Welcome

Empowering a healthy tomorrow

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)**

<231> Heavy Metals

<231> Deletion Date	o Jan 1, 2018
Omission of General Chapter <231>	Published in USP 38–NF 33
Publish/Post list of monographs and Chapters with cross reference to <231>	Posted on July 2014 and Jan 14, 2015
Delete cross-references to General Chapter <231> Heavy metals from all individual monographs	Marked up for deletion in USP 38 and 39 and following publications with delayed implementation on Jan 1, 2018

<231> Heavy Metals

Go to Document Section... Go

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

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. 1S (*USP40*)

Key changes in USP 40 S1

Table 1: Permitted Daily Exposures for Elemental Impurities

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Key changes in USP 40 S1

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

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

Key changes in USP 40 S1

Table 2: Elements to be Considered in the Risk Assessment

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Key changes in USP 40 S1

- **ANALYTICAL TESTING**
  - 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

<231> and Veterinary Product Monographs

- 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

<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

<661.1> PLASTIC MATERIALS OF CONSTRUCTION

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

- General Chapters: <659> Packaging and Storage Requirements, <661> Plastic Packaging Systems and Their Materials of Construction, <661.1> Plastic Materials of Construction, <661.2> Plastic Packaging Systems for Pharmaceutical Use
- 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>.

Elemental Impurities and Water

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]

Elemental Impurities in Pharmaceutical Waters

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.**

Element	Parenteral Daily PDE (µg/day)	Parenteral Daily LVP Dose (µg/mL[a])	US EPA National Primary Drinking Water Regulations (µg/mL[b])	WHO Drinking Water Guidelines (µg/mL[b])	Result of 2-log Reduction of EI Concentration for WFI (µg/mL[c])
Cadmium	2	0.001	0.005	0.003	0.00005
Lead	5	0.0025	0.015	0.01	0.00015
Inorganic arsenic	15	0.0075	0.01	0.01	0.0001
Inorganic mercury	3	0.0015	0.002	0.006	0.00006

a Concentration based on a daily dose of 2000 mL, and all drug product elemental impurities coming from the water component.
b Drinking Water Regulations state these Maximum Contaminant Levels (MCLs) as mg/L, which equals µg/mL or ppm.
c Determined from the greater of the US EPA Regulations column and WHO Guidelines column for each element, then divided by 100 (2–log).

New Topic

Element Specific Chapters In USP-NF

Element Specific Chapters

- *Arsenic ⟨211⟩*
- *Iron <241>*
- *Lead ⟨251⟩*
- *Mercury ⟨261⟩*
- *Selenium ⟨291⟩*

Element Specific chapters in the USP-NF

Stim Article in PF 42(4)

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Future of Element-Specific Chapters in the *USP–NF*

USP's Chemical Analysis Expert Committee and Kahkashan Zaidi[a]

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?

Table 1. Number of Monographs with References to Element-Specific Chapters by Type

	Excipients	Drug Substances/ Drug Products	Dietary Supplements	Food	Biologics
Number of monographs	150	272	256	166	12

- 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

- 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**

5.60.30. Elemental Impurities

Effective·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·

Early Implementation

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.**

Original Posting: 20-Jul-2010; Last Update: 08-Feb-2016

General Chapters and Related Information

- Publishing in Pharmacopeial 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, 2013:
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures
- General Notices
- Standards-setting Record
- Revision Plan (updated March 27, 2015)

Frequently Asked Questions

- FAQs on the Implementation of USP General Chapters <232> Elemental Impurities—Limits <233> Elemental Impurities—Procedures, and <2232> Elemental Contaminants in Dietary Supplements (updated 27-Mar-2015)
- FAQs: Rationale for USP's Proposed Standards for Elemental Impurities (updated 14-Jan-2015)

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 reinstate the references to General Chapter <231> Heavy Metals and specify that General Chapter <231> will remain in effect until January 1, 2018.

Questions

Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow