Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeial Convention

August 29, 2016

Also submitted electronically to http:/www.regulations.gov

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

Subject: Comments of USP on Elemental Impurities in Drug Products Guidance for Industry (Draft Guidance); Docket Number FDA-2016-D-1692

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) welcomes the Food and Drug Administration's (FDA) issuance of the draft guidance, "Elemental Impurities in Drug Products Guidance for Industry."[1] This draft guidance provides clarity and assistance to human drug product manufacturers regarding the control of elemental impurities consistent with implementation of International Council for Harmonisation (ICH) guidance for industry "Q3D Elemental Impurities," and pursuant to the USP requirements for the control of elemental impurities in USP General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures*.

USP shares with FDA a common public health mission and goal of improving patient safety across all medicines, and USP values our longstanding partnership with FDA. USP has an open, collaborative and transparent process for setting public quality standards for medicines, and has worked collaboratively with FDA as well as industry on the development of these chapters. USP has also worked closely with the ICH to ensure alignment of its elemental impurity standards with the ICH Q3D Guideline for Elemental Impurities.

USP applauds the FDA recommendations set forth in this draft guidance, as well as the proactive timing of its availability. USP appreciates the efforts by FDA through the guidance to create alignment and consistency broadly with ICH Q3D and USP General Chapters <232> and <233>. USP agrees with the key recommendations set forth in the draft guidance and would like to take this opportunity to provide a number of specific recommendations or requests:

1. Regarding section "B" entitled "USP General Chapters <232> and <233>," located in the draft guidance's background, USP would like to bring to your attention that USP's list of elements and the associated permitted daily exposure (PDE) are currently being revised to fully harmonize them with ICH Q3D. The USP comment period for this revision has closed, and the ballot for approval by the Chemical

USP–U.S.
12601 Twinbrook Parkway
Rockville, MD 20852–1790, USA
+1-301-881-0666

USP–Switzerland
Basel

USP–India
Hyderabad

USP–China
Shanghai

USP–Brazil
São Paulo

USP–Ghana
Accra

USP–Ethiopia
Addis Ababa

USP–Indonesia
Jakarta

[1] Docket No. FDA-2016-D-1692: "Elemental Impurities in Drug Products; Draft Guidance for Industry." Available at: https://federalregister.gov/a/2016-15704 (accessed August 11, 2016)

Analysis Expert Committee will occur in October 2016. USP respectfully requests that lines 84-86 of the guidance are revised to reflect this alignment.

2. The last sentence in section "B" states that, "Until General Notices 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements makes the General Chapters applicable for all drug products with USP monographs on January 1, 2018 (the implementation date), these General Chapters would be enforceable only if they are referenced in a particular monograph." Please note that USP does not intend to add references to chapter <232> in monographs prior to the implementation date. Chapter <232> will be implemented through General Notices 5.60.30, and it allows for early implementation of the standard.[2]

3. We believe that greater clarity could be achieved by removing the section that indicates the guidance "does not address biologics." Specifically, USP suggests that lines 42 and 43 on page 2 of the Draft Guidance[3] be deleted because they are confusing and contradictory in the context of the guidance.

   The letter and the spirit of both ICH Q3D and USP General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* are inclusive of all chemical and biologic medicines. As set forth, the Draft Guidance affirmatively states that it is applicable to compendial and noncompendial human drug products marketed pursuant to the regulatory pathways that include new drug applications (NDAs) or abbreviated new drug applications (ANDAs), or under an FDA monograph pursuant to the over-the-counter (OTC) drug review process.[4] The guidance does not affirmatively state in the "Introduction," or elsewhere in the document, that it is applicable to human drug products marketed pursuant to a biologics license application (BLA). As such it is already clear that BLA products are beyond the scope of the guidance.

   USP is concerned that the inclusion of the specific language in lines 42 and 43 will create confusion, particularly for those products that are approved as NDAs or ANDAs that are or may be considered a biological product pursuant to one of the varying, whether scientific or regulatory, definitions, for example, insulin products. Furthermore, USP is concerned that as currently written these sentences connote

[2] **5.60.30. Elemental Impurities in USP Drug Products and Dietary Supplements** •Effective January 1, 2018, elemental impurities will be controlled in official drug products according to the principles defined and requirements specified in *Elemental Impurities—Limits* ⟨232⟩. Effective January 1, 2018, elemental contaminants are controlled in official dietary supplements according to the principles defined and requirements specified in *Elemental Contaminants in Dietary Supplements* ⟨2232⟩. Also effective January 1, 2018, general chapter *Heavy Metals* ⟨231⟩ will be omitted and all references to it in general chapters and monographs will be deleted. Early adoption of the requirements in ⟨232⟩ and ⟨2232⟩ are permitted by USP, and if ⟨232⟩ or ⟨2232⟩, as applicable, is fully implemented with respect to a particular drug product or dietary supplement in advance of the January 1, 2018 date, that product and its ingredients will no longer need to comply with applicable ⟨231⟩ requirements to be considered by USP to be in conformance with *USP–NF* requirements.• (RB 1-Apr-2015). Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/gn-rb.pdf (accessed August 11, 2016).

[3] "Elemental Impurities in Drug Products Guidance for Industry." (FDA Draft Guidance) Available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm509432.pdf (accessed August 11, 2016)

[4] 21 CFR § 330 Over-the-counter (OTC) human drugs which are generally recognized as safe and effective and not misbranded

that additional information will be developed specifically for control of elemental impurities in biological products, and we are not aware that this will be forthcoming or is intended.

4. Finally, the draft guidance makes several references to the concept of applying a risk-based approach to control elemental impurities. USP agrees that this is a very important and critical component in support of the overarching recommendations. To achieve a better understanding of this concept, USP respectfully submits that it would be beneficial for the guidance to provide more information that expands on this topic.

USP thanks you again for the opportunity to provide comments for your consideration, and looks forward to continued areas of successful collaboration. If you have questions or would like additional information regarding USP's comments, please contact Kahkashan Zaidi, Ph.D., Principal Scientific Liaison, General Chapters at kxz@usp.org or (301) 816-8269.

Sincerely,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer