June 20, 2016

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

Re: Docket No. FDA-2016-D-0973: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance "Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" (Draft Guidance).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.

We find this Draft Guidance to be thorough and well-considered. It takes into account several approaches to utilizing change protocols for postapproval changes. It would be helpful for the Draft Guidance to state that the content requirements should follow the current common technical document (CTD) format. Finally, it will be important that this Guidance is aligned with the final ICH Q12 guideline once complete. To this end, BIO notes that continuity and consistency of terms across various guidances and guidelines will be necessary in order to ensure clarity for both Sponsors and Regulatory Authorities.

We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart.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/

Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 22-25:	The Draft Guidance states, "A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC postapproval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality)." The term comparability has several connotations that are not aligned with CFR 21 601.12 and can lead to some confusion. CFR 21 601.12 (e) does not specifically mention "comparability protocols" but rather "protocols" to demonstrate the lack of adverse effect for specific types of manufacturing changes. Manufacturing changes are not limited to process changes but can include method transfers, the use of alternative or revised assays and other changes not traditionally associated with comparability studies. Additionally, since the regulation also calls for submission of validation studies that are generally considered outside the scope of the comparability exercises, the use of the term "comparability protocols" can be confusing and too limiting. Therefore, BIO suggests the more general term postapproval change management protocol (PACMP) that aligns with ICH.	In light of this potential confusion, BIO suggests using the ICH terminology, PACMP, as continuity and consistency across regulatory guidelines and guidances is important. We also recommend FDA include changes to the drug substance as well as using the CP for the analytical procedure and acceptance criteria, as noted in Section E, and suggest editing the text to read: "A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC postapproval change(s) (e.g., manufacturing process, analytical methods, acceptance criteria) on the identity, strength, quality, purity, and potency of a drug substance, drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality)."

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Line 39:	The Draft Guidance encourages applicants to employ "Effective use of knowledge and understanding of the product and manufacturing process". Though it may be implied in the bullet, we recommend explicitly calling out and encouraging Sponsors to leverage historical data and not just product knowledge in order to promote continuous manufacturing improvement.	BIO suggests including historical data in either this bullet or a subsequent bullet.
II. BACKGROUND		
Lines 89-93:	The Draft Guidance states, "If a change has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product, as these factors may relate to the safety or effectiveness of the drug (a moderate change) (a minor change), an applicant may proceed with the change, but must notify FDA of the change in the next annual report in accordance with 21 CFR 314.81 or 21 CFR 601.12(d), as applicable."	This section of the Draft Guidance discusses minor changes, however contains a reference to a moderate change. We suggest deleting this reference for clarity: "If a change has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product, as these factors may relate to the safety or effectiveness of the drug ~~(a moderate change)~~ (a minor change), an applicant may proceed with the change, but must notify FDA of the change in the next annual report in accordance with 21 CFR 314.81 or 21 CFR 601.12(d), as applicable."
III. OVERVIEW		
Lines 136-140:	The Draft Guidance states, "In addition, depending on the extent of available knowledge regarding the product and process, the associated risk of the proposed change(s), and the control strategy in effect, the Agency may be able to approve a protocol that justifies reporting certain changes in a manner	To facilitate efficient and effective CP development it would be helpful if FDA could provide examples of possible CP changes that may be suitable for a CBE-type supplement or an annual report, perhaps in the Appendix.

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	not requiring approval from FDA prior to distribution of a product produced with the change (i.e., a CBE-type supplement or an annual report)."	
Lines 179-181:	The Draft Guidance states, "Once submitted by the applicant and approved by FDA, a submission containing a CP provides an applicant with an agreed-upon plan to implement the proposed change(s), and in many cases, justification to report the implementation of the propose change(s) in a reduced reporting category."	BIO suggests editing the typographical error so the text reads: "Once submitted by the applicant and approved by FDA, a submission containing a CP provides an applicant with an agreed-upon plan to implement the proposed change(s), and in many cases, justification to report the implementation of the proposed change(s) in a reduced reporting category."
Lines 182-183:	The Draft Guidance states, "Once approved, the CP serves as a commitment by the applicant to perform the specified activities outlined in the CP that can justify a reduced reporting category." An applicant may wish to submit a CP for a proposed change and later due to other circumstance determine that the change is not necessary or not desired. However, we note that as currently written, it appears that the applicant must implement the change even if it proves to be detrimental to the product, supply chain or patient.	We suggest editing the text to read: "Once approved, when the applicant implements the change, the applicant agrees to follow the commitment ~~the CP serves as a commitment by the applicant to perform the specified activities~~ outlined in the CP ~~that can~~ to justify a reduced reporting category."
IV. COMPARABILITY PROTOCOL SUBMISSION-CONTENT RECOMMENDATIONS		
A. Summary		
Lines 214-215:	The Draft Guidance reads "The detailed information described in sections B. though F. below should be provided in the CP submission."	BIO suggests editing the typographical error in this section to read:

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		"The detailed information described in sections B. ~~though~~ through F. below should be provided in the CP submission."
B. Description of and Rationale for the Proposed Change(s)		
C. Supporting Information and Analysis		
D. Comparability Protocol for the Proposed Change(s)		
Lines 267-268:	The Draft Guidance states, "These tests and studies should be performed at commercial manufacturing scale."	Many manufacturing operations and postapproval changes that might be covered by a CP are scalable and should be allowed to be performed at less than commercial scale. BIO suggests editing the text to read: "It is recommended that these tests and studies ~~should be~~ are performed at commercial manufacturing scale; however, other scales may be justified according to scale-up and postapproval changes (SUPAC) and ICH Q5 as long as the batches are representative of the commercial process."
Lines 275-279:	The Draft Guidance states, "Comparative assessment of quality attributes before and after the change(s) should be included as a component of the planned tests and studies. A side-by-side comparison should be performed, if feasible. However, depending on the type of change, control strategy and level of risk, you can develop and implement a CP without such a comparative evaluation if, for example, the evaluation does not contribute to assurance of product quality."	BIO believes it would be helpful if FDA could provide examples of when a comparative assessment would not be necessary.
E. Proposed Reduced Reporting Category		
F. Other Information		

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Lines 338-341:	The Draft Guidance states, "We also recommend that the CP provide that the site will not distribute product manufactured with the change(s) until the site's quality control unit has confirmed that the criteria specified in the protocol have been met and approved the implementation of the change."	It is unclear why this statement is being recommended for inclusion in the application as elsewhere (Lines 417-418) the Draft Guidance indicates that if an approved criteria is not met then the resulting product must not be released. As such, we suggest that the Guidance not include a requirement for this statement. It may be helpful to include guidance on a path forward in the event that CP criteria are not met.
Line 343:	The Draft Guidance recommends that "an estimated timeline for implementation of the change(s) should be provided, if applicable." It is unclear under what conditions this request is applicable and why timelines which frequently change are helpful to the Agency. Many potential changes are designed to ensure future product availability in the event of a stock out of a critical material and are often never implemented. Further, the recommendation of submitting an estimated implementation timeline with a CP submission could be easily misinterpreted, even with the disclaimer "where applicable". Additionally this could be counter-productive in cases where a CP is intended to be executed multiple times.	BIO would appreciate the inclusion of further clarity on what is applicable and confirmation that potential changes that have no timeline should be excluded. This would also be a good place to link to Appendix C (see comment at line 654); in situations where the applicant provides an implementation timeline, the Agency could consider changes not deemed appropriate for a CP to then be acceptable for consideration with the timeline provided. We also suggest including "if available" to allow applicants to propose future changes that may or may not be implemented depending on various factors: "an estimated timeline for implementation of the change(s) should be provided, if available or applicable.[x]" [x]see Appendix C
V. MODIFICATIONS TO AN APPROVED COMPARABILITY PROTOCOL		

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Line 349:	Section V describes potential modifications to an approved CP; however, it does not include the deletion of an approved CP from a market authorization.	BIO suggests that FDA include a comment in this section on how an approved CP can be deleted during the lifecycle of an application in case there is no further intention to use it.
Lines 367-368:	The Draft Guidance includes the following as being able to be submitted as a CBE-30 supplement, "Inclusion of an additional approved application in a previously approved CP which covers an identical change(s) that affects multiple applications"	BIO believes that it is unclear what is meant by "inclusion of an additional approved application in a previously approved CP which covers an identical change(s) that affects multiple applications." We ask FDA to clarify this portion of the Draft Guidance.
VI. IMPLEMENTATION OF CHANGES ACCORDING TO AN APPROVED COMPARABILITY PROTOCOL		
Lines 413-415:	The Draft Guidance states, "After a change(s) is made according to an approved CP for which the reporting category does not require prior approval, you should collect and analyze process validation and commercial-scale data to establish whether implementation of the change(s) has been successful (see section IV. D.)."	The specific reference to "an approved CP for which the reporting category does not require prior approval" is unclear. It seems to imply additional testing requirements for "lesser reporting category changes" beyond the approved CP, and the performance and product quality monitoring processes performed under the quality management system as described in ICH Q10. We would therefore recommend the text in Lines 413-415 be deleted.
Lines 417-420:	The Draft Guidance states, "If the data collected do not meet the approved criteria in the CP or there is an otherwise unwanted or unpredicted outcome, product manufactured by the altered process must not be distributed. In addition, you should include a statement in the next annual report confirming that the change(s) has not and will not be implemented under the provisions of the CP."	BIO notes that there is no impact to product quality by not implementing the change. Furthermore, this recommendation is not consistent with the regulation under CFR 21 601.12 (d) which only requires reporting of changes that have been implemented and was not designed for reporting potential changes that were not implemented. Including the information in the Annual Report seems unnecessary or redundant. As such, BIO suggests deleting.

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Lines 424-426:	The Draft Guidance states, "Regardless of the reporting category in the approved CP, ongoing verification beyond that reported can and should be performed under your pharmaceutical quality system to continue to evaluate and ensure that there is a lack of adverse effect of the change(s) on product quality."	The term "ongoing verification" could be construed by some as the need to repeat steps in the CP. BIO recommends editing the text to read: "Regardless of the reporting category in the approved CP, ~~ongoing verification beyond that reported can and~~ the monitoring of process performance and product quality should be performed under your pharmaceutical quality system to continue to evaluate and ensure that there is a lack of adverse effect of the change(s) on product quality."
VII. REPORTING CHANGES MADE IN ACCORDANCE WITH AN APPROVED COMPARABILITY PROTOCOL		
Lines 478-479:	The Draft Guidance states, "After a CP is approved, annual reports for each affected application should provide updates on the status of changes covered by the CP."	BIO notes that this recommendation is not consistent with the regulation under CFR 21 601.12 as the regulation only requires reporting of changes that have been implemented and was not designed for reporting status updates of changes that were not implemented. As such, we suggest editing the text to read: "After a CP is approved, annual reports for each affected application should provide updates on the status of changes implemented under ~~covered by~~ the CP."
VIII. APPENDIX-QUESTIONS AND ANSWERS ON COMPARABILITY PROTOCOLS		
A. General		
Line 486:		BIO suggests FDA add a sample question related to analytical testing and method/lab transfers and the ability to leverage a CP to provide industry the flexibility to transfer methods to sites on an as needed basis.

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Line 503:	It is unclear what type of changes "modification of the approved labeling" includes. This could include changes to the clinical indication, or could include changes affecting container closure or shelf-life extension. The later changes should not be excluded from a comparability protocol.	BIO suggests editing the bullet to read: "Changes that require modifications of the approved labeling with regards to efficacy and safety of the product."
Line 505:	FDA lists certain CMC changes as likely to result in unacceptably high or uncertain risk to product quality and includes changes in API supplier.	Changes in API supplier for a small molecule product are not likely to result in unacceptably high or uncertain risk to product quality. This position is supported by the fact that other FDA guidances allow changes in API supplier to be submitted as a CBE-30, provided that the site has had a GMP inspection (see Guidance for Industry Changes to an Approved NDA or ANDA). Also, industry experience reflects that changes to an API supplier generally is not a high risk CMC change. Additionally, API supplier changes may be appropriate for a CP, if a GMP inspection is not warranted. A CP for a site of manufacturing may also be used for multiple Drug Substances and would be applicable under a Comparability Protocol. As such, BIO asks FDA to delete the reference to changes in API supplier from this list.
B. Formulation (Component and/or Composition) Changes		
C. Manufacturing Site Changes		
Line 654:	See comment at line 343 regarding submitting an estimated implementation timeline with a CP submission.	In situations where the applicant provides an implementation timeline, the Agency could consider changes

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		not deemed appropriate for a CP to then be acceptable for consideration with the timeline provided. BIO suggests adding the following sentence: "If a timeline, including the implementation plan with sufficient detail on the new site (i.e. execution activities regarding GMP operations) is provided, a site change could be considered within scope of a CP."
D. Manufacturing Process Changes		
E. Specification, Including Analytical Procedure (Methods), Changes		
F. Packaging Changes		
G. Process Analytical Technology Changes		