USP Chapters <232> and <233>
Implementation Strategy

Kahkashan Zaidi, Ph.D.
Principal Scientific Liaison
General Chapters
U.S. Pharmacopeia
OUTLINE

- USP Chapter <231> Heavy Metals
- Chapters <232>
  - Harmonization with Q3D
  - Veterinary Products
- Chapter <233> Harmonization
- Other USP Chapters impacted by <231> Deletion
- Implementation
USP’s Approach

- Delete <231> Heavy Metals
  - Over 1200 references in the USP-NF

- Introduce Three New Chapters:
  1. <232>Elemental Impurities—Limits (Official But Not Implemented)
  2. <2232>Elemental Contaminants in Dietary Supplements (Official But Not Implemented)
  3. <233> Elemental Impurities—Procedures (Official)
<table>
<thead>
<tr>
<th>&lt;231&gt; Deletion Date</th>
<th>Jan 1, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omission of General Chapter &lt;231&gt;</td>
<td>Published in USP 38–NF 33</td>
</tr>
<tr>
<td>Publish/Post list of monographs and Chapters with cross reference to &lt;231&gt;</td>
<td>Posted on July 2014 and Jan 14, 2015</td>
</tr>
<tr>
<td>Delete cross-references to General Chapter &lt;231&gt; Heavy metals from all individual monographs</td>
<td>Marked up for deletion in USP 38 and 39 and following publications with delayed implementation on Jan 1, 2018</td>
</tr>
</tbody>
</table>
Acacia
(a kay’ sha).

DEFINITION
Acacia is the dried gummy exudate from the stems and branches of Acacia senegal (L.) Willd. or of other related African species of Acacia (Fam. Leguminosae).

IDENTIFICATION
• A.
  Analysis: To 10 mL of a cold solution (1 in 50) add 0.2 mL of diluted lead subacetate TS.
  Acceptance criteria: A flocculent, or curdy, white precipitate is formed immediately.

IMPURITIES
• ARSENIC, Method II (211): NMT 3 ppm
• LEAD (251): NMT 10 ppm

Delete the following:
• HEAVY METALS, Method II (231): NMT 40 ppm (Official 1-Jan-2018)

SPECIFIC TESTS
• Boron CONTENT
Chapter <232> and Harmonization with Q3D
Key changes in USP 40 S1

- Requirements/language for Drug Substance and excipients

- Tables 1 & 3 (previously Table 2) revised to add additional elements

- Added a new section and new table (Table 2) to clarify risk assessment

- Analytical testing

- Format changes
Key changes in USP 40 S1

Drug substances and Excipients

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. However, elemental impurity levels present in drug substances and excipients must be known, documented, and made available upon request. However, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data, or if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using Table 2 in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment.
### Table 1: Permitted Daily Exposures for Elemental Impurities

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
<th>Oral PDE µg/day</th>
<th>Parenteral PDE, µg/day</th>
<th>Inhalation PDE, µg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pb</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>As</td>
<td>1</td>
<td>15</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Hg</td>
<td>1</td>
<td>30</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Co</td>
<td>2A</td>
<td>50</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>V</td>
<td>2A</td>
<td>100</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Ni</td>
<td>2A</td>
<td>200</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Tl</td>
<td>2B</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Au</td>
<td>2B</td>
<td>100</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Pd</td>
<td>2B</td>
<td>100</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Ir</td>
<td>2B</td>
<td>100</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Os</td>
<td>2B</td>
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<td>10</td>
<td>1</td>
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<tr>
<td>Rh</td>
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<td>100</td>
<td>10</td>
<td>1</td>
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<tr>
<td>Ru</td>
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<td>1</td>
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<tr>
<td>Se</td>
<td>2B</td>
<td>150</td>
<td>80</td>
<td>130</td>
</tr>
<tr>
<td>Ag</td>
<td>2B</td>
<td>150</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Pt</td>
<td>2B</td>
<td>100</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Li</td>
<td>3</td>
<td>550</td>
<td>250</td>
<td>25</td>
</tr>
<tr>
<td>Sb</td>
<td>3</td>
<td>1200</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>Ba</td>
<td>3</td>
<td>1400</td>
<td>700</td>
<td>300</td>
</tr>
<tr>
<td>Mo</td>
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<td>3000</td>
<td>1500</td>
<td>10</td>
</tr>
<tr>
<td>Cu</td>
<td>3</td>
<td>3000</td>
<td>300</td>
<td>30</td>
</tr>
<tr>
<td>Sn</td>
<td>3</td>
<td>6000</td>
<td>600</td>
<td>60</td>
</tr>
<tr>
<td>Cr</td>
<td>3</td>
<td>11000</td>
<td>1100</td>
<td>3</td>
</tr>
</tbody>
</table>
# Key changes in USP 40 S1

Table 3: Permitted Concentrations of Elemental Impurities for Individual Component Option

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
<th>Oral Concentration μg/g</th>
<th>Parenteral Concentration μg/g</th>
<th>Inhalation Concentration μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td>1</td>
<td>0.5</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Pb</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>As</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Hg</td>
<td>1</td>
<td>3</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Co</td>
<td>2A</td>
<td>5</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>V</td>
<td>2A</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ni</td>
<td>2A</td>
<td>20</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Ti</td>
<td>2B</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Au</td>
<td>2B</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Pd</td>
<td>2B</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ir</td>
<td>2B</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Os</td>
<td>2B</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Rh</td>
<td>2B</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ru</td>
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<td>Sb</td>
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<td>Ba</td>
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<td>140</td>
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</tr>
<tr>
<td>Mo</td>
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<tr>
<td>Cu</td>
<td>3</td>
<td>300</td>
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</tr>
<tr>
<td>Sn</td>
<td>3</td>
<td>600</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Cr</td>
<td>3</td>
<td>1100</td>
<td>110</td>
<td>0.3</td>
</tr>
</tbody>
</table>
### Table 2: Elements to be Considered in the Risk Assessment

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
<th>If Intentionally Added (All Routes)</th>
<th>If Not Intentionally Added</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Cd</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Pb</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>As</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Hg</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Co</td>
<td>2A</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>V</td>
<td>2A</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ni</td>
<td>2A</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ti</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Au</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Pd</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ir</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Os</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Rh</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ru</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Se</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ag</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Pt</td>
<td>2B</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Li</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Sb</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ba</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Mo</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cu</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Sn</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cr</td>
<td>3</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
If, by process monitoring and supply-chain control, manufacturers can demonstrate compliance, then further testing may not be needed. When testing is done to demonstrate compliance, proceed as directed in *Elemental Impurities—Procedures (233)*. and minimally include arsenic, cadmium, lead, and mercury in the *Target Elements evaluation*.

1S (USP40)
Veterinary Products
Veterinary Products are **out of scope**

Should we remove heavy metals testing from these monographs?

- 197 official monographs
  - 76 are drug substance monographs.
  - Not all of these have labeling to indicate for vet use only.
- Many vet drug products contain drug substances that are also used in human formulations
- Human drug product may also have an approved vet product.
Veterinary Products

- **USP** will remove all references to <231> from Vet monographs

- **CVM’s Approach:**
  - Allowing use of <231> only in case of low risk materials/products (provide a copy of the test method in an annual report or in the CMC technical section for a new product.)
  - For all other products, companies are required to use risk based approach per <232> and Q3D
  - Use <233>
  - Provide test method and justification in cases where proposed limits exceed USP <232> limits in your annual report.
  - Appropriate justification should be provided if test results for elemental impurities are listed on supplier certificates of analysis but not confirmed for supplier verification.
  - **CVM can request additional information on a case-by-case basis (e.g. for high risk materials).**
<233> Elemental Impurities--Procedures
Q3D—Harmonized analytical procedures should be established by the pharmacopoeias for determining levels of metal impurities, with allowance for use of any appropriate validated procedure for a particular application.

USP Chapter <233> Elemental Impurities—Procedures

- Sample Preparation
- Procedures
- Validation requirements

Harmonization through PDG
New Chapters

- <730> Plasma Spectrochemistry
- <1730> Plasma Spectrochemistry—Theory and Practice
- <735> X-Ray Fluorescence
- <1735> X-Ray Fluorescence Spectrometry
Chapters Impacted by <231> Deletion

1. <381> ELASTOMERIC CLOSURES FOR INJECTIONS

2. <661> PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

3. <661.1> PLASTIC MATERIALS OF CONSTRUCTION

4. <661.2> PLASTIC PACKAGING SYSTEMS FOR PHARMACEUTICAL USE

5. <661.3> PLASTIC COMPONENTS AND SYSTEMS USED IN PHARMACEUTICAL MANUFACTURING
EXTRACTABLE METALS

- **Aluminum**: Solution S3 (see Table 3) contains NMT 0.4 mg/L (ppm), corresponding to 1 mg/g.
- **Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium**: Report the measured value in Solution S3 at values above 0.01 mg/L (ppm), corresponding to 0.025 mg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 mg/g.
- **Titanium**: Solution S3 contains NMT 0.4 mg/L (ppm), corresponding to 1 mg/g.
- **Zinc**: Solution S3 contains NMT 0.4 mg/L (ppm), corresponding to 1 mg/g.
<661> Series– Intent to Revise Notice


- Targeted Official Date: 01–May–2017, Revision Bulletin (Postponement)

- Delay until May 1, 2020 the implementation of new requirements of General Chapters <661.1> and <661.2> as currently specified in General Chapter <659>.
Chapter <1231> Water for Pharmaceutical Purposes: proposed revision in PF 43 (2)

- Comment deadline was May 31, 2017
- Stimuli article in Pharmacopeial Forum:
  Elemental Impurities in Pharmaceutical Waters. PF 39(1) [Jan.–Feb. 2013]
Chemical purification technologies for **Purified Water** are similarly efficient in removing EI as those for **Water for Injection** production. Since all sterile waters are prepared from Purified Water or Water for Injection, the assurance of compliance to (232) extends to **sterile waters**, provided there are no elemental impurities added during processing, packaging, delivery, or storage.

<table>
<thead>
<tr>
<th>Element</th>
<th>Parenteral Daily PDE (µg/day)</th>
<th>Parenteral Daily LVP Dose (µg/mL&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>US EPA National Primary Drinking Water Regulations (µg/mL&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>WHO Drinking Water Guidelines (µg/mL&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>Result of 2-log Reduction of EI Concentration for WFI (µg/mL&lt;sup&gt;c&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium</td>
<td>2</td>
<td>0.001</td>
<td>0.005</td>
<td>0.003</td>
<td>0.00005</td>
</tr>
<tr>
<td>Lead</td>
<td>5</td>
<td>0.0025</td>
<td>0.015</td>
<td>0.01</td>
<td>0.00015</td>
</tr>
<tr>
<td>Inorganic arsenic</td>
<td>15</td>
<td>0.0075</td>
<td>0.01</td>
<td>0.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>Inorganic mercury</td>
<td>3</td>
<td>0.0015</td>
<td>0.002</td>
<td>0.006</td>
<td>0.00006</td>
</tr>
</tbody>
</table>

<sup>a</sup> Concentration based on a daily dose of 2000 mL, and all drug product elemental impurities coming from the water component.

<sup>b</sup> Drinking Water Regulations state these Maximum Contaminant Levels (MCLs) as mg/L, which equals µg/mL or ppm.

<sup>c</sup> Determined from the greater of the US EPA Regulations column and WHO Guidelines column for each element, then divided by 100 (2–log).
Element Specific Chapters In USP-NF
Element Specific Chapters

- Arsenic \( \langle 211 \rangle \)
- Iron \(<241>\)
- Lead \( \langle 251 \rangle \)
- Mercury \( \langle 261 \rangle \)
- Selenium \( \langle 291 \rangle \)
Future of Element-Specific Chapters in the USP–NF

USP’s Chemical Analysis Expert Committee and Kahkashan Zaidi

ABSTRACT

The Chemical Analysis Expert Committee (CAEC) is evaluating the idea of removing element-specific chapters and limit tests in monographs from the USP–NF. The CAEC is considering the effect of this proposal, as well as the effect of retaining these chapters and limit tests. The CAEC strongly encourages comments and discussions regarding this proposal.
Element Specific Chapters

Limit tests and references to element specific chapters are included in about 1000 monographs?

Are these specific element chapters and limit tests in monographs unnecessary?

Are there known quality- or safety-related reason to maintain the specific elemental impurity limit(s) in drug substances or excipients?

With (233) in place, analytical procedures specific to individual elements are no longer necessary?

Removing references and (special) limits from drug product monographs would align those monographs with (232), providing industry with only one set of elements and limits, as well as one analytical procedure.
<232> Implementation
Structural Hierarchy

General Notices (GN)
- Overarching – Apply to all chapters and monographs

General Test Chapters
- Tests and assays applying to multiple monographs
- Supersede GN if conflicting

Monographs: API, Excipients, Drug Products
- Supersede both GN and Chapters if conflicting

General Information Chapters
- Guidance
- Do not contain specifications
Implementation through General Notices

- 5.60.30. Elemental Impurities in USP Drug Products and Dietary Supplements Effective January 1, 2018

- No reference to <232> will be in monographs

- No new requirements for Drug substances and Excipients
Effectively 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, 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
USP General Notices:

3.10. Applicability of Standards

• Early adoption of revised standards in advance of the official date is allowed by USP unless specified otherwise at the time of publication.

FDA supports and encourages the early adoption of ICH Q3D and USP <232>/ <233> before the implementation date.
Key Issue: Elemental Impurities

In the News: Read about the Impact of Elemental Impurities on drug quality at our Quality Matters blog.


General Chapters and Related Information

- Publishing in Pharmaceutical Forum 42(2) (Mar–Apr, 2016)
- <232> Elemental Impurities—Limits
- Published in USP 39–NF 34, official May 1, 2016:
- <232> Elemental Impurities—Limits
  - Incorporates correction to units in Table 2 in the Drug Substance and Excipients section, which was published as an Erratum on May 29, 2015. Otherwise unchanged from USP 38–NF 33. Second Supplement Revision (posted 10–Dec–2015)
- Published in USP 38–NF 33, Second Supplement, official December 1, 2015:
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures
- Revision Bulletin, official February 1, 2019:
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures
- General Notices
- Standardsetting Record
- Revision Plan (Updated March 27, 2016)

Frequently Asked Questions

- FAQs: Rationale for USP’s Proposed Standards for Elemental Impurities (updated 14–Jan–2016)

Updates

June 1, 2015: USP posts Notice of Intent to Revise for multiple monographs and general chapters that were revised in the Second Supplement to USP 38–NF 33 to reinsert the references to General Chapter <231> Heavy Metals and specify that General Chapter <231> will remain in effect until January 1, 2016.
Thank You

Empowering a healthy tomorrow