Elemental Impurities in Drug Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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TABLE OF CONTENTS

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance provides recommendations regarding the control of elemental impurities of human drug products[2] marketed in the United States consistent with implementation of International Council for Harmonisation (ICH) guidance for industry *Q3D Elemental Impurities*.[3] This draft guidance will also assist manufacturers of compendial drug products in responding to the issuance of the United States Pharmacopeia (USP) requirement[4] for the control of elemental impurities. Specifically, this draft guidance makes recommendations on the following:

- How applicants submitting new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for noncompendial drug products should control elemental impurities as described in ICH Q3D. ICH Q3D contains recommendations on applying a risk-based approach to control elemental impurities and permitted daily exposure (PDE).
- How manufacturers of compendial drug products that are not marketed under an approved NDA or ANDA can comply with USP General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* and the Federal Food, Drug, and Cosmetic (FD&C) Act.
- How holders of NDAs or ANDAs for compendial drug products should report changes in chemistry, manufacturing, and controls specifications to FDA to comply with General Chapters <232> and <233> and 21 CFR 314.70.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] Prescription and nonprescription.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] USP General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures.*

- How manufacturers of noncompendial drug products[5] that are marketed without an approved NDA or ANDA should control elemental impurities.

This guidance does not include specific recommendations on the evaluation of toxicity data for potential elemental impurities, application of a risk-based approach to control elemental impurities in drug products, or PDE. For this information, please refer to ICH Q3D.

This guidance does not address biological products. Holders of approved or pending biologics license applications should refer to ICH Q3D.[6]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. ICH Q3D

ICH guidance for industry *Q3D Elemental Impurities* contains recommendations for manufacturers of human drugs and biologics on applying a risk-based approach to control elemental impurities and PDE.

ICH Q3D recommends that manufacturers conduct a product risk assessment by first identifying known and potential sources of elemental impurities. Manufacturers should consider all potential sources of elemental impurities, such as elements intentionally added, elements potentially present in the materials used to prepare the drug product, and elements potentially introduced from manufacturing equipment or container closure systems. Manufacturers should then evaluate each elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the established PDE. If the risk assessment fails to show that an elemental impurity level is consistently less than the control threshold (defined as being 30 percent of the established PDE in the drug product), additional controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. These additional controls could be included as in-process controls or in the specifications of the drug product or components. ICH Q3D also discusses options for different dosage forms and special circumstances that might affect the risk assessment conclusions.

[5] Including nonprescription (over-the-counter) products marketed under an FDA monograph.

[6] The Center for Biologics Evaluation and Research products that are covered by this guidance are those regulated as NDAs/ANDAs.

B. USP General Chapters <232> and <233>

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.

USP worked closely with ICH to align its new General Chapters with ICH Q3D. General Chapter <232> endorses a risk-based approach to the control of elemental impurities such as described in ICH Q3D. Of the 24 elements for which ICH Q3D provides a PDE, 15 are covered by General Chapters <232> and <233>. The ICH Q3D PDE values for those 15 elements were adopted in the General Chapters.

General Chapter <232> requires control of elemental impurities in finished drug products but does not require routine testing of the drug product. Depending on the source of an elemental impurity and the risk that its level in the finished drug product will exceed the PDE, alternative approaches can be taken. For example, routine testing could be performed on the components (active pharmaceutical ingredient (API) and excipients) instead of the finished drug product. If the risk that the amount of an elemental impurity will exceed its PDE in the drug product is sufficiently low, no routine testing for that impurity need be performed. General Chapter <232> requires assurance of compliance to the specified levels when elemental impurities are known to be present, have been added, or have the potential for introduction.

Upon implementation, General Chapters <232> and <233> will replace General Chapter <231> *Heavy Metals*. A planned provision in the USP–National Formulary (NF) General Notices will make General Chapters <232> and <233> applicable to all articles in the compendia except for those articles specifically excluded in <232>. USP may retain other specific metal limit tests (e.g., General Chapter <211> *Arsenic*) that appear in a particular monograph.[7] In some cases, USP monographs and General Chapters may specify impurity limits that differ from General Chapter <232>. When specific limits are included in a monograph, or in a General Chapter referenced by a monograph, those limits are the official limits with which manufacturers must comply.

General Chapters <232> and <233> are currently official, and the revised versions that align with ICH Q3D became official on December 1, 2015 (second supplement to USP 38–NF 33). 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.

[7] For USP's implementation plan, see http://www.usp.org/usp-nf/key-issues/elemental-impurities.

III. RECOMMENDATIONS

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–NF requirements (see below).

A. New Compendial NDA or ANDA Drug Products

Upon implementation of General Chapters <232> and <233>, all new NDAs and ANDAs for drug products with an official USP monograph will be expected to meet the requirements for control of elemental impurities described in General Chapters <232> and <233>.[8] For elemental impurities listed in ICH Q3D but not in General Chapter <232>, FDA recommends that the applicant follow the recommendations in ICH Q3D.

Applicants submitting new NDAs and ANDAs for compendial drug products after June 1, 2016, but before the USP implementation date should follow the recommendations in ICH Q3D for all of the elemental impurities listed therein.[9]

B. New Noncompendial NDA and ANDA Drug Products

Applicants submitting new NDAs and ANDAs after June 1, 2016, for drug products without an official USP monograph should follow the recommendations for the control of elemental impurities as described in ICH Q3D.

C. Compendial Drug Products Not Approved Under an NDA or ANDA

Marketed compendial drug products not approved under an NDA or ANDA (e.g., nonprescription over-the-counter (OTC) drug products marketed under an FDA OTC monograph) are subject to the provisions of the FD&C Act, General Chapters <232> and <233>, and current good manufacturing practice documentation requirements described in 21 CFR parts 210, 211, and, if applicable, 212. Therefore, upon implementation of General Chapters <232> and <233>, these products will be expected to meet the requirements for control of elemental impurities described in General Chapters <232> and <233>. Appropriate documentation demonstrating compliance must be maintained at the manufacturing site to be available for Agency review during an inspection.[10]

[8] See section 501(b) of the FD&C Act (21 U.S.C. 351(b)).

[9] Because of their close similarity, there is little distinction between following the recommendations of ICH Q3D and the requirements of General Chapter <232>.

[10] 21 CFR parts 211 and 212.

For elemental impurities listed in ICH Q3D but not in General Chapter <232>, FDA recommends that the manufacturer of the drug product follow the recommendations in ICH Q3D by January 1, 2018. This is consistent with the adoption schedule described in ICH Q3D.

D. Noncompendial Drug Products Not Approved Under an NDA or ANDA

Marketed drug products not approved under an NDA or ANDA that do not have an official USP monograph (e.g., nonprescription OTC products marketed under an FDA monograph) should follow the recommendations for the control of elemental impurities as described in ICH Q3D. Appropriate documentation demonstrating compliance must be maintained at the manufacturing site to be available for Agency review during an inspection.[11]

FDA recommends that manufacturers follow the recommendations in ICH Q3D by January 1, 2018.

E. Changes to Approved NDAs and ANDAs

An applicant with a drug product already approved under an NDA or ANDA may have to make changes to the conditions established in the approved application[12] to comply with General Chapter <232> (if the product has an official USP monograph) or to follow the recommendations in ICH Q3D (for elemental impurities listed in ICH Q3D but not in General Chapter <232>, or if the product does not have an official USP monograph). Any changes to conditions established in the approved application should be reported in accordance with applicable regulations and guidances (§ 314.70 and the guidance for industry *Changes to an Approved NDA or ANDA*[13]).

FDA anticipates that most approved drug products marketed in the United States do not contain any elemental impurities that exceed the PDEs described in General Chapter <232> and ICH Q3D. For drug products that do not exceed the PDEs, complying with General Chapters <232> and <233> or following the recommendations in ICH Q3D will involve performing a risk assessment and perhaps implementing changes, such as establishing new in-process controls or including additional controls in the specifications of the drug product or drug product components (e.g., APIs, excipients, container closure system components). Such changes made to comply with General Chapters <232> and <233> are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product and must be documented by the applicant in the next annual report in accordance with 21 CFR

[11] Ibid.

[12] Section 314.70(a)(1)(i) states that, other than the exceptions or alternatives provided in § 314.70(a)(1)(ii), an "applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in an application."

[13] See also guidances for industry *Changes to an Approved NDA or ANDA Questions and Answers* and *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*.

314.81(b)(2).[14] Similarly, such changes made to follow the recommendations in ICH Q3D must also be documented by the applicant in the next annual report.[15]

If a drug product approved under an NDA or ANDA does not meet the requirements described in General Chapter <232> or the recommendations in ICH Q3D, documenting changes in an annual report is not appropriate. Applicants should consider whether higher limits for elemental impurities should apply to the drug product or whether manufacturing changes could reduce elemental impurity amounts. Manufacturing changes implemented to reduce the amounts of elemental impurities should be submitted according to existing postapproval CMC change guidance documents.[16] FDA recognizes that the requirements described in General Chapter <232> and the recommendations in ICH Q3D are not appropriate for all drug products. (For example, they may not be applicable for radiopharmaceuticals or products to which metals have been intentionally added.) Applicants should discuss drug products that do not meet General Chapter <232> or ICH Q3D with the appropriate OPQ review division.

Applicants must make changes to comply with General Chapter <232> by the implementation date. Applicants should make changes to follow the recommendations in ICH Q3D by January 1, 2018.

F. Documentation Related to the Control of Elemental Impurities

As described in ICH Q3D and General Chapters <232> and <233>, the first step in a risk-based approach to the control of elemental impurities is performing a risk assessment. Manufacturers should use the results from the risk assessment to determine which elemental impurities are likely to be present in the drug product and whether current controls for those elemental impurities are adequate. If additional controls should be put in place, the results of the risk assessment can also help determine which types of controls should be used. For example, the risk assessment can help determine whether establishing new in-process controls or including additional controls in the specifications of components would be adequate or whether manufacturers should include additional controls in the specifications of the drug product.

Because the risk assessment is important to the justification of the manufacturer's controls on elemental impurities, manufacturers should include the risk assessment (or a summary of the risk assessment[17]) in the documentation related to the control of elemental impurities.

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[14] See also § 314.70(d).

[15] Normally, adding to a specification or changing the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess are considered changes that have a moderate potential to have an adverse effect and therefore should be documented in changes being effected (CBE) supplements (§ 314.70(c)(6)(i)). However, the changes described above have a reduced potential to have an adverse effect on the drug product compared with other potential changes covered by these regulations because (1) in the situation described above, the elemental impurities in the drug product do not exceed the PDEs listed in ICH Q3D, and (2) the changes are being made to follow ICH Q3D, which, because it has been adopted as an FDA guidance document, reflects current Agency thinking on the control of elemental impurities.

[16] See footnote 13 and § 314.70.

[17] See training materials for ICH Q3D available at www.ICH.org.

- For new drug products submitted under an NDA or ANDA, applicants should include a summary of the risk assessment in any new application to which General Chapters <232> and <233> or ICH Q3D apply. (For information about the implementation schedule for new applications, see sections III.A and III.B). The P.2 section (Pharmaceutical Development) is an appropriate location for the risk assessment summary. When additional controls are warranted, supporting material should be appropriately cited in the summary.
- For drug products already approved under an NDA or ANDA, if changes are made to the controls on elemental impurities to comply with General Chapters <232> and <233> or to follow the recommendations in ICH Q3D, applicants should include a summary of the risk assessment in any supplemental application or annual report describing those changes. Even if no changes are made, FDA recommends that applicants include a summary of the risk assessment in the next annual report following the completion of the risk assessment.
- For drug products not approved under an NDA or ANDA, manufacturers should include the risk assessment in the documentation maintained at the manufacturing site for Agency review during an inspection.

Documentation on the control of elemental impurities should also include descriptions of the controls. This should include acceptance criteria associated with any analytical testing and, if appropriate, the analytical procedures and validation information. If the controls include routine testing of drug product components (e.g., APIs, excipients, container closure system components), these tests can be performed by the drug product manufacturer or, if applicable, by properly qualified suppliers as described in 21 CFR 211.84(d)(2). The full risk assessment should be maintained at the drug product manufacturing site.

G. Quantitative Analytical Procedures for Elemental Impurities

For drug products with an official USP monograph, General Chapter <233> describes the analytical procedures that ordinarily would be used to determine the amount of elemental impurities in drug products or drug product components. These analytical procedures can be used for routine testing of materials or for performing a risk assessment.

General Chapter <233> also describes criteria for acceptable alternative procedures. If the analytical procedures described in General Chapter <233> cannot be used for a specific item associated with the drug product or its components (e.g., APIs, excipients, container closure system components), USP permits the use of alternative procedures in accordance with General Notices and Requirements 6.30, Alternative and Harmonized Methods and Procedures. The alternative procedure must meet the validation requirements described in General Chapter <233>. Alternative procedures should be properly described, and if used for routine testing, their suitability must be verified under actual conditions of use as described in 21 CFR 211.165(e) and 211.194(a)(2) or, if applicable, 212.70(b).

For drug products without an official USP monograph, or for elemental impurities listed in ICH Q3D but not in General Chapter <232>, manufacturers should follow the recommendations in

ICH Q3D. ICH Q3D does not describe specific analytical procedures for routine testing of materials or for performing a risk assessment. FDA recommends that manufacturers use the analytical procedures described in General Chapter <233> or, if those analytical procedures cannot be used for a specific item, analytical procedures that meet the validation requirements described in General Chapter <233>. Any analytical procedure used to test for elemental impurities should be properly described, and if used for routine testing, its suitability must be verified under actual conditions of use as described in §§ 211.165(e) and 211.194(a)(2) or, if applicable, 212.70(b).

H. Validation of Analytical Procedures

Validation is the process of demonstrating that an analytical procedure is suitable for its intended purpose. Analytical procedures for both risk assessments and routine testing should be validated, but the validation criteria (e.g., accuracy, precision, detection limits) can depend on the analytical procedure's intended purpose.

ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* and FDA guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* provide recommendations pertaining to the validation of analytical procedures. These recommendations were developed for analytical procedures used for routine testing of drug products and drug product components. In addition, General Chapter <233> describes factors that should be considered during the validation of analytical procedures that are alternatives to the procedures described in that General Chapter. The suitability of a compendial analytical procedure (e.g., the analytical procedures described in General Chapter <233>) should be verified under actual conditions of use.[18]

Manufacturers should establish that the analytical procedures used during risk assessments possess characteristics (e.g., accuracy, precision, specificity) such that the manufacturers can be reasonably certain (e.g., at the 95-percent confidence level) that the measurements can be relied upon to decide whether to include routine testing of materials in the control strategy. This decision depends on whether the amounts of the elemental impurities in the materials are consistently below control thresholds. The analytical procedures should be validated with this goal in mind.

I. Early Adoption

Given that ICH Q3D and General Chapters <232> and <233> provide significant improvements over existing approaches, FDA supports and encourages their early adoption before the implementation date. In the case of compendial products, upon early adoption of General Chapters <232> and <233>, products and any components are not expected to demonstrate compliance with General Chapter <231>.

[18] See §§ 211.165(e), 211.194(a)(2), and 212.70(b); General Chapter <1226> *Verification of Compendial Procedures*; and guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics*.