

# Elemental Impurities: New USP chapters <232>, <233>, and <2232> and Frequently Asked Questions Regarding Their Implementation

By Impact Analytical



## About Impact Analytical

Impact Analytical is a contract analytical testing laboratory that provides testing for four main sectors: specialty chemicals including polymers and silicon materials, medical devices, pharmaceuticals, and agricultural products. Impact Analytical provides release testing, R&D support, method development and validation, extractable/leachable studies, stability studies, actives quantitation, raw materials testing, problem solving, and competitive analysis. Impact Analytical is ISO 9001:2015 certified, DEA licensed, FDA registered, cGMP and GLP compliant.

## New USP Chapters

Drug products and dietary supplements for the US market will soon have to comply with the new elemental impurities requirements and testing set forth by the USP General Chapters <232> Elemental Impurities—Limits, <233> Elemental Impurities—Procedures, and <2232> Elemental Contaminants in Dietary Supplements. The USP recognized that the current chapter <231> Heavy Metals was obsolete, and it will be eliminated completely on 1/1/2018, when the new chapters will be officially implemented.

These new chapters include the use of modern procedures and analytical equipment and establish the limits for acceptable levels of elemental impurities in drug products and dietary supplements. These changes will affect not just the drug manufacturers but also the raw materials supplier for active pharmaceutical ingredients (APIs) and/or excipients.

## Frequently Asked Questions Regarding the New Chapters from the United States Pharmacopeia (USP) Website<sup>1</sup>

- 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.*

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### Classification of Metals for Consideration under New Guidance

Class	Metals	Toxicity
Class 1	As, Cd, Hg, and Pb	Significantly toxic across all administration routes and have limited or no use in pharmaceutical manufacturing.
Class 2		Toxicity based on administration route
Class 2A	Co, V, Ni	Relatively high probability of toxicity based on administration route
Class 2B	Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt	Relatively low probability of toxicity based on administration route
Class 3	Li, Sb, Ba, Mo, Cu, Sn, Cr	Relatively low toxicity (high PDEs) by the oral route of administration, but may require consideration in the risk assessment for the inhalation and parenteral routes

#### 4. 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.*

#### 5. 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.*

For years Impact Analytical has been providing elemental analysis for our clients. When you work with us, our experts will consult with you right from the start to help determine what elemental impurities service we can assist you with. Our laboratory, which operates under cGMP/GLP guidelines, is able to analyze drug products, API's, and excipients. Utilizing modern techniques such as inductively coupled plasma – optical emission spectroscopy (ICP-OES) and inductively coupled plasma – mass spectrometry (ICP-MS), Impact Analytical can identify and quantify a wide range of trace elements including each of the metals listed in USP 232, 233, and 2232.

At Impact Analytical we have the sample preparation capabilities you need to prepare your product for analysis. Many drug products require closed vessel microwave digestion to break down and dissolve the elemental constituents of the product. We can provide microwave digestion along with other popular preparation techniques such as hot plate digestion, hydrofluoric acid (HF) digestion, extractions, evaporation, separation, and sample milling amongst others. Call 855.427.6583 or click below to talk to an expert today.

#### References

<sup>1</sup> <https://www.usp.org/sites/default/files/usp/document/FAQs/ei-implementation-faq-2015-03-27.pdf>