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U.S. Pharmacopeial Convention

USP Chapters <232> and <233> Implementation Strategy

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Chapter <231> Heavy Metals - Issues

1. Difficulties in reproducibility
   - Monitor solutions/standards change with time, recovery issues
2. Difficulties with reagents – safety issues
   - All procedures generate H_2S (USP via thioacetamide reaction with base). H_2S more toxic than cyanide
   - Thioacetamide not allowed in California and several European countries (EP uses Na_2S)
3. Nondiscriminatory screening test
   - Not element specific
   - Sensitivity varies by element
   - Only a few elements respond at required sensitivities
4. Visual comparison test
   - Limits based on visual acuity, not toxicology

Elemental Impurities

- <232> Elemental Impurities-Limits
- <233> Elemental Impurities – Procedures
- <2232> Elemental Contaminants in Dietary Supplements
- General Notices

Table 1: Elemental Impurities for Drug Products
USP 39--Official

Element	Oral Daily Dose PDE (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)
Inorganic Arsenic	15	15	2
Cadmium	5	2	2
Lead	5	5	5
Inorganic Mercury	30	3	1
Chromium	11000	1100	3
Copper	3000	300	30
Molybdenum	3000	1500	10
Nickel	200	20	5
Palladium	100	10	1
Platinum	100	10	1
Vanadium	100	10	1
Osmium	100	10	1
Rhodium	100	10	1
Ruthenium	100	10	1
Iridium	100	10	1

Table 2. Example Concentration Limits for Components of Drug Products with a 10-g Maximum Daily Dose

Elements	Concentration Limits (µg/g) for Components Used in Oral Drug Products	Concentration Limits (µg/g) for Components Used in Parenteral Drug Products	Concentration Limits (µg/g) for Components Used In Inhalation Drug Products
Cadmium	0.5	0.2	0.2
Lead	0.5	0.5	0.5
Inorganic arsenica	1.5	1.5	0.2
Inorganic mercury	3	0.3	0.1
Iridium	10	1	0.1
Osmium	10	1	0.1
Palladium	10	1	0.1
Platinum	10	1	0.1
Rhodium	10	1	0.1
Ruthenium	10	1	0.1
Chromium	1100	110	0.3
Molybdenum	300	150	1
Nickel	20	2	0.5
Vanadium	10	1	0.1
Copper	300	30	3
a See Speciation section.			

ICH Q3D vs USP <232> Second supplement USP 38

Element	Class2	Oral PDE µg/day		Parenteral PDE, µg/day		Inhalation PDE, µg/day	
		ICH	USP	ICH	USP	ICH	USP
As	1	15	15	15	15	2	2
Cd	1	5	5	2	2	2	2
Hg	1	30	30	3	3	1	1
Pb	1	5	5	5	5	5	5
Co	2A	50	-	5	-	3	-
Mo	2A	3000	3000	1500	1500	10	10
Se	2A	150	-	80	-	130	-
V	2A	100	100	10	10	1	1
Ag	2B	150	-	10	--	7	-
Au	2B	100	-	100	-	1	-
Ir	2B	100	100	10	10	1	1
Os	2B	100	100	10	10	1	1
Pd	2B	100	100	10	10	1	1
Pt	2B	100	100	10	10	1	1
Rh	2B	100	100	10	10	1	1
Ru	2B	100	100	10	10	1	1
Tl	2B	8	-	8	--	8	-
Ba	3	1400	-	700	-	300	-
Cr	3	11000	11000	1100	1100	3	3
Cu	3	3000	3000	300	300	30	30
Li	3	550	-	250	-	25	-
Ni	3	200	200	20	20	5	5
Sb	3	1200	-	90	-	20	-
Sn	3	6000	-	600	-	60	-

Harmonization with Q3D---Today

	Q3D	USP <232>
Scope	Harmonized	Harmonized (Exception: TPNs)
List of Elements	24	15 Not Included: Tl, Au, Se, Co, Ba, Sn, Li, Sb and Ag
PDEs	Harmonized For 15 Elements	Harmonized For 15 Elements
Other Routes	Harmonized	Harmonized
Implementation	Harmonized	Harmonized

Key changes Proposed in PF 42(2)

- To be official in USP 40 1S
- Metals and limits aligned with ICH Q3D:
  24 elements divided in four classes (1, 2A, 2B, and 3)
- Additional guidance on risk assessment:
  A new table is being added that identifies elemental impurities for inclusion in the risk assessment according to the route of administration

Table 1: Permitted Daily Exposures for Elemental Impurities

PF 42(2)

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

Table 3: Permitted Concentrations of Elemental Impurities for Individual Component Option (PF 42(2))

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

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

<232> Elemental Impurities

- **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*)

Harmonization with Q3D---USP 40 Supp 1

	Q3D	USP <232>
Scope	Harmonized	Harmonized (Exception: TPNs)
List of Elements	Harmonized (24)	Harmonized (24)
PDEs	Harmonized	Harmonized
Other Routes	Harmonized	Harmonized
Implementation	Harmonized	Harmonized

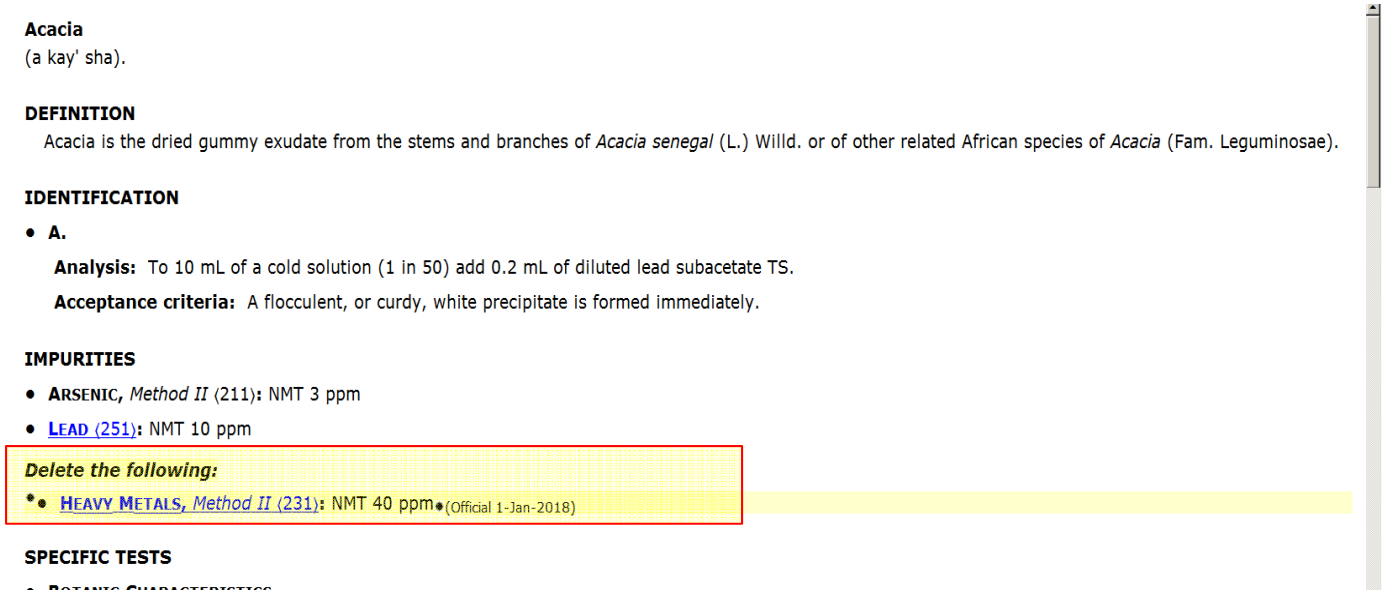
<232> Implementation

USP General Notices:

- **5.60.30.** Elemental Impurities in USP Drug Products and Dietary Supplements 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 no longer need to comply with applicable ⟨231⟩ requirements to be considered by USP to be in conformance with USP–NF requirements.(**RB 1-Apr-2015)

USP's Approach

- **Delete <231> Heavy Metals**
  - **Over 1200 references in the *USP-NF***
- **Introduce Three New Chapters:**
  - **<232>Elemental Impurities—Limits (Official But Not Implemented)**
  - **<2232>Elemental Contaminants in Dietary Supplements (Official But Not Implemented)**
  - **<233> Elemental Impurities—Procedures (Official)**



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

Other Element Specific Chapters

- ***Arsenic*** **⟨211⟩**
- ***Lead*** **⟨251⟩**
- ***Selenium*** **⟨291⟩**
- ***Mercury*** **⟨261⟩**

Other 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.

Other Chapters

1. 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

2. What will be the future of USP chapters that provide specific information regarding the analysis of individual elements, such as arsenic (As) [Arsenic ⟨211⟩], lead (Pb) [Lead ⟨251⟩], selenium (Se) [Selenium ⟨291⟩], mercury (Hg) [Mercury ⟨261⟩], and others?
3. What about USP monographs that may have limit tests for specific elements and refer to their respective element-specific chapters for methodology (see Table 1)?
4. What about USP monographs that include limits for specific elements that differ from the limits established in ⟨232⟩?

Implementation – USP

ICH Q3D step 4 published	Dec 16, 2014
Implementation of <232> and <2232>	o Jan 1, 2018 Via USP General Notices
Omission of Chapter <231>	o Jan 1, 2018
Delete cross-references to General Chapter <231> Heavy metals from all individual monographs	o Jan 1, 2018 o Deletion Marked up---USP 38 and following publications with delayed implementation on Jan 1, 2018

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

Contacts

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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

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Thank You