December 14, 2018

From: Pharma & Biopharma Outsourcing Association
10 Alta Vista Dr.
Ringwood, NJ 07456

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

RE: Comments from Pharma & Biopharma Outsourcing Association (PBOA) on Docket No. FDA-2018-D-1609 "*Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation*".

Dear Sir/Madam,

On behalf of the Pharma & Biopharma Outsourcing Association ("PBOA"), a trade association representing Contract Manufacturing Organizations and Contract Development & Manufacturing Organizations ("CDMOs"), I am pleased to offer feedback on the recent ICH Q12 draft guidance, "*Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation*". The PBOA's Quality Technical Group, composed of Quality leads from more than a dozen of our member companies, has discussed this draft guidance and outlined some questions and concerns that we offer for consideration prior to your finalizing this document. We embrace the concept of incorporating a culture of continuous improvement into the manufacture of pharmaceutical products and recognize the challenges faced by such a highly regulated industry to adopt such a culture when it takes years to implement changes.

We appreciate the efforts of ICH on helping create definition to lifecycle management and encourage the adoption of the principles of continuous improvement. The harmonization of language and terminology around PACs will be a much-needed benefit of Q12. We are concerned that the approach does not appear to be uniformly embraced by global markets, and we are skeptical as to whether Q12 will provide the intended flexibility to encourage continuous improvement in the pharmaceutical industry. With the varying expectations across the global regulatory agencies, we question whether it is realistic that a PACMP can be effectively and proactively managed to smooth the process of continuous improvement.

With Q12, ICH proffers to reduce regulatory burden of CMC post-approval changes and encourage change management through existing Pharmaceutical Quality Systems. Recently the FDA published a guidance on Post-Approval Changes to Drug Substances (docket FDA-2018-D-3152) that allows greater flexibility in the management of PACs through Pharmaceutical Quality

Systems. We recommend that Q12 be harmonized with the FDA's guidance to afford a more standardized approach across Drug Substances and Drug Products.

In addition to these general concerns and observations, we offer the following comments and questions for consideration as this guidance evolves:

- How is this guidance intended to be applied to older products that did not include ECs in the product development programs, original submissions, and lifecycle management plans that may not be up to today's standards?
- If agencies hold generic products to this level of development and control, generic development will likely be impeded. We don't deny the benefits of thorough product development or control of manufacturing processes; however, generic products are seldom developed with the same level of rigor that is applied to newer products, as their economics do not support that investment. Often CDMOs find themselves negotiating how much development is justified and necessary to support ANDA submissions.
- CDMOs are not always successful in obtaining a copy of the submission from the License Holder and may not have prior knowledge of the PACMP elements or the ECs. Sharing this information is at the discretion of the License Holder.
- There are references to Annex IIA, IIB, and III, but no references to Annex I. As a general comment, if these Annexes are not read in the context provided in the draft guidance sections, they are very difficult to follow. More introduction would improve these supplemental sections:
    - In 1.1 (line 11) the Objectives section references Q10 Annex I, which actually seems to refer to Q12 Annex I.
    - In Annex IIA (line 438), is the process of a site transfer proposed to not require approval prior to implementation as long as this change is defined in the PACMP? It is hard to imagine a scenario where bringing on a new manufacturer can be accomplished *without* prior approval and possibly a PAI.
- In Chapter 2 the relationships between CDMOs and License Holders would benefit from additional definition to the roles and responsibilities defined around the categorization systems and what should be considered as requiring prior approval vs. notification.
- In Chapter 3.3 the License Holder is specified as having responsibility for "*managing changes to and maintenance of the approved marketing application*". We fully agree with this, but CDMOs find that enforcement of lifecycle management changes is almost always a factor in site inspections of manufacturing facilities that do *not* have responsibility for these changes.
- In Chapter 4.1, the PACMP is suggested to be submitted with the original MAA or subsequently as a stand-alone submission. What is the format envisioned for such a "stand-alone" submission? Is there a plan for how this will be managed, or will that have to be determined by the specific regional regulatory body? Introducing a new document such as the PACMP will likely slow down approvals and challenge smaller development organizations that may not always consider long-term post-approval development plans, while providing limited value.

- Filing the PACMP with the original submission is likely to have limited value due to the inability to predict the future needs of the product. We would recommend filing a PACMP as a post-approval amendment to the submission when there is enough product knowledge to create value in this document, and when the regulatory agencies will be able to give the document the attention it deserves without slowing down application reviews.
- The responsibility of CDMOs in this process will require transparent communication with their customers. As specified in the last sentence of the third bullet in Chapter 6.2, "*the organisation responsible for batch release should be aware of all relevant changes and where applicable, be involved in the decision making*". This is not always the case between CDMOs and the License Holder. We could not agree more with this message and recommend that the final bullet under this section is a key message that should be mentioned in nearly all the other chapters of this document, particularly in Chapters 4, 5, and 7. Sharing of information openly in both directions is not always embraced between CDMOs and their customers, the License Holders. Implementation of this guidance will require contracts and relationships to evolve to meet the updated standards, particularly with regard to change management, and this should be openly acknowledged.
- In Chapter 8, marketed products are identified as benefiting from planned changes through a PACMP. What is the proposed submission, review, and approval process for new PACMPs to be submitted for marketed products? Under what scenario might a post-implementation notification be justified for a marketed product where a PACMP wasn't part of the original MAA?

PBOA appreciates the opportunity to review and provide comments pertaining to the draft guidance. We look forward to working with ICH and FDA in their efforts to improve the flexibility and adopt continuous improvement in the manufacture of high-quality pharmaceutical products.

Thank you for considering our views.

Respectfully,

Chris Verbicky, Ph.D., M.B.A.
Director, Scientific and Regulatory Affairs
PBOA

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