sections 3.2.S.5 (Reference Standards or Materials) and 3.2.P.6 (Reference Standards or Materials), BIO suggests clarifying whether this is applicable for primary reference standards and not for secondary standards, since management of secondary reference standards typically happens through the PQS. BIO recommends the following changes: "Qualification protocols for new and existing primary reference standards or materials."
Line 208; page 10:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	The operating conditions are investigated in process characterization studies and thus the claimed process parameter ranges should be considered as the established conditions and not the target settings. Thus, in CTD section 3.2.P.3.3 (Description of Manufacturing Process and Process Controls), BIO recommends the following change: "Sequential procedural narrative, including certain information in the control strategy that assures process performance and product quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions ~~(including target settings)~~, input materials."
Line 208; page 11:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	While it is understood that a given section will include both established conditions as well as elements that are not considered to be established conditions, the reporting requirements for elements of an application that are not considered established conditions are unclear. BIO asks FDA to

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		provide clarity regarding the expectations for reporting changes to information in the application that are not considered established conditions. While it is noted that postapproval stability commitments are considered to be established conditions, the stability data sections are not. We ask FDA to clarify whether the stability data generated under new postapproval stability protocols are required to be submitted in annual reports.
Line 208; page 11:	This section lists the sections of the Common Technical Document (CTD) that often contain established conditions.	For existing reference standards, the requalification protocol is provided. Thus, in CTD section 3.2.P.6, BIO recommends the following change: "Qualification or requalification protocols for new and existing reference standards or materials."
B. ESTABLISHING CONDITIONS AS PART OF THE APPLICATION SUBMISSION AND REVIEW		
Lines 212-219:	The Draft Guidance recommends that the applicant's summary of the proposed established conditions in the application be provided in a tabular format.	To ensure the Agency and Industry agree on when an Established Condition is changed, it is proposed that changes to these conditions be outlined in the Quality Overall Summary (QOS) for post approval variations. However, if FDA requires this summary in tabular format, BIO asks FDA to provide an example of this formatting. Further, we ask FDA to please clarify if it is appropriate to include in the list of established conditions the intended reporting mechanism for changes to the conditions (*i.e.,* annual report, CBE, PAS).

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Lines 223-227:	The Draft Guidance states, "Demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions. As such, those parameters may be determined to not be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report."	It is not clear which sections of the application should articulate "risk mitigation to allow for greater operational flexibility for certain parameters typically considered established conditions." BIO suggests articulating what sections should provide risk mitigation, or provide examples of this proposed content.
Lines 223-227:	The Draft Guidance states, "Demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions. As such, those parameters may be determined to not be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report."	It is not clear whether adequate demonstration of risk mitigation would result in the ability to report changes to established conditions in a lower reporting category than those outlined in the guidance documents listed in lines 77-88. BIO requests that FDA provide clarity regarding how the "operational flexibility" for certain parameters will be communicated to the applicant.
Lines 225-228:	The Draft Guidance states, "As such, those parameters may be determined to not be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report. FDA will consider the established conditions to be finalized at application approval or licensure."	It is not clear how the FDA will communicate the finalized established conditions. Based on this statement as well as instruction on providing a summary of the established conditions (lines 212-219), there seems to be an expectation to tabulate the established conditions. BIO suggests providing more specific guidance on how FDA will notify the Sponsor of the final established conditions, once approval is received. Additionally, further clarification should be provided on how an inspector will know the established

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		conditions for each product at the facility to guide what is in scope of the Pharmaceutical Quality System (PQS) and was is not.
Lines 236-238:	The Draft Guidance states, "For legacy products for which the applicant did not submit an original application with a clear delineation of the established conditions, FDA intends to develop a process by which application could obtain clarification regarding established conditions."	BIO suggests that FDA remove this text from the guidance and instead state that legacy products are excluded from the scope of the guidance. Additionally, it may be helpful for FDA to develop a new guidance regarding legacy products which would include how an applicant could take a stepwise approach to developing clear delineation of established conditions for such products.
C. CHANGES TO ESTABLISHED CONDITIONS		
Lines 258-262:	The Draft Guidance discusses providing FDA with an updated summary of established conditions and supportive information.	BIO asks FDA to clarify if the summary of established conditions in Section 2.3.1, both written and tabular, needs to be updated for supplemental applications or if the tabular summary needs to be included in Section 1.13.5 for annual reports.