

Date: December 14, 2018

VIA WEB

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

SUBJECT: Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation; Draft Guidance for Industry [Docket No. FDA-2018-D-1609].

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) appreciates the FDA for the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance for industry “Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; International Council for Harmonisation Draft Guidance.”

PPTA is the international trade association and standards-setting organization for the world’s major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. Plasma protein therapies are primarily used in the treatment of a particular set of rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies include clotting therapies for individuals with bleeding disorders, immunoglobulins (IG) to treat a complex of diseases in persons with severe autoimmune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult-onset emphysema and substantially limits life expectancy, and albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

PPTA provides the following comments in hopes that they assist in providing a framework to facilitate the management of post-approval chemistry, manufacturing, and controls changes for new and marketed pharmaceutical drug substances and drug products, including marketed chemical and biotechnological/biological products.

General Comments	Rationale
<p>The goal of ICH Q12 in achieving a harmonized approach regarding technical and regulatory considerations for lifecycle management to benefit patients, industry and regulatory authorities is commended.</p> <p>However, there is concern that in certain ICH regions the proposed guideline is not aligned or fully compatible with the established legal framework with regard to the use of Established Conditions (ECs) and Product Lifecycle Management (PLCM). In order to fully realize the impact of this document, ICH regions will need to make strides in addressing this to build the appropriate infrastructure and update existing guidance to point to the tools and enablers described in ICH Q12.</p> <p>Further, for established products, already marketed products, although Chapter 8 suggests that ECs can be proposed as a post-approval change and Post-Approval Changes for Marketed Products (PACMPs) can be used for proposed changes, it is not clear how the Market Authorization Holder (MAH) are to establish the ECs, the PLCM document, and/or PACMPs and have these negotiated and approved by the Regulatory Agencies in some jurisdictions. Specifically, these mechanisms are not discussed in current local regulations nor guidances.</p>	<p>Each jurisdiction will need to work towards building infrastructure and amending existing legislation and/or guidelines to enable the use of the tools described in ICH Q12 in order for the benefits of ICH Q12 to be realized.</p> <p>There needs to be a clear process on how to submit and gain agreement on ECs, PLCM and PACMP for already licensed products to avoid significant work for both regulators and industry.</p>
<p>The scope of ICH Q12 includes “drug-device combination products” yet the content mostly addresses characteristics of drug development.</p> <p>It is recommended that a footnote be added to the scope, indicating that there may be specific aspects of drug-device combination products (i.e. device functionality and performance) that should be considered. Furthermore, it should be acknowledged that there are other systems available for device development, risk</p>	<p>The document reflects key considerations for managing changes to pharmaceuticals, and focus mostly on changes to process. Drug delivery devices have additional considerations, specifically changes to the device design. Additionally, there are other systems that are used in the development of devices. The MAH should consider where</p>

<p>management and quality system management of devices and that it is up to the MAH to determine how best to integrate those processes with ICH Q8, Q9 and Q10 to apply to the combination products.</p>	<p>these differences can be complementary to the corresponding ICH Q8, Q9 and Q10 guidelines to ensure a comprehensive approach for combination products.</p>
<p>Provision of a template for PACMP.</p>	<p>Although there are examples in the Q12 Annex, it would be useful for Industry to have a template for the PACMP as this would aid writing by Industry and Review by Agencies. Although there is an outline in Section 4.3, a detailed template would aid all parties.</p>
<p>General Comments</p>	<p>Rationale</p>
<p>The importance of an established Pharmaceutical Quality System (PQS) as discussed in ICH Q10 is mentioned in chapter 6, however, the importance of establishing a robust and effective PQS should be emphasized throughout the document. It is suggested that the information in Appendix 2 be moved up the front of the document. MAH and regulators will only benefit from the tools and enablers described in ICH Q12 if the concepts originally intended in ICH Q8 through to ICH Q10 are realized and implemented in an effective manner across industry.</p>	

Specific Comments to the Text

Location	Proposed Change	Rationale
<p>Page 1, Line 14</p>	<p>and continual improvement in the <u>pharmaceutical and</u> biopharmaceutical sector, strengthening quality assurance and</p>	<p>As outlined in Section 1.2 Scope, this guidance is applicable to NCEs and biopharmaceuticals. However, this sentence only refers to the biopharmaceutical sector which could be misleading to readers.</p>

<p>Page 5, Lines 174 - 182</p>	<p>ECs in a submission are either implicit or explicit:</p> <p>Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.</p> <p>Explicit ECs are specifically identified and proposed by the MAH together with their proposed reporting category as part of a regulatory submission (see Chapter 3.2.3). This guideline provides the opportunity to identify explicit ECs and associated reporting categories. Unless otherwise specified by regional requirement, identifying explicit ECs for a given product is not mandatory.</p>	<p>The definition of implicit versus explicit ECs is not clear. It is also not clear how this is then applied when different regions have different regulatory requirements. Ultimately, ECs should be negotiated based on the MAHs product and process knowledge based on scientific justification and rationale. Defining them as either implicit or explicit is considered not necessary.</p>
--	--	--

Location	Proposed Change	Rationale
<p>Page 6, Lines 201 - 204</p>	<p>These should include critical process parameters (CPPs and CQAs, as defined in ICH Q8(R2)), as well as key process parameters (KPPs), as well as potentially other which are 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 as it relates to product quality. <u>Noting that as knowledge and experience is accumulated regarding how product performance relates to material attributes and process parameters, some parameters may not ultimately remain</u> ECs.</p>	<p>As a process is developed and improved over commercialization what were originally identified as KPPs for having the potential to impact the manufacturing process may change or be seen not to impact the process.</p> <p>Further, the term KPP may not be universally used across industry. Instead, focus should be on the concepts already established in ICH Q8 and on product and process knowledge, scientific rationale, and the potential any parameter may have on product quality attributes.</p>

<p>Page 8, Figure</p>	<p>Is the process parameter either a <u>CQA</u> or <u>CPP</u> or <u>KPP</u>?</p>	<p>In line with comment above, some KPPs may not ultimately be ECs depending on knowledge and experience with the process.</p>
<p>page 15, Lines 509 – 515.</p>	<p>8. <u>Some Common Post-Approval Changes for Marketed Products</u></p> <p>Marketed products can benefit from the application of ECs and PACMPs as described in this guideline. Specifically, ECs and reporting categories can be proposed for a marketed product via a post-approval regulatory submission; a PACMP can also be proposed for planned change(s) to a marketed product. In addition, such products would also <u>It is recognized that in addition to leveraging ECs and PACMP, some product or process changes could also</u> benefit from additional approaches to facilitate changes. <u>As such, this chapter describes an example strategy for a structured approach for frequent more common CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability).</u></p>	<p>Suggest changes in introductory paragraph and title of this section in order to clarify the intent of this section. Also to clarify that this is an example of a structured approach for some changes, but not to imply that a similar structured approach could not also be leveraged for other types of changes.</p>

PPTA appreciates your consideration of our concerns and welcomes the opportunity to discuss them further. Should you have any questions or require additional information please do not hesitate to contact me at: bspeir@pptaglobal.org or (443) 433-1110.

Thank You,



Bill Speir
Senior Director, State Affairs