December 12, 2018

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

Re: Docket No. FDA-2018-D-1609: Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on "Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Draft Guideline or Guideline).

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.

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.

In general, we believe the Draft Guideline is based on good philosophical concepts which could potentially provide useful regulatory tools and enablers such as Established Conditions (ECs), Post-Approval Change Management Protocols (PACMPs) and Post-Approval Lifecycle Management (PLCM); these tools and enablers should subsequently increase the predictability and efficiency of post approval CMC changes.

While we are encouraged by the work of the ICH Q12 working group, we are most concerned that many important concepts may not be able to be implemented in some regions. We offer both comments on high priority topics in the below letter and additional detailed comments in the tables that follow.

I. Regional Variability in Implementation may Impede Harmonization

Objectives of the draft ICH Q12 Guideline clearly state that the intent is to reduce extensive regulatory oversight and enhance industry's ability to manage many changes under the Product Quality System (PQS). Additionally, Q12 aims to encourage international

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harmonization of technical and regulatory requirements for lifecycle management for drug and biological products. However, as currently written it will be difficult to realize this stated goal.

The Guideline states that in certain ICH regions, Q12 is not fully compatible with the established legal framework with regard to the use of ECs and the PLCM (lines 25-30). While we are pleased to see that FDA has confirmed that in the US Q12 is fully compatible with established legal framework and fully supported by FDA (footnote 2), we are concerned that this regional incompatibility will impact the broader harmonization efforts and will not reduce the burden on either industry or regulators. Regulatory processes across the ICH regions need to be harmonized and the purpose of ICH is to promulgate this harmonization across its regions.

As a result of this stated conflict with established legal framework, the Guideline in its current form leaves a lot of room for regional regulatory interpretations (notably, the term "region/regional" is mentioned multiple times). In this context, there is a real risk of divergence across countries/regions, both in terms of approved ECs and reporting categories, which are by default regional as well. Divergence in regional implementation might lead to different sets of approved ECs for different scopes and even more divergence in regulatory documentation and approval timelines and requirements. In addition, and due to many regional exceptions and transition periods, the regulatory burden can be even greater due to new and old concepts affecting regulatory documents and different understanding from different authorities. The original goal to harmonize and facilitate lifecycle management across regions is not obvious at this stage since the Guideline lacks a harmonized approach on technical and regulatory considerations for lifecycle management.

To achieve an appropriate level of harmonization ICH Q12 would benefit from inclusion of unified approaches to the change category classification based on level of risk associated with the change, data requirements for specific changes, and the time associated with the regulatory review of the specific submission by the Health Authority (HA). These details are provided in recent WHO guidance on variations, with the guidance on variations for bio-therapeutics including the most advanced thinking. We suggest that ICH Q12 references existing WHO guidance on post-approval changes, which we consider complementary to ICH Q12 principles, in order to promote global regulatory convergence.

For instance, individual regulatory authorities may request changes to the proposed ECs and reporting categories as reflected in PLCMs during their initial review. This would lead to diverging and customized sets of ECs for the Marketing Authorization Holder (MAH) to manage across the product lifecycle, and therefore introduce greater complexity. The Guideline should outline measures to facilitate the harmonization of the ECs, PLCMs, and PACMPs across the ICH regions.

Further, concerted implementation efforts are needed consistently across ICH regions for harmonized implementation of the Guideline. Moreover, and importantly, all regional agency and HA Guidelines that touch upon the principles and recommendations in ICH Q12 Guideline should be replaced with the ICH Q12 when appropriate, or should be updated to align with the ICH Q12 Guideline.

Finally, allowing for the lack of harmonization as currently written in this Guideline may be setting a concerning precedence for future new and/or revised ICH guidelines. BIO is concerned by this potential precedence and the potential impact on the effectiveness of ICH and its harmonization efforts as a whole.

II. Scope and Organization

The Guideline specifies in lines 32-37 that the Guideline applies to pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products. The Guideline also applies to drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product. However, when discussing combination products, it is unclear whether ICH Q12 applies to the drug constituent part, the device constituent part, and/or the combination product as a single entity. Additional content is needed within the Guideline to provide more clarity and understanding on how to apply the Q12 concepts to these products. BIO believes that additional examples and specifics related to combination products in the Guideline and Annex would be extremely beneficial in order to ensure clarity on the applicability of Q12 to these products.

While we appreciate that the Guideline applies to "pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products" (lines 33-35), we would appreciate the Guideline explicitly stating that while the concepts in Q12 are applicable and may be used for applications for these products, the traditional/existing current approach is also still acceptable. It will be left up to the MAH to decide which approach is best used for their product and to discuss with the regulator to come to an agreement to move forward. While BIO believes the concepts in the Q12 Guideline are a good approach and contain useful regulatory tools and enablers in order to support a lifecycle approach for products, there may be certain products or product types where this approach may not be ready to be implemented; those products could still use the traditional approach. The Q12 approach is a good tool in a suite of options for management of a product's post-approval changes and BIO appreciates the acceptance of its concepts as appropriate. We believe that the Q12 approach should be able to be used throughout the ICH regions, should the MAH decide to do so.

BIO believes that the Guideline can significantly benefit from the chapters being reordered. We understand during development the order might have been helpful. However, moving forward an order of: General principles with chapters 2 & 7; Post Approval Change Management with chapters 3 & 6 (first part); and tools with chapters 4, 5, 8 and 6 (second part) would allow for better implementation.

III. Established Conditions (ECs)

The EC section provides clarity on the binding and non-binding elements in a dossier and a distinction of implicit and explicit ECs. The decision tree in Figure 1 enables the clear distinction that a non-critical or non-key process parameter is not an EC and does not require reporting to Health Authorities. The current draft also provides clarity on expectations about changes done at a contract manufacturing organization (CMO).

As mentioned above in Section I, the Guideline notes that when the relevant legal frameworks in those regions are reviewed, the concepts in ICH Q12 will be considered. However, until that is done, to the extent possible, ICH Q12 concepts for ECs and PLCM will be considered under the existing regulatory framework in those ICH regions. There should be more clarity and assurance of this. Further, notably, the timing of the review and updates of the legal frameworks is not clear. There should be more definitive timeline and path forward for the updates.

In order to improve this section, we suggest the following:

- Clearly state that explicit ECs (as defined by the MAH) are not mandatory.
- Clearly state that continuing to use the "traditional" approach (only implicit ECs are used) is acceptable. This is of value in cases where development timelines are accelerated (e.g., breakthrough therapies, generics).
- State that ECs proposed and justified in a manufacturing process description should be those inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) that are necessary to assure product quality. These should include critical process parameters (CPPs, defined in ICH Q8(R2)), as well as parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency.
- Clarify how reporting categories relate to changes in ranges for specifications: tightening or widening ranges should not have the same reporting categories.
- Adding more details on ECs for analytical methods. The concept of ECs for analytical methods is described in a high level manner providing less details and examples of which method parameters implicitly would be considered EC and how mechanistic understanding between parameters and performance would help to lower the associated reporting category. No statement is made to which extent flexibility would be granted (e.g., change within the same technology by changing from HPLC to UPLC). An example in Annex I would be welcome.
- Clarify the procedural aspects for ECs in referenced submissions concerning the confidential information. A referenced system (e.g., Drug Master File (DMF)), which is based on some regional legislation, gives opportunity to DMF holders to provide confidential information directly to the HAs. In this manner also ECs located in the restricted part (RP) of the DMF and their changes should be reported directly to HAs. In some regions (i.e., US) there is a possibility for annual reportable changes (notifications) to be submitted by the DMF holder itself. The DMF holder is responsible for informing the MAH in general about the planned changes (enough information to MAH to be able to evaluate a change) but details of the confidential part are not shared.

Additionally, the Draft Guideline suggests that reporting categories can pro-actively be defined for changes to ECs. This makes the assumption that the type of change to the EC is known. For a given EC there can be a number of changes that could take place; as such, defining a change category for all possible changes would be onerous.

IV. New Concepts that Lack Clarity

The Draft Guideline introduces several new concepts that that will need further clarification before this Guideline can be effectively adopted. For example:

Implicit ECs and Explicit ECs: As currently written, the concepts of implicit ECs are not well defined. We find that the current definition enables a wide scope of elements to be categorized as implicit ECs. It does not seem necessary to create this category of ECs, or make the distinctions between the approaches to define ECs. We strongly recommend removing the distinction between implicit and explicit ECs and maintain a single category of ECs within the Guideline. However, if the concept of implicit and explicit ECs are maintained in the Guideline, then specific examples of implicit ECs and explicit EC should be included within the document.

Process Consistency: The term "process consistency" is used within the Guideline but is not a defined term or concept within ICH Q8 or Q11. Q11 states that "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". Q11 also states that "Process validation can include the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance". Q8 does not include these types of statements, but does state that "The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product".

It is unclear whether "process consistency" refers to business-specific criteria such as cycle times for unit operations (e.g., reactions, crystallization, drying) and is not an established condition per se. Since neither Q8 nor Q11 defines "process consistency", the term can be left to interpretation. The Q12 Guideline should either clearly define what it meant by process consistency or the term should be removed from the Guideline. BIO suggests that consistency is related to the capability of the process to consistently produce product that meets the critical quality attributes (CQAs).

Key Process Parameters (KPPs): The term KPP is not a defined term or concept within ICH Q8 or ICH Q11, while Critical Process Parameters (CPP) and non-CPP have been well defined and broadly adopted by industry and regulators. BIO believes that the current definition of KPP is not workable and needs to be further clarified with extensive discussion between stakeholders; as a result BIO believes it should be removed from the Guideline.

As written in this Guideline, the definition of KPP indicates that the KPP must be tightly controlled to assure process consistency as it relates to product quality. We acknowledge that there can be parameters which impact process performance and are important to control, but are not CPPs. However, it should not be necessary to automatically designate these parameters as ECs. BIO believes that as currently defined, there remains potential for significant overlap and confusion with CPPs and therefore the current definition will not be helpful in identification of ECs.

As mentioned, BIO recommends removing the KPP concept completely and keeping the CPP/non-CPP framework, until such a time that a more concrete definition of KPP can be agreed to with extensive input from all stakeholders.

V. Post-Approval Change Management Protocol (PACMP)

BIO believes that the current Draft Guideline will harmonize the PACMP concept across ICH regions as the possibility of reporting multiple changes for one product or across several products in one PACMP will reduce reporting burden. PACMPs will be useful for repeat changes (e.g., cell banks). They will reduce the risk of rejection of changes by the HA and improve predictability.

In order to improve this section, we suggest the Guideline clearly state that PACMPs are valid for an unlimited period of time unless the risk changes. Asking to state the approval date of a PACMP in a filing (lines 443-447) may suggest that it is only valid for limited period of time. This appears unnecessary as the PACMP should only be invalid if the risk changes.

VI. Product Lifecycle Management (PLCM)

The newly introduced Lifecycle Management (LCM) concept will encourage companies and regulators to think along the product lifecycle and adopt a LCM strategy. Outlining the LCM plans in a PLCM document will improve communication within and between MAHs and HAs, and lead to internal and external transparency.

However, making the PLCM document part of the regulatory filing could potentially add unnecessary duplication and administrative regulatory burden considering the submission and maintenance of ECs, PLCM documents, and PACMP without significant added benefit. An additional complexity lies in the difficulties inherent to long-term planning in a rapidly changing environment and, for generic products, gaps between the submission and commercial phase. We acknowledge that the PLCM document is currently proposed as optional; however, BIO notes that optional elements in a Guideline tend to become mandatory requirements as time passes.

We recommend rather than making the PLCM a regulatory submission, maintaining the PLCM information as part of the PQS to maintain linkage between registration and the PQS (lines 419-424) (452-455) and make it available for inspections.

If the PLCM document is maintained as regulatory submission relevant:

- The location and format/content of the PLCM document should be harmonized to avoid creation of multiple dossiers across ICH regions; BIO suggests inclusion in Module 1 of the CTD.
- It should contain only ECs and related reporting categories (as applicable) in order to avoid replication of information within the NDA/BLA; in particular summary of control strategy is already mentioned in ICH Q11 6.2 as part of S.4.5. or other appropriate CTD section. It is moreover confusing if PLCM should contain submitted PACMP or only approved PACMP and post approval commitments.

The Guideline should clearly indicate how ECs should be listed to confirm whether ECs and their corresponding submission categories should be linked in the PLCM document, or whether a PLCM must be required in order to capture ECs. The current description in this

regard is vague, and the examples in the Annex could lead to misinterpretation. For example, Section 3 (lines 201-202) states that the rationales and associated reporting categories for the ECs should be provided within the appropriate CTD sections in Modules 3. However, Section 5.1 (lines 466-567) states that the PLCM document serves as the central repository in the MAA for ECs and their reporting categories. As such, we recommend including an example of a PLCM document within the Guideline or Annex.

VII. Other General Comments:

In its current form, this Guideline would require significant resources and expertise specifically dedicated to its implementation and compliance. For example, regulatory tools such as ECs, PACMP, and PLCM would need to be identified or compiled, then maintained through the product lifecycle. The preparation and work could add significant regulatory burden not only to the sponsors, but also to the regulators who have to review and approve these documents.

It is unclear if any or all of the tools/enablers (i.e., ECs, PACMP, PLCM) are expected in new NDAs when Q12 is implemented. It is also unclear how ECs can or should be applied to NDAs approved prior to Q12. BIO recommends that this information be provided in Sec 1.3, possibly as a new paragraph at the end of 1.3 or as a new subsection 1.4.

Due to the complexity of this guideline, ICH should consider developing Q12 training, as well as other supplemental work products.

VIII. Inclusion of a Question and Answer (Q&A)

The Draft Guideline contains new concepts as well as unclear terminology and phrases that might only be understandable to those who were closely involved in the preparation of the guideline. To address this, we suggest to develop a general Question and Answer (Q&A) document to clarify certain topics in support of ICH Q12 implementation.

The Q&A could provide guidance to questions such as:

- How will it be ensured that appropriate harmonization throughout the regions is achieved (classification, documentation requirement)?
- Is the traditional approach going to be accepted also in the future for new developments?
- Do ECs need to be provided with new submission or can they be defined post-approval?
- Will HAs recognize the same ECs or will we have different sets of ECs across different regions?
- Do ECs need to be defined for all CTD sections or can they also be defined for only some sections? BIO strongly suggests that ECs do not need to be defined for all CTD sections but instead for particular sections throughout.
- How often through the life-cycle should ECs be reviewed and in which cases is it mandatory to update them? BIO believes that ECs should be reviewed and updated in line with changes having a potential impact on quality, efficacy, and safety.
- Can a post-approval regulatory commitment used to revise ECs be suggested by the MAH or only by the HA?

- Can a "general" PACMP be also used for changes like CEP update or change in excipient supplier and subsequently lower reporting category?
- Can a PACMP be used without defining the ECs? BIO believes that a PACMP can be used without ECs being defined.
- How does ICH Q12 consider the confidentiality of a DMF system? Procedural aspects for ECs concerning confidential information in referenced submission should be clarified in more detail.
- What will the transition period (from the time point when the Guideline comes into force until it is accepted by the majority of HAs) look like?

Conclusion:

BIO appreciates this opportunity to comment on "Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management." Specific, detailed comments to both the Core Guideline and the Annex are included in the following charts. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
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/S/
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SPECIFIC COMMENTS TO CORE GUIDELINE

SECTION	ISSUE	PROPOSED CHANGE
1. INTRODUCTION		
1.1 Objectives		
Lines 3-5:	The Draft Guideline states, "The concepts outlined in prior ICH Quality Guidelines (ICH Q8, Q9, Q10 and Q11) provide opportunities for science and risk-based approaches for drug development and risk-based regulatory decisions." BIO believes that regulatory decisions should also be science and risk-based.	BIO suggests editing the text to read: The concepts outlined in prior ICH Quality Guidelines (ICH Q8, Q9, Q10 and Q11) provide opportunities for science and risk-based approaches for both drug development and ~~risk-based~~ regulatory decisions.
Lines 8-10:	The Draft Guideline states, "Experience with implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realisation of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8 (R2) and Q10 Annex I."	BIO suggests the Guideline give examples of technical and regulatory gaps and specifically how ICH Q12 addresses the gaps in previous guidelines. This would add clarity to the passage. If no examples are available, we recommend omitting "technical and regulatory" from the sentence.
Lines 10-11:	BIO suggests clarifying the meaning of the term "commercial".	BIO suggests editing the text to read: This guideline addresses the new marketing authorizations and ~~commercial~~ post-approval phase of the product lifecycle (as described in ICH Q10).
Lines 25-30:	The Draft Guideline states, "In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions (ECs) referred to in Chapter 3 and with the Product Lifecycle Management (PLCM) referred to in Chapter 5 as outlined in this guideline. These concepts will,	While BIO is pleased to see the footnote to this section noting that the Q12 Guideline is fully compatible with established legal framework we are concerned that this statement will hinder consistent implementation across regions which could discourage companies from using this approach.

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	however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions.[2]"	Further, this will impact the harmonization efforts and will not reduce the burden on both industry and regulators. Regulatory processes across the ICH regions need to be harmonized, and the purpose of ICH is to promulgate this harmonization across its regions. Additionally, allowing for this lack of harmonization may also be setting precedence in future new/revised ICH guidelines. BIO is greatly concerned with the precedence this may set for future ICH work. Please see more detailed comments on this point above in Section I of our comments.
1.2 Scope		
Lines 36:	The definition of biotechnological/biological products is not clear, especially related to vaccines.	BIO suggests editing the text to ensure clarity regarding the inclusion of vaccines in the scope of the document: This guideline applies to pharmaceutical drug substances (i.e., active pharmaceutical ingredients) and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products, including vaccines. The guideline also applies to drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product.
1.3 ICH Q12 Regulatory Tools and Enablers		
Lines 83-98:		The text in this section is repetitive to the previous text and as such BIO suggests deleting from the Guideline.

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2. CATEGORISATION OF POST-APPROVAL CMC CHANGES		
Lines 100-150:	Much of the content in this section does not appear to add much value to the overall Guideline. The first two paragraphs seem to be written for member regulators to develop their regulatory framework rather than for lifecycle management by sponsors. The last two paragraphs then discuss the risk-based categorization which is already covered by existing regulations and guidance documents. We recommend removing these four paragraphs from the guideline. Additionally, we recommend incorporating the change reporting category examples from the ICH Q12 Annex 1, page 2, lines 33-38 and incorporating them into this section of the guideline for clarity.	BIO suggests deleting the text in lines 100-111, lines 129-150 and editing the text in lines 112-128 to read: Regulatory authorities are encouraged to utilize a system that incorporates risk-based regulatory processes for (a) requesting approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC changes, with associated information requirements and, where applicable, timeframes for decision. Such a system would include the following categories for regulatory communications with one or more levels in each case: • Prior-approval: Certain changes are considered to have sufficient risk to require regulatory authority review and approval prior to implementation and are requested by the MAH in a suitably detailed regulatory submission. An inspection may be associated with such changes. This Prior Approval (PA) category includes submission types such as PAS, Type II, PCA, etc. • Notification: Certain moderate- to low-risk changes are judged to not require prior approval and generally require less information to support the change. These changes are communicated to the regulatory authority as a formal notification that takes place within a defined period of time before or after implementation, according to regional requirements. This Notification Low (NL)

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		category includes submission types such as AR, Type IA, MCN, etc. A mechanism for immediate notification is useful when prior approval is not required, but timely awareness of the change by the regulator is considered necessary. This Notification Moderate (NM) category includes submission types such as CBE-30, Type IB, MCN, etc. In addition, the lowest risk changes are only managed and documented within the PQS and not reported to regulators, but may be verified on routine inspection. This category is classified as Not Reported (NR).
Lines 106-109:	Packaging components are not part of the production process, but part of the file as stated in the container closure system.	BIO suggests editing the text to read: In such a regulatory system, the types of changes in the drug substance, drug product, production process, primary packaging components, quality controls, equipment, and facility that invoke communication with regulatory authorities are classified with regard to the potential to have an adverse effect on product quality of the drug product.
Lines 112-116:	BIO suggests minor clarifications to improve the text.	BIO suggests editing the text to read: Regulatory authorities are encouraged to utilise a system that allows the firm to incorporate~~s~~ risk-based regulatory processes for (a) requesting approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC

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		changes within the PQS, with associated information requirements and~~,~~ where applicable, timeframes for decision. Such a system would include the following categories for regulatory communications with one or more sub-category levels in each case:
Lines 112-128:	Lines 112-115 outlines three risk-based approaches for communicating CMC changes "…(a) requesting approval from the regulatory authority, (b) notifying the regulatory authority, or (c) simply recording CMC changes, with associated information requirements….." However, lines 117-126 outline two bullets for "Prior-approval" and "Notification". For consistency, a third bullet should be added to correspond to the lowest risk CMC changes.	BIO suggests including a "no notification" bullet as indicated below: • No notification: the lowest risk changes are only managed and documented within the PQS and not reported to regulators, but may be verified on routine inspection We also suggest cross-referencing the WHO guidelines on PAC in this section.
Lines 121-126:		BIO recommends that this outline of "Notification" is better aligned to the Annex where there are 2 discrete types of Notification according to risk. The "Notification" outline mentions "immediate" notification. This should be further defined and explained (e.g., per EU Type IA_{IN}.)
Lines 121-126:	The section on "Notification" should include the concept that some notification requires a waiting period (e.g., CBE-30) and discuss the NM and NL terms which are extensively used in the appendix.	BIO suggests editing the text to read: …according to regional requirements. Some regions have multiple notification categories with different time requirements for reporting and implementing changes. Reporting requirements that allow immediate implementation of the change are at

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		times called "Notification Low" (NL), whereas reporting requirements that have a mandatory waiting period before implementing the change are sometimes called "Notification Moderate" (NM).
Line 126:	For non-prior-approval changes, a comment is made that an inspection may be necessary. A statement around inspections would be beneficial for the notification changes.	BIO believes that an inspection would not be expected for these changes and suggests the text be edited to reflect this. In addition, the lowest risk changes are only managed and documented within the PQS and are not reported to regulators, but may be verified on Site inspection or through desk assessment.
Lines 129-130:	The Guideline states "Harmonisation or convergence toward a system of risk-based categorisation of post-approval changes is encouraged as an important step toward achieving the objectives of this guideline."	BIO suggests editing the text to read: Harmonisation or convergence toward a system of risk-based categorisation of post-approval changes is expected and should be adopted by participating ICH countries as an important step toward achieving the objectives of this guideline.
Lines 137-144:	The Guideline states, "The use of a lower category for request/notification if certain criteria/conditions are met and the relevant supporting documentation is provided as described in regional regulatory guidance; the need for regulatory inspection associated with the change may preclude the ability to use a lower category. Options for possible regulatory convergence regarding the association of a certain type of change with a particular category when reasons for being	BIO suggest the guideline include examples of when this could occur. For instance, the possible proposal by MAH of notification categories based upon a thorough risk based categorization and supported by the relevant rational and documentation is allowed, subject to regulatory authorities' assessment and approval We also suggest editing the text to read:

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	different from other regulatory authorities are not clearly established."	Options for possible regulatory convergence and predictability in decision-making regarding the association of a certain type of change with a particular category when reasons for being different from other regulatory authorities are not clearly established.
3. ESTABLISHED CONIDTIONS (ECs)		
3.1 Introduction		
Lines 161-163:	We recommend including the definition of "established conditions" using the definition from the FDA draft guidance Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products; Guidance for Industry issued in May 2015. In some countries, ECs may not be entirely within the legal framework, but in the regulatory domain. Including this definition encompasses both the legal and regulatory domains.	BIO suggests editing the text to read: Established Conditions (EC) are defined as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product. ECs are ~~legally~~ binding information (or approved matters) considered necessary to ~~assure~~ reliably produce a quality product of time ~~product quality~~. As a consequence, any change to ECs necessitates a submission to the regulatory authority.
3.2 Definition of ECs and Their Role in the Regulatory Submission		
Lines 162-163:	The Guideline states that since ECs are legally binding information "any changes to ECs necessitates a submission to the regulatory authorities". As written, a submission implies a variation requiring approval. Given the risk/impact of the change, a notification may be sufficient.	BIO suggests editing the text to read: As a consequence, any change to ECs necessitates a submission or notification to the regulatory authority.
Line 168:	Throughout the Guideline, it is noted that the reporting categories for ECs should be established. BIO believes that the reporting category for a change	BIO suggests that the Guideline make it clear that there is inherent flexibility in the initial reporting categories for ECs.

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	to an EC should be dependent on the type or magnitude of the change, and not simply the fact that it is an EC of a certain type.	
Lines 175-177:	The definition of implicit ECs indicates that there are possibly ECs that the MAH will be unaware of until they make a change in the process.	As discussed in Section V of this comment letter we strongly recommend removing the distinction between implicit/explicit ECs and maintain a single category of ECs within the Guideline. However, if the concept of implicit ECs are maintained in the Guideline, then specific examples of implicit ECs and explicit EC should be included within the document.
Lines 181-182:	The Draft Guideline states, "Unless otherwise specified by regional requirement, identifying explicit ECs for a given product is not mandatory." It is our understanding that ICH Q12 proposes explicit ECs as an additional option not yet contained in regional guidance, and that explicit ECs are not mandatory; this should be stated clearly.	BIO suggests removing the reference to "unless otherwise specified by regional requirement" from this portion of the test.
Lines 183-185:	The Guideline states that the MAH should define the ECs and their reporting categories and rational. It is unclear where reporting categories should be defined in the CTD.	BIO asks that the Guideline define where in the CTD reporting categories and rational should be provided.
Lines 183-185:	BIO believes that clarity is needed on the interplay of implicit and explicit Established Conditions. As the guideline currently reads, an applicant with approved explicit ECs could later be asked by a health authority to conform to previously unknown implicit ECs.	BIO suggests adding the following text at line 185: An applicant solely using an explicit EC approach for parts of the dossier (e.g., process description, analytical method(s)) or for the complete dossier should provide a statement that there are no additional associated implicit ECs.

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Lines 184-185:	It is stated that the MAH may propose a different reporting category than provided by the regional regulations. This type of flexibility stands in stark contrast with legal requirements in certain regions (e.g., EU.) It sets an expectation with non-EU firms that such flexibility should be allowed. Overall, the document struggles to accommodate EU law and it is difficult to see how any of the proposed flexibility can be implemented in EU without a willingness of the EC to revise the directives and variations guideline, accordingly.	
Lines 186-187:	The Draft Guideline states, "The MAH should provide rationales for the ECs and associated reporting categories in the appropriate CTD sections in Module 3." BIO believes that this requirement should only apply to explicit ECs. Additionally, not all regions use Module 3 for this information.	BIO suggests editing the text to read: The MAH should provide rationales for any explicit ~~the~~ ECs and associated reporting categories in the appropriate CTD sections in the appropriate CTD sections ~~Module 3~~.
Lines 191-192:	The Draft Guideline states, "This chapter outlines approaches to define ECs for manufacturing processes and analytical methods." Analytical methods are considered separately. We recommend including the section number where identification of ECs for analytical procedures are discussed.	BIO suggests editing the text to read: This chapter outlines approaches to define ECs for manufacturing processes and analytical methods (see section 3.2.3.2).
Lines 195-196:	Manufacturing experience can also provide insight into the extent of ECs.	BIO suggests editing the text to read:

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	Additionally, it is not clear whether the Guideline is recommending that ECs be identified for all module 3 sections of the marketing application which contain ECs or whether an applicant can propose ECs to the health authority for only one section in module 3 (i.e., is it all or nothing). We recommend that the Guideline provide the flexibility for ECs to be identified and proposed for only one CMC section of the CTD.	The extent of ECs may vary based on the firm's development approach, manufacturing experience, and potential risk to product quality. The applicant may choose to identify ECs and related reporting categories for only one CTD section in order to obtain agreement with the health authority on how that section will be maintained.
Lines 198-204:	The Draft Guideline introduces the topic of KPPs.	As discussed in Section V above, BIO believes that the current definition is not workable and needs to be removed from the guideline.
Line 213-226:	The current definition of "parameter based" is misleading in that it mostly describes "minimal development" approach, which is terminology consistent with ICH Q8(R2). Enhanced development can be used to support a parameter (i.e., input) based approach, a performance (i.e., output) based approach, or a hybrid approach to ECs. BIO recommends rewording these definitions, describing minimal vs. enhanced development and parameter vs. performance based approach. Additionally, it can be mentioned that the Q8 design space is a parameter based approach. The examples in the Annex should be updated according to the revised terminology.	BIO suggests the following changes to this section: • A minimal development approach, in which product development prior to a regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes. Often the lack of understanding of the relationship between parameters and process outputs leads to a large number of ECs. • Retain the current definition of "enhanced development approach" • A parameter based approach relies on the controls of the process inputs (e.g., process parameters and material attributes) to provide assurance of product quality. This approach is consistent with the design space concept, as discussed in ICH Q8(R2). • Retain the current definition of "performance based approach"

SECTION	ISSUE	PROPOSED CHANGE
		• EC will be defined based on the data available at time of filing. Multiple approaches to development can support definition of EC.
Line 227:	Reference to "this approach" is vague, given that three different approaches are described immediately above.	BIO suggests editing the text for clarity as follows: When considering ~~this approach~~ a performance-based approach, it is important to ensure that all relevant parameters and material attributes…
Lines 229-232:	The sentence is confusing because it points to scenarios where performance based approach is not acceptable, but includes a performance based example. BIO recommends modifying the example to parameter based approach.	BIO suggests editing the text to read: In certain cases, such as a path-dependent process where a specific outcome cannot fully be defined (e.g., fluid bed granulation and drying), select parameters ~~or attributes~~ may need to be specified as ECs (e.g., process parameters that impact ~~differences in~~ granular properties and that can affect the final product quality).
Lines 234-235:	The sentence "use of this guidance should not lead to a less detailed description of the manufacturing process …" may lead to confusion.	BIO suggests the text be clarified that it is the change management expectations for the process and commitments that are differentiated by the ECs concept and this is achieved explicitly using the EC concept (not by omission / simplification of detail from the manufacturing process description). BIO suggests revising the text for clarity.
Figure 1, page 8:	Footnote 1 indicates that the decision tree does not apply for performance-based approaches. Comparable information for performance-based approaches would be needed but was not found in	BIO believes that Figure 1 can also be applicable for performance-based approaches and suggests removing footnote 1, or including an explanation or separate decision tree for reporting categories for

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	the document otherwise it is not clear what should be done differently for performance-based approaches.	performance-based approaches so it is clear what is expected in those cases.
Figure 1, page 8:	Current Figure 1 treats CPPs and KPPs as the same related to classification as prior approval vs. notifiable changes. However, it is highly unlikely that a KPP would ever be classified as a prior approval change, in which case it likely should have been deemed a CPP. Additionally, considerations of the control strategy should be able to render a KPP as non-reportable (i.e., a non-EC).	BIO believes that consideration of the control strategy in EC classification of KPPs would help to provide consistency with performance based and hybrid approaches.
Figure 1, page 8:		BIO suggests the following suggests splitting the "Notification" cell into two cells: "Notification Moderate" (NL) and "Notification Low" (NL), and include examples (NM: CBE-30, Type IB; NL: AR, Type IA) for each of these types of notifications.
Figure 1, page 8:		BIO suggests that a similar figure be created for analytical method.
Line 248:	Footnote 4 states that "In some cases, moderate risk changes may require prior approval." This is not a useful comment as it confuses the risk-based approach by adding uncertainty to the reporting of EC changes. Exceptions need to be comprehensively listed or very clear guideline provided. We suspect the footnote is intended to accommodate the EU legal position but without clarity the statement only serves to confuse all regions. Also, see lines 553-555.	

SECTION	ISSUE	PROPOSED CHANGE
Line 249:	The term "post-change monitoring" is not clear.	BIO suggests editing the text for clarity as follows: Information regarding product-specific post-approval change activities, such as ~~post-change monitoring~~ continuous process verification or enhanced monitoring after the change, may be provided as supporting information to aid in the determination of ECs and associated reporting categories.
Lines 257-272:	Any analytical procedure that meets the ATP or method validation criteria would be adequate for it intended purpose.	BIO suggests deleting lines 259-268 and editing the remaining text to read: ECs related to analytical procedures should include elements which assure performance of the procedure. Any method that meets the requirements of the Analytical Target Profile (ATP) or the method validation acceptance criteria would be suitable for analysis. Appropriate justification should be provided to support the identification of ECs for analytical procedures. A suitably detailed description of the analytical procedures in Module 3 is expected to provide a clear understanding regardless of the approach used to identify ECs for analytical procedures. As these procedures change over time, they along with the data demonstrating the methods suitable should be provided in annual reports, maintained at the site, or by other "do and tell" means. Use of this guideline should not lead to providing a less detailed description of analytical procedures in the MAA.

SECTION	ISSUE	PROPOSED CHANGE
Lines 264-268:	The current description of performance based approaches is unclear related to content and associated expectations.	BIO suggests editing the text to read: To establish a performance based approach for analytical methods, ~~when there is~~ an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies is needed. Multi-variate experimental approaches (e.g., design of experiments) are typically used to study the impact of method parameters on method performance criteria, interactions among method parameters, and method robustness. For performance based approaches, ECs are focused on method specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.
Line 273:	The section on "revision of EC's" should be clarified that it covers classification of, value of, and reporting of ECs.	BIO suggests adding the following text after the first sentence of this section: Such changes can include: reclassification of an EC to a non-EC, reclassification of a non-EC to an EC, changing the value of an EC, or changing the reporting category of an EC.
Lines 274-276:	The Draft Guideline states, "It may be necessary to change approved ECs as a result of knowledge gained during the product lifecycle (e.g., manufacturing experience, introduction of new technologies or changes in the control strategy)."	It is unclear how changes to ECs will be communicated (i.e., supplement or notification). As such, BIO asks that a mechanism for reporting this change be provided.

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Lines 282-284:	While BIO understands that certain changes may not be suitable for proposal under a PACMP we believe that changes that need to be supported by a BE study should NOT be excluded from scope. It is very reasonable to state the change and what BE/PK data will be evaluated to support the change.	BIO suggests the Guideline include changes that would require generation of PK data in the scope of PACMP application.
Lines 285-286:	The Draft Guideline states, "Revisions to ECs could also be made utilising an approved post-approval regulatory commitment, as appropriate."	It is unclear whether the commitment proposal must be suggested by the HA or whether the MAH could also suggest the proposal. BIO suggests that either the HA or the MAH can suggests revisions to ECs.
3.3. Roles and Responsibilities		
Lines 292-294:	The Draft Guideline states, "Maintenance of the marketing application (including aspects that are not identified as ECs) should follow regional expectations."	BIO asks that the Guideline be clarified whether the regional expectations refer to procedural aspects. Differences in change category due to regional expectations do not lead to harmonized approach for post-approval change management.
Lines 295-299:	The Draft Guideline discusses Drug Master Files. In order to guaranty confidentiality in referenced submissions (i.e., DMF), the holder of the referenced submission can provide confidential information directly to the HAs. In some regions (i.e., US) there is a possibility for annual reportable changes (notifications) to be submitted by DMF holder itself. The DMF holder is responsible to inform the MAH in general about the planned changes (enough information to MAH to be able to evaluate a change) but details of the confidential part are not shared.	BIO suggests editing the text to read: For any referenced submission (e.g., Type II Drug Master File, Active Substance Master File, etc.) in a marketing application, the holder of the referenced submission has a responsibility to report changes to their ECs and the proposed reporting categories for those changes to the MAH referencing their submission, so that the MAH can assess the impact of the change and report any related change to the ECs found in the approved MAA, as necessary and per regional requirements.
4. POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)		

SECTION	ISSUE	PROPOSED CHANGE
4.1 Definition of a PACMP		
Lines 306-311:	In the Guideline, it states that PACMP could be submitted when a MAH "intends" to make a change. This implies that a PCAMP should only be submitted when it is known a change will be made. However, it could be beneficial to submit PACMPs for changes likely to occur during the lifecycle of a product, even if it is not currently planned.	BIO suggests editing the text to read: A protocol describes the CMC change an MAH ~~intends to~~ may implement during the commercial phase of a product, how the change would be prepared and verified, including assessment of the impact of the proposed change, and the suggested reporting category in line with regional requirements, i.e., a lower reporting category and/or shortened review period as compared to similar change procedure without an approved PACMP.
Lines 318-320:	Re-evaluating the proposed approach prior to execution of the protocol would ensure the validity of the PACMP. Revising the text to state this re-evaluation would occur "as needed" will help to alleviate the sponsor's regulatory burden. If the text "on a regular basis" is maintained, then a specific timeframe should be specified.	BIO suggests editing the text to read: Once approved, in cases where implementation (see "step 2" below) is pending, there is an assumption that the proposed approach is reevaluated by the MAH ~~on a regular basis~~ as needed and its validity reconfirmed prior to implementation of the change(s).
Lines 341-316:	The Guideline states that "The PACMP requires approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met in order to implement the change(s)." It is possible that a change may be made and not meet the requirements of the PACMP. This should not preclude submission, just the reporting category of the submission.	BIO suggests editing the text to read: The PACMP requires approval by the regulatory authority, and the conditions and acceptance criteria outlined in the protocol must be met in order to implement the change(s) through a reduced reporting category outlined in the PACMP.

SECTION	ISSUE	PROPOSED CHANGE
Lines 318-326:	The Draft Guideline discusses PACMPs. We recommend that this section be clarified as reconfirming the validity of the protocol should be performed prior to executing the change and, if necessary, a revised or new PACMP may be submitted to the HA for approval.	BIO suggests editing the text to read: Once approved, in cases where implementation (see "step 2" below) is pending, there is an assumption that the validity of the proposed approach is ~~re-evaluated by the MAH on a regular basis and its validity~~ reconfirmed prior to implementation of the change(s). Specifically, before implementing the change(s), the risk assessment provided in the initial PACMP submission should be reviewed by the MAH to ensure that the outcomes of that risk assessment as they pertain to the planned change(s) are still valid. If the review of the initial risk assessment indicates an increased level of risk associated with execution of the change, the previously approved reporting category should be followed or a consultation with the relevant regulatory authority should be sought.
4.2 Application of a PACMP		
Line 336:	The Draft Guideline states, "A PACMP typically involves two steps:"	For clarity, BIO suggests editing the text to read: A PACMP process typically involves two steps:
Lines 354-356:	BIO believes that clarification is needed between a major (or consequential update) vs. minor (inconsequential) update.	For clarity, BIO suggests editing the text to read: However, minor unanticipated modifications of the process or controls related to the intended change and inconsequential changes not affecting the technical principles of the protocol are normally considered within scope, if appropriately justified.
4.3 Elements of a PACMP		

SECTION	ISSUE	PROPOSED CHANGE
Line 362:	The description of the PACMP and components to be included are focused on manufacturing process changes. It is conceivable that a PACMP could also be put in place for change to analytical methods including method transfers.	BIO suggests that a description should be included outlining conditions needed in a PACMP to support changes in analytical testing.
Line 371:	The Guideline discusses "a list of specific test and studies to be performed to evaluate the potential impact of the proposed change(s)."	BIO suggests editing the text to read: "a list of specific test, in-process tests (as defined by ICH Q6A), and studies to be performed to evaluate the potential impact of the proposed change(s)."
Lines 371-373:	The PACMP should be able to reference analytical methods elsewhere in the submission, rather than providing the full description.	BIO suggests editing the text to read: The PACMP should include a reference to appropriate approved CTD section or suitable description of the performance characteristics of the analytical procedures and proposed acceptance criteria for each test or study.
Lines 378-379:	Laboratory and pilot scale data could be appropriate for this data.	BIO suggests editing the text to read: Where applicable, supportive data from previous experience with the same or similar products at relevant scale related to:
Line 381:	Per section 4.2, Step 2 is the implementation step. This text is redundant and can be removed.	BIO suggests editing the text to read: Proposed reporting category for ~~the implementation of~~ step 2 of the PACMP.
Lines 382-383:	Ongoing verification may not be needed for simple changes.	BIO suggests editing the text to read:

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		Confirmation that ongoing verification will be performed under the PQS to continue to evaluate and ensure that there is no adverse effect of the change(s) on product quality, as appropriate.
4.4 Modification to an Approved PACMP		
Lines 394-399:		BIO suggest adding text to clarify that a change in non-EC listed in PACMP should not require a notification to HA.
Lines 396-399:	It is stated that depending on the type of PACMP protocol changes, notification or prior approval supplement is required. However, a prior approval process is lengthy (up to 4 months) and does not provide much advantage to the industry.	BIO suggests that the Guideline recommend a shorter review period for changes to PACMP, which would be beneficial and would encourage industry to use this tool to its fullest potential for lifecycle management.
4.5 Types of PACMPs		
Lines 408-417:	The terminology "Broader protocol" seems to apply solely to a PACMP that will support multiple products.	BIO suggests changing the term "Broader Protocol" to "Multiproduct PACMP" or similar.
5. PRODUCT LIFECYCLE MANAGEMENT (PLCM)		
Line 481:	This section is specific to the PLCM Document and not product lifecycle management in general.	For clarity, BIO suggests changing the title of this section to: 5. PRODUCT LIFECYCLE MANAGEMENT (PLCM) DOCUMENT
Line 418:	The Draft Guideline discusses the PLCM document.	In order to fully recognize the value of the PLCM document, it is recommended that post-approval reporting categories should be aligned within the ICH member countries. Otherwise a unique PLCM needs to be written for each region.

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Line 418:	It is unclear where the PLCM resides in the CTD and what is its structure. This is a new requirement that seems difficult to interpret and may add a burden without providing a benefit. In most cases the MAH will not know at the time of the application what LCM programs will be pursued.	BIO believes the details of the PLCM need to be clarified in order to be utilized efficiently.
5.1 PLCM Document: Scope		
Lines 426-430 and 462-465:	It is not clear how the PCLM document prescribed in ICH Q12 Guideline fits in with the FDA's Established Conditions guidance requirement that the ECs be included in Module 2.3. Further, the FDA has a white paper on QOS. It is not clear whether all these approaches are consistent with each other or redundant and serve the same purpose. We recommend that the submission of PCLM in CTD Module 2.3 should suffice since it is stated that PCLM should be the central repository of ECs and it could be placed in either CTD Module 1, 2 or 3.	BIO suggests that submission of the PLCM be in Module 1 and the submission of ECs and related reporting categories (as applicable) outlined in Module 2.3 (i.e. QOS) approach should be specified.
Lines 429-430:	The Draft Guideline states, "Submission of the PLCM document is encouraged; however, the document is expected when the MAH proposes explicit ECs."	For clarity, BIO suggests including a statement that the PLCM document is not required if the implicit EC approach is used. We also suggest editing the text to read: Submission of the PLCM document is ~~encouraged~~ optional; ~~however, the document is expected~~ when the MAH proposes explicit ECs and is not required if the implicit EC approach is used."
5.2 Submitting the PLCM Document		

SECTION	ISSUE	PROPOSED CHANGE
Lines 454-455:	Under submission of the PLCM document it states that "the PLCM document will contain ECs and associated reporting categories." However, earlier in this section it states that EC and the associated reporting categories should be located in the relevant sections of the CTD. It seems redundant and potentially confusing to have these items listed in multiple locations in the CTD.	BIO suggests defining one location for EC and associated reporting categories be captured. For instance Module 3 for individual ECs with supportive documentation and rational, and then a summary of ECs with reporting categories proposed in Module 2.3
5.3 Maintenance of the PLCM Document		
5.4 Format and Location of PLCM Document		
Lines 464-465:	The PLCM should be in a common location to minimize divergence between regions. We recommend the PLCM be located in CTD Module 1 based on current practices from multiple regions (e.g., Health Canada CPID, Japan Application Form).	BIO suggests editing the text to read: The PLCM document ~~can~~ should be located in ~~either~~ ~~the~~ CTD Module 1~~, 2, or 3 based on regional recommendations~~**.** Further, BIO would like to reiterate that the PLCM is a communication tool without an associated regulatory activity, and as a result should be maintained as part of the PQS, available on inspection.
6. PHARMACUETICAL QUALITY SYSTEM (PQS) AND CHANGE MANAGEMENT		
Lines 467-497:	The Guideline states that if PQS is not compliant, the flexibility of this guideline could not apply. However, it is unclear how the Agency would apply this. Would it be an inspectional observation? Which aspects of this guideline not apply? Is it the proposed reporting categories?	BIO suggests replacing this entire section with the following: Changes should be managed under a compliant PQS per the ICH Q10 guidelines. Consistent with the basic requirements of ICH Q10, an effective change management system is necessary for implementation of this guideline and is summarised in Appendix 2.

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	Further, This entire section is redundant to the principles in ICH Q10 Pharmaceutical Quality System. This content can be addressed by referring to the ICH Q10 guideline.	If this section is not removed, BIO asks for clarification on how and when an assessment of a noncompliant PQS will be made by Health Authorities. We also suggest deleting lines 472-473: An effective PQS as established in ICH Q10 and in compliance with regional GMPs is the responsibility of a firm (manufacturing sites and MAH where relevant) and it is not the intent of this guideline to require a specific inspection assessing the state of the PQS before the firm can use the principles in this guideline. ~~The conduct of routine inspections in connection with submitted marketing applications and surveillance will nevertheless continue as foreseen by regional regulatory requirements~~
6.1 General Considerations		
Lines 474-475:	BIO suggests rewriting this portion of the text for clarity. Additionally, it is stated that if PQS is not compliant, the flexibility of this guideline could not apply. However, it is not clear how the Agency would determine and apply this. For example it should be specified whether it would be an inspectional observation. Also, it should be specified that which aspects of this guideline that confer flexibility would not apply. For example, it should be specific whether the proposed reporting categories would be affected.	BIO suggests editing the text to read: ~~In the event that the PQS is found not to be compliant, it may result in restrictions on the ability to utilise flexibility in this guideline.~~ The unrestricted ability to use the flexibility in this guideline requires a PQS that is found, on inspection, to be compliant. Additionally, BIO believes it would be helpful for the Guideline to indicate how and when an assessment of a noncompliant PQS will be made by Health Authorities.
6.2 Management of Manufacturing Changes in the Supply Chain		
7. RELATIONSHIP BETWEEN REGULATORY ASSESSMENT AND INSPECTION		

SECTION	ISSUE	PROPOSED CHANGE
Lines 498-508:	This topic is not relevant to ICH Q12 and as such, can be removed from this guideline. Alternatively, this text can be incorporated into section 1.2, "Scope", at the beginning of this guideline.	BIO suggests either removing this section from the Guideline or incorporating the text into section 1.2, "Scope", at the beginning of this guideline.
Lines 500-502:	The Draft Guideline states, "Facility-related information obtained on inspection should be available to assessors and the most recent PLCM document, when applicable, should be available to inspectors."	For clarity, BIO suggests editing the text to read: Facility-related information obtained on inspection should be available to assessors and the most recent PLCM document, when the explicit EC approach is used ~~applicable~~, should be available to inspectors. Further, BIO would like to reiterate that the PLCM is a communication tool without an associated regulatory activity.
8. POST-APPROVAL CHANGES FOR MARKETED PRODUCTS		
8.1 Structured Approach to Analytical Procedure Changes		
Lines 516-663:	Chapter 8 is about changes to marketed products. Additionally, the term "structured approach" can lead to misinterpretation.	BIO suggests that this chapter focus on common principles which can be applied to frequent changes (manufacturing, analytical) to legacy products (in section 8.1.). Additionally, we suggest the Guideline use a different term than "structured approach". If the term continues to be used, we recommend additional clarification be provided regarding the following: • Is it required for applicants to first identify and obtain approval for Established Conditions (EC) to be able to use the structured approach? • When filing the structured approach for approval, where would it be presented in the dossier?

SECTION	ISSUE	PROPOSED CHANGE
		• How does the structured approach differ from a Post Approval Change Management Protocol (PACMP)? The very detailed explanation of a "structured approach" to analytical changes should be placed in the Appendix. Other examples (e.g., manufacturing changes) should be explained as well and added as Appendix.
Lines 517-523:	BIO believes that more detail needs to be provided for the concepts of ECs for analytical methods to ensure a common understanding and implementation by industry and regulatory agencies. In particular a flow chart/decision tree (similar to Figure 1 for manufacturing processes) would be helpful.	BIO suggests the following language: Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent analytical procedures that are fit for purpose. For products for which ECs for analytical procedures have been defined, the path for changes outlined in Section 3.2.3.2 should be followed. An approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products, for which ECs have not already been defined, is described below. If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities.
Lines 518-519:	BIO suggests adding "or better" to the text. Additionally, the stated concept of lesser reporting category for implementation of "equivalent"	BIO suggests editing the text to read: The intent of this chapter is to incentivize structured implementation of equivalent or better analytical procedures that are fit for purpose.

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	analytical method is difficult to apply based on the provided principles in 8.1.1.	We also suggest that specific examples be included.
Line 523:	It is unclear that this approach for changes to marketed products does not require refiling of ECs for those products.	BIO suggests adding the following sentence at the end of the paragraph: The strategy does not require definition and filing of established conditions for the products using these approaches.
Lines 524-534:	The Guideline discusses situations that are out of scope. Changes to predictive models with multivariate methods are excluded but it is not clear why this should be the case. This is a perfect example of where change implementation prior approval (or notification) should be possible in order to encourage model maintenance. Predictive models are intended to continue learning based on additional data collected.	BIO recommends allowing predictive models to be in scope of prior approval categorization at least in some cases, and then give expectations for when this is acceptable and when regulatory oversight prior to implementation may be needed. This can be done based on risk. For example, if the model maintenance leads to a tightening or more restrictive "pass" condition that is not safety related or due to unexpected quality issues, then it can be implemented without prior approval. If the model maintenance leads to a broadening, then it requires prior assessment. Additionally, if these situations are out of scope it is unclear where would one go to assess how to update them. This is important to multi-attribute type methods that cover multiple assays.
Lines 531-533:	For use the "structured approach to analytical method changes" the following testing is excluded from this approach.	BIO suggests allowing these assays to follow the outlined "structured approach to analytical testing"

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	It is unclear why these tests would be excluded from such an approach. It seems foreseeable that these types of changes could follow the structured approach or be part of PACMP to allow for timely implementation of superior technologies in these fields.	or allow for changes to these assays to be implemented as part of PACMPs.
Lines 537-540:	While it is acknowledged that the flexibility provided in Chapter 8.1 may not be available in all regions and in all situations (i.e., some specific changes may require prior approval as defined in regional regulatory framework), the disclaimer devalues this chapter that strives for convergence and to allow a first harmonization step towards same risk understanding and categorization of minor analytical changes.	BIO suggests deleting these lines.
Lines 543-544:	It is not clear whether the structured approach could still be followed for entirely new analytical methods which use the same general principle (e.g., chromatography with spectroscopic detection). We recommend that registration of a new method using the same general principle be included in the example of a structured approach to be consistent with the overall intent of the Guideline.	BIO suggests editing the text to read: The high-level description of the original method and the revised or new method should be the same (e.g., chromatography with spectroscopic detection).
Lines 545-546:	Clarification should be made that equivalent performance of analytical methods is demonstrated through conformance to equal or more stringent validation acceptance criteria. Current language is unclear if equivalence is determined by direct comparison of validation results between methods	BIO suggests editing the text to read: Validation results should demonstrate that the revised method is equivalent to or better than the original method as demonstrated by conformance to

SECTION	ISSUE	PROPOSED CHANGE
	(e.g., average recovery values). Direct comparison is not advised as results may vary within acceptable ranges from experiment to experiment.	equal or more stringent validation acceptance criteria. Alternatively, as by definition, any analytical procedure that meets the ATP or method validation criteria would be fit for use; the text could be edited as follows: Method qualification ~~Validation~~ results should demonstrate that the revised method meets the requirements of the Analytical Target Profile (ATP) or the method validation acceptance criteria ~~is equivalent to or better than the original method~~.
Lines 555-556:	The Draft Guideline discusses specification changes.	BIO notes that this approach cannot be used to introduce significant changes to the specified quality of the pre- and post-change product. There can be instances when the introduction of an improved method can lead to specification change (e.g., addition of a specific attribute to a specification, when this attribute is not monitored by the earlier methodology). Such instances are not seen as significant changes to the quality of the product when it is demonstrated that the proposed new method shows the pre- and post-change product quality to be essentially similar and therefore can be included as part of the approach. (This comparison of pre- and post-change material using the new method is considered an important part of the change management of an analytical methodology.)
Line 580:	It is not clear what is meant by a prospective review.	BIO suggests testing that the previous method validation with the previous technique will need to be

SECTION	ISSUE	PROPOSED CHANGE
		evaluated against the new technique to ensure equivalence.
Line 595:	The Guideline discusses validation protocol.	This statement seems to imply that methods need to be run side by side. Could statistics be considered as well with EACs?
Lines 626-629:	HA notification would not normally be required if there is no change to the method description in the approved marketing application so there is a concern that more regulatory submissions may be now required. In addition, this section appears to contradict what was stated earlier (lines 543-544) regarding the requirement for no change to the high level description to be able to follow the structured approach. It is unclear how much change to the high level method description is allowable before needing to provide post-implementation notification.	
8.2 Data Requirements to Support CMC Changes		
Line 637:		We applaud the inclusion of science- and risk-based approaches to stability testing in support of post-approval changes in Q12 Step-2. However, the guidance provided in Sec 8.2.1 is conceptual and high level and lacks specifics or examples. As a result, global acceptance of science- and risk-based approaches to post-approval stability testing may not be realized. BIO recommends that a new Annex be established to provide specifics and examples.
9. GLOSSARY		

SECTION	ISSUE	PROPOSED CHANGE
Line 668:	The Guideline gives a definition of KPPs.	As discussed in Section V above, BIO believes that the current definition is not workable and should be removed from the Guideline.
10. REFERENCES		
APPENDIX 1: COMMON TECHNICAL DOCUMENT SECTIONS THAT CONTAIN ECs		
Lines 690-691:	BIO believes that clarity is needed regarding that "delivery system" refers to a drug delivery system for a combination product.	For clarity, BIO suggest editing the text to read: For ~~delivery system~~ information related to the drug delivery system for a drug-device or biologic-device combination product, the location or the relevant content within the CTD structure may vary depending on the design of the particular product and region
Line 691:	For biologics which are not fully characterized, the predictive structure only might not be sufficient to define the molecule and additional input/results from properties S.1.3 and elucidation structure and characterization S.3.1. might be identified as ECs.	Sections S.1.3. and S.3.1. might include ECs and therefore should be identified accordingly.
Line 691:	For CTD sections 3.2.S.4.2 and 3.2.P.5.2, it currently reads as if the applicant should reference ICH Q12.	BIO suggests editing the text to read: For levels /details of ECs for analytical methods, reference is made to Chapter 3.2.3.2 – Identification of ECs for Analytical Procedures
Line 691:	The level of detail of this A.1 section may vary a lot from one company to another, so expected ECs for facility and equipment could maybe be clarified (also not to overlap with GMP).	We propose that the facilities description is not part of Established Conditions but maintained as part of the PQS and level of details integrated with GMP regional regulation and guidance; relevant critical equipment/line and associated process parameters are interrelated and to be described as part of

SECTION	ISSUE	PROPOSED CHANGE
		3.2.S.2.2 or 3.2.P3.3, although currently requested in ICH M4Q for biotech products only.
APPENDIX 2: PRINCIPLES OF CHANGE MANAGEMENT		
General:	Examples of a small molecule (tablet product) is provided.	For ease of understanding examples of a biological product and a combination product is requested. Clarification should also be provided on whether implicit ECs could also be included.
Lines 702-704:	Current statement #4 includes non-required elements under the change management system.	BIO suggests editing the text to read: Requires a science and data based risk assessment ~~and risk categorization of the proposed change including the management of risk in the event the proposed change is not implemented~~;

SPECIFIC COMMENTS TO ANNEX

SECTION	ISSUE	PROPOSED CHANGE
General:	The Annex lacks examples to provide sufficient guidance for implementation of ICH Q12.	BIO suggests adding additional examples should be provided for: • Analytical methods, including the two scenarios discussed in lines 295-301: (1) approaches that include operational parameters including system suitability, and (2) those utilizing method specific performance criteria • Small molecule drug substance, including parameter and performance based approaches • An EC for vaccines (e.g., cell culture step) • A drug-device combination product
General:	All performance based examples provided in the text are based upon utilization of process analytical technologies (PAT). Performance based approaches are equally scientifically sound for traditional end product testing, provided that the conditions are met that "all relevant parameters and material attributes that have a potential to impact product quality are monitored and equipment used remains qualified in order to assure a stable process".	BIO suggests including an example which covers, for example drug substance synthesis step, comparing a parameter and performance based approach using conventional analytical testing.
ANNEX I: ECs – ILLUSTRATIVE EXAMPLES		
Lines 26-29:	It is unclear what "specific ECs mean". It could be read that additional regional requirements could be expected, even if explicit ECs are proposed by the applicant.	BIO suggests deleting this text from the Annex.
Page 3:	The performance based approach discussed here is only valid if the blending operation does not have a potential to impact other CQAs, such as dissolution.	BIO suggests editing the text to read:

SECTION	ISSUE	PROPOSED CHANGE
	For this example, it should be mentioned that this aspect was studied and not found to be significant.	The NIR method and blend homogeneity specifications are ECs. Additionally, it is demonstrated that extended blending does not affect dissolution. Typical operating conditions…
Page 3:	"Equipment type" could be construed as the make and model of the equipment.	BIO suggests replacing "equipment type" with "equipment operating principle" or "equipment class".
Page 4:	The roll size should not be an EC in the performance based approach as the ribbon density approach is equipment independent.	BIO suggests making a separate category for "Equipment size" (10 cm). The reporting category for equipment size should be: Parameter/Minimal approach (PA), Enhanced Approach (NM), Performance based approach (NR).
Page 3 and 5:	With regards to the reporting categories presented in the tables for the small molecule and biologic example, it is not clear how the reporting category relates to proposed changes in ranges (widening versus tightening). For instance for homogeneity, NM is proposed for the specification <5% RSD (IPC). It is unclear how the reporting categories are defined when tightening or widening the specifications, and how they will differ (since the risk is different). Can you widen or delete an acceptance range post approval with a notification low (NL) reporting category based on a risk assessment? Shouldn't the reporting categories correspond to a lower regulatory risk for the performance based approach as more is known about the manufacturing process?	BIO suggests clarifying how reporting categories change when widening or tightening ranges.

SECTION	ISSUE	PROPOSED CHANGE
Annex I A: Chemical Product		
Line 40:	It is not clear how parameters are extracted from the process flow to prepare the EC tables.	A process flow is provided however, for better clarity, we suggest to also provide the narrative of the manufacturing process description (P33). This may help to better understand how the parameters are extracted from the module to prepare the EC tables (lines 66-67).
Page 3:	Enhanced approach: If the PSD of the API demonstrated no impact on dissolution or absorption, why not considering it as "NR" or "NL"? It demonstrated no impact on quality, so it should fulfil criteria for low or no reporting required.	BIO suggests changing the reporting category to "NR" or "NL".
Page 3:	It is a common approach for Industry to manufacture batches at low and large batch size to define a range. A range for the batch size is also extremely useful for continuous manufacturing and continuous processes.	BIO suggests adding a range for the parameter "Scale 10x" in the parameter based approach or enhanced approach.
Page 4:		The example describes power blending and roller compaction unit operations for a drug product. BIO suggests a similar unit operation based example for manufacturing a small molecule API should be included.
Annex I B: Biological Product		
Pages 5 and 6:	The example for reporting categories does not seem to be aligned with the small molecule example. It is unclear why in the small molecule example has a reporting category associated with each parameter (including not reportable), however in the biological example, not every parameter has a reporting category.	BIO suggests aligning the two case examples.

SECTION	ISSUE	PROPOSED CHANGE
Pages 6-8:	The terminology "Input X", "Output Y", "Input Z", and "Input xx" can be confusing.	BIO suggests include an example such as: Input X (e.g., initial total cell density).
ANNEX II: PACMP – ILLUSTRATIVE EXAMPLES		
Annex II A: PACMP Example 1		
Lines 81-82:	Why are DP stability studies needed if lines 93-94 state that there is no change in synthetic route, control strategy, impurity profile or physicochemical properties?	BIO suggests removing the requirement for DP stability.
Annex II B: PACMP Example 2		
Lines 103-159:	This section is said to contain examples, but it actually contains example approaches. Additional data, such as the actual risk assessment and not mere mention of them, would be expected in the PACMP.	BIO suggests realigning this section to discuss "example approaches for PACMPS" rather than actual examples of PACMPs. Also, we suggest including more specifics about the information to be included in the submissions in Step 1 & Step 2.
Lines 128-129:	"Comparable" would be better to align with ICH Q5E terminology. In Japanese, consistent was translated as "identical" which is too strict.	BIO suggests editing the text to read: Analytical profiles from selected characterization tests of post-change material are ~~consistent~~ comparable with pre-change material in side-by-side comparison.
Line 133:	As above, "comparable" would be better to align with ICH Q5E terminology. In Japanese, consistent was translated as "identical" and it is too strict.	BIO suggests editing the text to read: Drug Substance degradation studies are ~~consistent~~ comparable with pre-change material.
Lines 140-143:	The scope of a PACMP should be limited by the science and risk of the change, not by its outcome.	BIO suggests deleting the following:

SECTION	ISSUE	PROPOSED CHANGE
		~~Typical process adaptations linked to scale and equipment differences at the donor and recipient site(s) are in scope of the protocol (e.g., change in raw material sourcing) whereas the scope excludes opportunistic significant process changes (e.g., changes to increase productivity/yield).~~
ANNEX III: PRODUCT LIFECYCLE MANAGEMENT DOCUMENT		
Illustrative Example		
Annex III:	No example of a PLCM document is provided for a biologic. The small molecule example provided in Annex III is similar to the example of ECs in Annex I and seems redundant.	BIO suggest adding an example of a PLCM for a biologic.