Plasma Protein Therapeutics Association

December 20, 2013
Reference No.: FDAA13023 **VIA WEB**

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

SUBJECT: International Conference on Harmonisation; Draft Guidance on Elemental Impurities [Docket No. FDA—2013—D—1156]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) thanks FDA for the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance entitled "Elemental Impurities."[1] PPTA understands that the draft guidance "includes the specific elements to be limited and the appropriate limits for impurities, and emphasizes control of supply chains and risk assessments [and] is expected to provide appropriate limits for impurities, consistent expectations for test requirements and regulatory filings, and a global policy for limiting elemental impurities, both qualitatively and quantitatively, in drug products and ingredients."[2] PPTA appreciates that the draft guidance was "[p]repared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [and] is intended to develop a harmonized approach for the control of elemental impurities that helps industry avoid the uncertainty and duplication of work resulting from differing requirements across ICH regions."[3]

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma-derived products and recombinant analogues, collectively referred to as plasma protein therapies, which are used in the treatment of a number 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. Plasma protein therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

[1] *See* FR Notice, 78 Fed. Reg. 63219 (October 23, 2013)
[2] *See id.*
[3] *See id.*

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Specific Comments/Questions

Section Page Line	Current Text	PPTA Comment	Proposed Text underline=addition strikethrough=deletion
Section 2 Page 1 Lines 41-45	"This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, crude products of animal origin, dialysate solutions not intended for systemic circulation or drug products containing elements that are intentionally included for therapeutic benefit."	The exclusion of blood derivatives including plasma and plasma derivatives should be clarified. Revise to exclude inhalation anesthetics administered as a part of gaseous mixtures.	"This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, <u>blood derivatives including plasma and plasma derivatives,</u> crude products of animal origin, dialysate solutions not intended for systemic circulation<u>,</u> ~~or~~ drug products containing elements that are intentionally included for therapeutic benefit<u>.</u> ~~.~~ <u>or inhalation anesthetics administered as a part of gaseous mixtures.</u>"
Glossary Page 16 Line 638		Add definition for inhalation anesthetics drug product.	**"<u>Inhalation Anesthetics:</u>** <u>Administered as part of gaseous mixtures</u>"
Section 2 Page 2 Lines 50-51	"The application of this guideline to existing marketed drug products will be addressed by regional regulatory processes."	Companies should have full visibility on how this will take place in practice, in particular how much time will be available for compliance. A 5 years transition period for compliance of existing marketed products was allowed by EMEA/CHMP/SWP/4446/2000. A similar timeframe should be in place for the ICH requirements since those are still evolving and significant resources and time may be necessary for compliance.	

		The ICH guideline defers elemental impurity compliance for legacy products to regional regulatory processes. Is the FDA going to refer the ICH guideline for both legacy and new products or will they reference the USP guidelines for legacy products?	
Section 5 Page 8 Line 306 (Table 5.1)		"no" in column Parenteral for Ba and Cr should be replaced by "yes"	
Section 5.6 Page 12 Lines 461-466	"If the total elemental impurity level from all sources in the drug product is consistently less than 30% of the PDE … , then additional controls are not required. "If the assessment fails to demonstrate that an elemental impurity level is below the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product."	The capability of analytical procedures could not, in some cases such as drug products with a high daily dose, allow a limit of quantification as low as 30% of the PDE. In this case, an assessment of the risk to reach the PDE should be possible that would conclude if additional controls are needed or not.	"If the total elemental impurity level from all sources in the drug product is consistently less than 30% of the PDE … , then additional controls are not required. "If the assessment fails to demonstrate that an elemental impurity level is below the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. <u>In case the limit of quantification of the analytical procedure or the limit of detection of a non-quantitative assay is higher than 30% of the PDE, an assessment of the risk of the elemental impurity concentration being higher than the PDE can be conducted to define if additional controls are necessary or not to ensure that the elemental impurity concentration remains consistently not higher than the PDE.</u>"

Section 7 Page 14 Line 558		For the sake of harmonization across regions (ultimate objective of ICH) and avoid the replication of tests with different methods for each region, it is important that companies can use alternatively methods of USP, European Pharmacopoeia and Japanese Pharmacopoeia without additional validation work to demonstrate the equivalence.	At the end of section 7, add: "Analytical procedures described in the United States Pharmacopoeia, European Pharmacopoeia or Japanese Pharmacopoeia for the control of elemental impurities can be used as interchangeable in the ICH regions provided they are validated according to the requirements of the originating pharmacopoeia and without additional validation work to demonstrate the equivalence between pharmacopoeia assays."

Conclusion

PPTA appreciates the opportunity to comment on the draft guidance and looks forward to continued work with FDA on developing a harmonized approach for the control of elemental impurities that helps industry avoid the uncertainty and duplication of work resulting from differing requirements across ICH regions. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully Submitted,

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