4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-1692]

Elemental Impurities in Drug Products; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled "Elemental Impurities in Drug Products." This guidance finalizes the draft guidance issued July 1, 2016, which provides recommendations regarding the control of elemental impurities of human drug products marketed in the United States consistent with the implementation of International Council for Harmonisation (ICH) guidance for industry entitled "Q3D Elemental Impurities" (ICH Q3D). This guidance will also assist manufacturers of compendial drug products in responding to the issuance of the United States Pharmacopeia (USP) requirement for the control of elemental impurities.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including

attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-D-1692 for "Elemental Impurities in Drug Products." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Danae Christodoulou, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 2602, Silver Spring, MD 20993-0002, 301-796-1342; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Elemental Impurities in Drug Products." This guidance provides recommendations regarding the control of elemental impurities of human drug products marketed in the United States consistent with implementation of ICH Q3D. The guidance will also assist manufacturers of compendial drug

products in responding to the issuance of the USP chapters for the control of elemental impurities.

USP introduced new limits and analytical procedures for elemental impurities in General Chapters <232> Elemental Impurities--Limits and <233> Elemental Impurities--Procedures. Their primary goals are to (1) set limits for acceptable levels of elemental impurities in finished drug products, and (2) update the methodology used to test for elemental impurities in drug products to include modern analytical procedures. ICH Q3D contains recommendations for manufacturers of human drugs and biologics on applying a risk-based approach to control elemental impurities and permitted daily exposure. USP worked closely with ICH to align its new General Chapters with ICH Q3D.

Because elemental impurities pose toxicological concerns and do not provide any therapeutic benefit to the patient, their levels in drug products should be controlled within acceptable limits. In general, FDA recommends that the manufacturer of any U.S. marketed drug product follow ICH Q3D recommendations to establish appropriate procedures for identifying and controlling elemental impurities in the drug product based on risk assessment and product-specific considerations, unless the drug product must comply with *USP-National Formulary* requirements. This guidance outlines approaches for implementation of USP <232>, <233>, and ICH Q3D in new and existing products.

This guidance finalizes the draft guidance issued July 1, 2016 (81 FR 43211). Since the draft guidance was issued, USP <232> was harmonized with ICH Q3D with respect to the all elements and their limits. Originally, prior to issuance of the draft guidance, USP <232> included a fraction (15) of elemental impurities (EIs) listed in ICH Q3D. A number of stakeholder comments to the draft guidance referred to the update and harmonization of USP

<232> with ICH Q3D, which is now reflected in the final guidance. In addition, a number of stakeholder comments requested clarification regarding the applicability of the guidance to biologics license applications (BLAs). The final guidance now states that "for control of EIs in approved or pending BLAs, see ICH Q3D." This differs from the draft, where it was stated that the guidance pertained to biotechnology products covered by new drug applications (NDAs).

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Elemental Impurities in Drug Products." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 314 for submitting NDAs and abbreviated new drug applications, including supplemental applications and annual reports, have been approved under OMB control number 0910-0001. The collections of information in 21 CFR parts 211 and 212 (current good manufacturing practices) have been approved under OMB control numbers 0910-0139 and 0910-0667.

III. Electronic Access

Persons with access to the internet may obtain the guidance at either https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, or

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.regulations.gov.

Dated: August 3, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-16984 Filed: 8/7/2018 8:45 am; Publication Date: 8/8/2018]