Frequently Asked Questions: Rationale for USP's Proposed Standards for Elemental Impurities (updated 14-Jan-2015)

Q. Why is USP revising its standards for elemental impurities?

A. USP is revising its standards for elemental impurities in the interest of better protecting public health. The revisions focus on two areas of work:

- Updating the methodology used to test for elemental impurities in drugs and dietary supplements to include procedures that rely on modern analytical technology; and
- Establishing limits for acceptable levels of elemental impurities (including, but not limited to, lead, mercury, arsenic, and cadmium) in drugs and dietary supplements.

Q. Why is any level of elemental impurities considered "acceptable?" Shouldn't the level always be zero?

A.The human body requires trace elements of many substances to function properly. For example, iron is an element that would be harmful or toxic beyond certain levels, but is frequently taken as a dietary supplement to help ensure healthy blood. The human body is also well suited to eliminate a small amount of most toxins. For most toxic elemental impurities, toxicologists have indicated that daily ingestion of low part-per-million levels constitutes a very low risk even in chronic applications.

Additionally, the definition of "zero" or "absence" is very easy in a general sense (i.e. there are zero apples in a basket) but much more difficult from a measurement perspective. Requiring that "zero" molecules of an impurity may be present bases the standard on the technical ability to make the measurement rather than making it health based. Basing the standard on the best available detection technology may be prohibitively difficult for users to implement and not best serve public health.

Q. What is wrong or deficient about the current test methodology?

A. The test methodology currently described in the USP–NF, was first introduced more than 100 years ago. The test can be difficult to conduct, and can fail to detect some important elementals such as mercury at toxicologically-relevant levels.

Q. Why has USP waited until now to revise standards for elemental impurities? Was there a specific event that prompted the revision?

A. USP undergoes regular re–evaluation and revision of all its standards to update their scientific and public health relevance. There was no specific event that triggered the revision of elemental impurities standards, but our scientific experts felt that the elemental impurity standards should be updated to incorporate modern methods and health information. As we have gained a better understanding of the limitations of the current methods, it has become clear that a revision is called for.

Q. How is USP approaching the revision?

A. USP is taking a risk–based approach that focuses on the likelihood of a given impurity being found in a drug or dietary supplement and on a consensus-based evaluation of the health implications of the impurity at levels that may be found. We have included toxicologists as well as chemists in the group of experts revising the standards to obtain the best available input on both health and methodology issues.

Q. Some in the pharmaceutical industry believe that USP is creating unrealistic, unworkable requirements for testing, which could lead to non–compliance and shortages of key medicines. For example, the article published in USP's Pharmacopeial Forum (PF) (2008, 34(5), page 1345) includes a list of 31 substances to be tested. And the proposed limits for each individual element may be unworkable across the many quality assurance labs that would be affected.

A. USP does not intend to burden industry with unwieldy and unnecessary testing requirements. The list in the PF article was intended as a proposal for discussion. As the revision moved forward, that list has been shortened. USP will not mandate the methodology that each lab must use. Manufacturers will have the flexibility to choose a test that best fits their processes.

Q. The proposed leeway for manufacturers to choose their own test methods is attractive because of the added flexibility. But doesn't that expose manufacturers to added risk of FDA rejection?

A. Potentially, but USP is going to great lengths to work with both FDA and industry to ensure widespread agreement on interpretation of the revised standard. And the revision will include two referee methods, which manufacturers can choose from if they want to ensure a means of demonstrating unquestioned compliance to the standard.

Q. Have imports posed an increased problem with elemental impurities? How is USP dealing with this?

A. To date, there have been no known incidents involving elemental impurities in pharmaceuticals. However, there are continuing concerns above the quality of imports. Ultimately, manufacturers are responsible for assuring conformance to FDA requirements and USP standards, no matter what the source. As more ingredients are sourced abroad, the presence of modern, scientifically sound quality standards will help protect both manufacturers and patients in the United States.

Support
Contact Information
Frequently Asked Questions
Compliance with the USP–NF
Compounding
Elemental Impurities, Rationale for USP's Proposed Standards
Equipment
Food Chemicals Codex (FCC)
<61> Microbial Examination of Nonsterile Products: Microbial Enumeration Tests
<62> Microbial Enumeration of Nonsterile Products: Tests for Specified Microorganisms
<467> Residual Solvents
<621> Chromatography
<661> Containers—Plastics
<711> Dissolution
<797> Pharmaceutical Compounding—Sterile Preparations
<800> Hazardous Drugs—Handling in Healthcare Settings
<823> Radiopharmaceuticals for Positron Emission Tomography (PET) —Compounding, Investigational, and Research Uses
<905> Uniformity of Dosage Units
<1092> The Dissolution Procedure: Development and Validation
Implementation of USP General Chapters <232> Elemental Impurities—Limits, <233> Elemental Impurities—Procedures, and <2232> Ele
Glycerin
Heparin
Microbiology
Pending Monographs
Reagents
Reagents, Reference Standards, and Impurities
Reference Standards
Standards-Setting Process
Total Organic Carbon and Conductivity Testing
USP and its Standards
USP Council of Experts and USP Expert Committees
USP Global Education and Training
USP–NF USB Flash Drive
USP Verification Services
Contact Information

Frequently Asked Questions Regarding the Implementation of USP General Chapters <232> Elemental Impurities—Limits, <233> Elemental Impurities—Procedures, and <2232> Elemental Contaminants in Dietary Supplements

Version 5: March 27, 2015

1. How will General Chapters <232> Elemental Impurities—Limits and <2232> Elemental Contaminants in Dietary Supplements become applicable to monographs? Will they apply to all monographs or just to drug products?

   General Chapters may be applied by reference in a monograph, by reference in an already applicable general chapter, or by a statement in General Notices that specifies their broad applicability. USP will apply General Chapters <232> and <2232> to monographs via General Notices provision 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements. General Chapter <232> will apply to drug products currently in the *USP-NF.* General Chapter <2232> will apply to finished dietary supplement dosage forms. The General Chapters also could be made applicable by reference in any monograph on a case-by-case basis.

2. When will conformance to General Chapters <232> and <2232> be required?

   As specified in the revision to General Notices 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements, January 1, 2018 is the date on which General Chapters <232> and <2232> will become broadly applicable to drug products (<232>) and finished dietary supplement dosage forms (<2232>) in the *USP-NF.* Only in the event that a monograph specifically references one of these General Chapters could they be required prior to January 1, 2018, and then only for the article covered by that specific monograph.

3. Are General Chapters <232> Elemental Impurities—Limits, <233> Elemental Impurities—Methods, and <2232> Elemental Contaminants in Dietary Supplements currently official?

   Yes. General Chapters <232> and <233> are official, and revisions thereto will become official on December 1, 2015. General Chapter <2232> became official August 1, 2013. Until General Notices 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements makes the General Chapters applicable on January 1, 2018 as anticipated, however, these General Chapters would necessarily be applicable only if they are referenced in a particular monograph.

4. Why doesn't General Notices provision 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements reference General Chapter <233> Elemental Impurities—Procedures?

   General Chapter <233> will be made applicable by being referenced in General Chapters <232> and <2232>, and thus does not need to be referenced separately in General Notices 5.60.30. General Chapter <233> already is applicable in certain cases through reference in currently official monographs (see question 1).

7. Will General Chapter <231> be omitted once General Chapters <232> and <2232> become applicable?

USP General Chapter <231> will be omitted once General Chapters <232> and <2232> become applicable on January 1, 2018. The removal of references to <231> from *USP-NF* monographs also will be official as of January 1, 2018.

8. Can I implement General Chapter <232> or <2232> in advance of January 1, 2018?

   General Notices 5.60.30 notes that early adoption of General Chapters <232> and <2232> will be permitted by USP. This will provide flexibility for users to implement the new requirements at a timing that is appropriate for their specific cases, and in such cases relieve such products and any constituent ingredients of having to conform to <231>. Given that General Chapters <232> and <2232> provide significant improvements over existing approaches in the control of elemental impurities, USP encourages users to implement the new methods as soon as reasonably possible.

9. Can manufacturers work with USP on a specific product that may not meet the limits of a particular element?

   USP hopes to work with FDA and with individual manufacturers on resolving scientific issues arising from the new Elemental Impurities requirements, balancing manufacturer interests with public health impact. Upon receipt of the appropriate supporting information, USP may propose a revision to the monograph to address its special requirements. Such requirements in a monograph, should the monograph be approved and become official, would take precedence over the requirements specified in <232> or <2232>.

Revision History:

Version 5: March 27, 2015

- Revised following the approval of General Notices, which was revised to indicate a January 1, 2018 implementation date for the elemental impurities standards specified in General Chapters <232> and <2232>.

Version 4: January 14, 2015

- General revisions to FAQs as part of the announcement of the January 1, 2018 date of applicability of General Chapters <232> and <2232>
- Added FAQ
  - 'Can I implement General Chapter <232> or <2232> in advance of January 1, 2018?'
- Deleted FAQ
  - 'Why is USP's revision to General Chapter <232> not fully aligned with the limits specified in the ICH Expert Working Group Q3D Step 2b draft?', as USP anticipates alignment with the limits specified in ICH Q3D Step 4

Version 3: December 27, 2013

- General revisions to FAQs as part of the announcement of the December 1, 2015 date of applicability of General Chapters <232> and <2232>

Version 2: June 7, 2013

- Added FAQs