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U.S. Pharmacopeial Convention

USP Chapters <232> and <233> Implementation Strategy

Kahkashan Zaidi
USP

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

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
Publish Omission of General Chapter <231>	o Published in USP 38–NF 33 with an official date of December 1, 2015
USP to publish/Post list of monographs and Chapters with cross reference to <231>	o Accomplished---July 2014 and Jan 14, 2015
Delete cross-references to General Chapter <231> Heavy metals from all individual monographs	o Accomplished---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

<232> Harmonization with Q3D---Today
USP 39

	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
Options	4 options	3 options
Implementation	Harmonized	Harmonized

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 mercurya	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.			

Key changes Proposed in PF 42(2)

- 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

<232> Revision in PF 42(2)

➢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*)

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---Future

	Q3D	USP <232>
Scope	Harmonized	Harmonized (Exception: TPNs)
List of Elements	Harmonized (24)	Harmonized (24)
PDEs	Harmonized	Harmonized
Other Routes	Harmonized	Harmonized
Options	4 options	3 options
Implementation	Harmonized	Harmonized

<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.

Implementation

- **Implementation through General Notices**
- **No reference to <232> will be in monographs**

<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 General Notices

- **3. CONFORMANCE TO STANDARDS**
  - **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.

Analytical Procedures

- **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**

  - **Proposed in PF 36(1) (2010)**
    - **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 [NEW--- In PF 42(3)]**

Other Element Specific Chapters

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

Other Element Specific chapters

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

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

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

- What is the future of element specific chapters?
- Are these specific element chapters and limit tests in monographs unnecessary unless there is a known quality- or safety-related reason to maintain the specific elemental impurity limit(s) in place for selected components (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.

USP Website

- **March 27, 2015**
- **General Chapters and Related Information**
- To be Published in **Second Supplement to USP 38-NF 33**: (**official on December 1, 2015)**
  - **<232> Elemental Impurities—Limits**
  - **<233> Elemental Impurities—Procedures**

- **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)

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

U.S. Pharmacopeial Convention

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Thank You

FDA Perspective and Expectations for Control of Elemental Impurities in Drug Products

ICH Q3D U.S. Training Workshop
Silver Spring, MD
August 22-23, 2016

Danae Christodoulou, Ph.D.

CDER/OPQ Office of New Drug Products

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Prospective Challenges

- Expectations for method validation: risk assessment vs. routine testing
- Pharmacopeial Challenges (In U.S., concern over differences between Q3D and <232>)
  - Harmonization between Q3D and <232> have minimized this concern.
- Application of the "control threshold"
  - A new concept in Q3D, intended as a tool for risk assessment
- Regulatory expectations
  - Where should risk assessment appear in CTD?
  - What is expected in the risk assessment summary?
  - Will expectations be consistent over time and across regions?
  - How will risk assessments for existing products be conveyed to regulatory authorities?
  - What information should suppliers provide to their customers?

Elemental Impurities Implementation Working Group at FDA

- Members: Review Divisions, OPQ-ONDP and OLDP, OPPQ, OTR and OND-PT, CBER
- Develop a Guidance for the regulated industry for implementation of ICH Q3D and <232>/<233>.
  - FDA Draft Guidance: Elemental Impurities in Drug Products*
  - recommendations for filing requirements and implementation timelines for new and existing drug products.
- Review and adopt training material developed by the ICH Q3D WG.

*See http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm509432.pdf or search FDA Guidance Elemental Impurities
Note: Harmonization of Q3D and <232> was published after this guidance was written. Appropriate corrections will be made in revision to reflect the harmonization .

Timeline considerations

- NDAs and ANDAs with USP Monographs
  - Follow recommendations of Q3D if submitted after 1 June 2016
  - Comply with USP <232>/<233> after 1 January 2018
- NDAs and ANDAs without USP Monographs
  - Follow recommendations of Q3D if submitted after 1 June 2016
- Compendial products not marketed under an approved ANDA or NDA (e.g., OTC)
  - Comply with USP <232>/<233> after 1 January 2018

Timeline considerations

- Non-compendial products not marketed under an approved ANDA or NDA (e.g., OTC)
  - Follow recommendations of Q3D after 1 January 2018
- Changes to conditions established in approved ANDAs and NDA needed to meet PDE recommendations of Q3D or comply with <232> PDEs
  - Report according to applicable regulations and guidance
  - See FDA Draft Guidance: Elemental Impurities in Drug Products, Section III.E for more details.

Timeline considerations

- FDA anticipates that most approved drug products marketed in the United States do not contain any elemental impurities that exceed the Q3D/<232> PDEs.
- Products that meet PDE recommendations of Q3D or comply with <232> PDEs
  - Perform risk assessment to determine if additional controls (e.g. upstream controls, specifications) are needed by 1 January 2018.
  - Document changes in the next Annual Report.
  - See FDA Draft Guidance: Elemental Impurities in Drug Products, Section III.E for more details.

Documentation and Risk Assessment

- New NDAs or ANDAs
  - Include a summary of the risk assessment application. Cite supporting material (e.g., controls) as warranted.
  - The P.2 section (Pharmaceutical Development) is an appropriate location for the risk assessment summary.
- Approved NDAs or ANDAs
  - Include a summary in the next annual report following the completion of the risk assessment. Document changes to controls.
  - See FDA Draft Guidance for details if drug products exceed PDEs and changes are implemented to reduce EI levels.
- For drug products not approved under an NDA or ANDA
  - Include risk assessment in the documentation maintained at the manufacturing site for Agency review during an inspection.

Risk assessment: Some potential considerations during review

- Intentionally added elements
- Contributions from raw materials derived from plant or marine origins.
- Contributions from raw materials that are mined, e.g.,
- inorganic drug substances and excipients.
- Contributions from manufacturing, e.g., high shear micronization using metal discs
- Leachable elemental impurities from container/closure.
- Extractables information from container/closure components typically included in a supplier Type III DMF.

Q3D Table 5-1:
Elements considered in the risk assessment

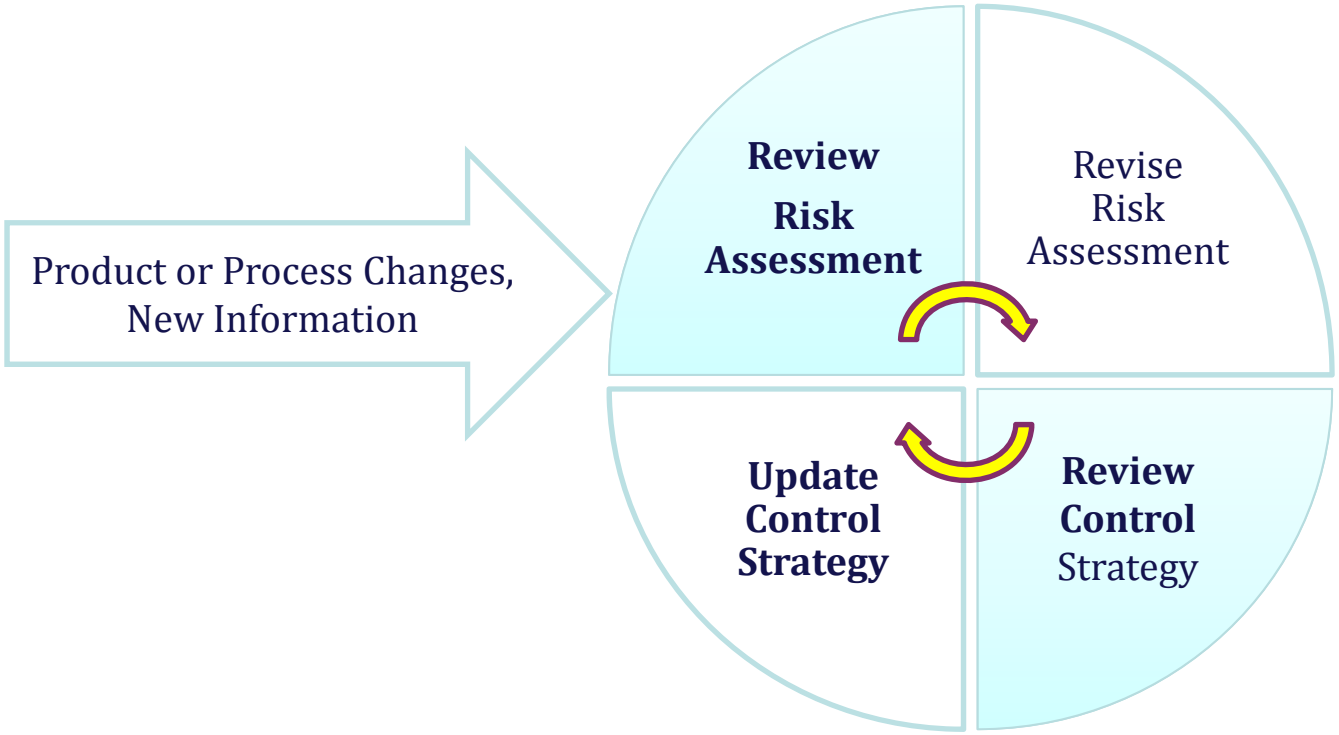
Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	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

Reference this table in the summary of the risk assessment.

Documentation (In Q3D Module 5)

Documentation to be maintained in Company Pharmaceutical Quality System	**Documentation to be included in regulatory dossiers (new or updates)**
Complete risk assessment document describing process, data used, data references and information needed to support dossier summary	Summary of product risk assessment process used
GMP related processes to limit the inclusion of elemental impurities	Summary of identified elemental impurities and observed or projected levels
Change management processes (defining triggers for product assessment or control strategy updates)	Data from representative commercial or pilot scale batches (component or drug product as appropriate)
Periodic review processes	Conclusion of the product risk assessment
Original data used in the product risk assessments, quality agreements, supplier qualification, etc.	

Life-cycle approach to Control Strategy (In Module 6)



GMP expectations for EI

- If risk assessment results in setting specifications in the drug substance and/or product, then
  - Testing Laboratories are subject to GMPs
  - Validation of analytical methods at the site and in the application
- If risk assessment confirms "minimal level" of EI, then
  - Risk assessment and any testing method(s) used during the risk assessment and results should be available during inspection and review.

Method Validation

- "Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose." [FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics, July, 2015]
- Analytical procedures for both risk assessments and routine testing should be validated, but the validation criteria (e.g., accuracy, precision, detection limits) can depend on the analytical procedure's intended purpose.

Method Validation for Risk Assessments

- Manufacturers should establish that the analytical procedures used during risk assessments possess characteristics (e.g., accuracy, precision, specificity) such that the manufacturers can be reasonably certain (e.g., at the 95-percent confidence level) that the measurements can be relied upon to decide whether to include routine testing of materials in the control strategy.
  - This decision depends on whether the amounts of the elemental impurities in the materials are consistently below control thresholds.
  - The analytical procedures should be validated with this goal in mind.

Early Adoption

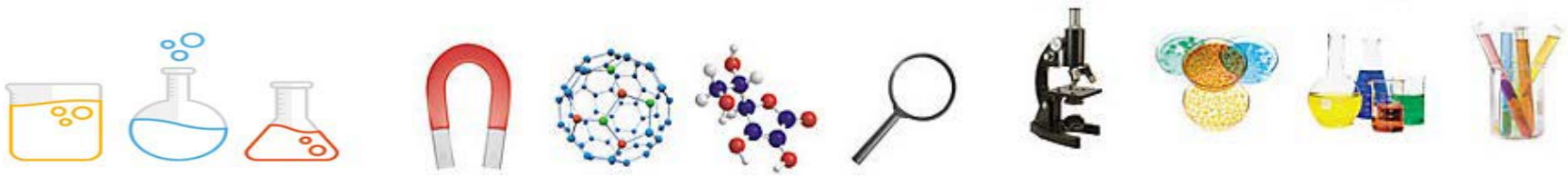
- FDA supports and encourages the early adoption of ICH Q3D and USP <232>/<233> before the implementation date.

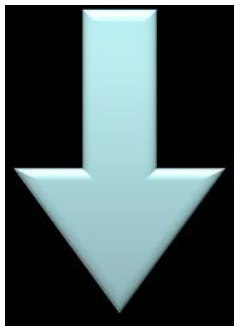
- In the case of compendial products, upon early adoption of General Chapters <232> and <233>, products and any components are not expected to demonstrate compliance with General Chapter <231>.

Drug Development

- Challenges with PDEs or “Acceptable exposure levels”?
- Analytical Methods limitations?
- Product specific considerations?
- We encourage you to contact the appropriate review divisions for guidance as needed during interdisciplinary or CMC-only meetings, EOP2 or pre- NDA meetings.

Proposed EI limit does not meet ICH





How does it link to the patient?

Examples

- Drug substance sourced from an ore
- EI-X is a theoretical impurity based on morphology of the naturally occurring raw material. EI-X confirmed by analytical method A but detection limit was high
- Levels in the drug product may exceed oral EI-X permissible exposure
- Drug product is a diagnostic with no chronic or intermittent use
- Resolution: EI-X and additional EI controls in the drug substance
- Firm proposed the development and validation of method B, with analytical test results from several pilot scale and production batches submitted for review

THANK YOU FOR YOUR ATTENTION!

EI WG Members

Danae Christodoulou, John Kauffman, John Leighton, Frank Holcombe, Matthew Vera, Pallavi Nithyanandan, Yana Mille, Rogelio Ruvalcaba, John Bishop (CBER)

OPPQ Ashley Boam and John Smith (retired)

ICH Q3D Compliance Challenges for Industry: Container Closure Systems and LVP Total Parenteral Nutrition

Tim Shelbourn, Eli Lilly and Company

Answers That Matter.

Presentation Outline

- Container closure system EI compliance challenges
  - Background on USP general chapter <661> series
  - Review of ICH Q3D
  - Compliance challenges
  - Points for consideration
- LVP Total Parenteral Nutrition EI compliance challenges
  - Characteristics of TPN solutions
  - Analytical challenges for EI analysis applying 2-L dose per Q3D PDEs
  - Points for consideration

Industry Challenges for EI Compliance: Container Closure Systems

USP <661> Series of General Chapters

- <661.1> Plastic Materials of Construction
  - Scope: To provide test methods and specifications for plastic materials of construction used in packaging systems…..establish potential safety effect
  - Guidelines: Materials that do not meet these requirements are not suitable for containers for these dosage forms unless the materials are established to be suitable by other means….
- <661.2> Plastic Packaging Systems for Pharmaceutical Use
  - Scope: The packaging system is constructed from well-characterized materials that have been intentionally chosen for use as established by testing according to <661.1>
- <661.3> Plastic Components and Systems Used in Pharmaceutical Manufacturing
  - Scope: Addresses the qualification of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical APIs and DPs
- <1661> Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to their User Safety Impact
  - Scope: The purpose is to communicate the key concepts behind <661.1> and <661.2>

ICH Q3D Container Closure Statement

5.3 Identification of Potential Elemental Impurities

Elemental impurities leached from container closure systems: The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. ***When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed.*** It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf- life of the product. ***Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed. This source of elemental impurities will typically be addressed during evaluation of the container closure system for the drug product.***

Industry Challenges for EI Compliance: Inconsistencies between <661.1> and ICH Q3D

- EI list in <661.1> is not consistent with Q3D:
  - Aluminum, titanium, zinc, zirconium, germanium, manganese, calcium are added
- EI list in <661.1> is not consistent with Q3D Risk Assessment for Parenteral Drug Products:
  - Class 1(As, Cd, Hg, Pb), Class 2A (V, Ni, Co) and Class 3 elements Sb, Cu, Li
- Specifications in <661.1> for EI limits are not consistent with PDE based permitted concentrations in Q3D
- Product safety based <661.1> EI Specifications are not self consistent amongst four polymers

Comparison of ICH Q3D Permitted Concentrations (100mL) and <661.1> Specifications

Elemental Impurity	ICH Q3D, Parenteral Permitted Concentration, 100mL Dose, µg/mL	USP <661.1> Limit, µg/mL in Extraction Solution S3[1] (polyethylene), µg/mL	USP <661.1> Limit in Extraction Solution S3 (cyclic olefins), µg/mL	USP <661.1> Limit in Extraction Solution S3 (polypropylene), µg/mL	USP <661.1> Limit in Extraction Solution S3 (PET and PET G), µg/mL	USP <661.1> Limit in Extraction Solution S3 (Plasticized PVC), µg/mL
Al	None	0.4	0.4	0.4	0.4	N/A
As	0.15	0.01	0.01	0.01	0.01	0.01
Ba	7	N/A	N/A	N/A	0.4	0.25
Ca	None	N/A	N/A	N/A	N/A	35
Cd	0.02	0.01	0.01	0.01	0.01	0.01
Co	0.05	0.01	0.01	0.01	0.01	0.01
Cr	11	0.02	0.02	0.02	0.02	0.02
Cu	3	None	None	None	None	None
Ge	None	N/A	N/A	N/A	0.4[2]	N/A
Hg	0.03	0.01	0.01	0.01	0.01	0.01
Li	25	None	None	None	None	None
Mn	None	N/A	N/A	N/A	0.04	0.04
Ni	0.2	0.01	0.01	0.01	0.01	0.01
Pb	0.05	0.01	0.01	0.01	0.01	0.01
Sb	0.9	N/A	N/A	N/A	0.4[2]	N/A
Sn	6	1	1	1	N/A	1
Ti	None	0.4	0.4	0.4	0.4	N/A
V	1	0.04	0.04	0.04	0.04	0.01
Zn	None	0.4	0.4	0.4	0.4	100
Zr	None	0.04	0.04	0.04	N/A	N/A

[1]Solution S3 (Acid Extraction): 100-g material/250mL 0.1N HCl
[2]Solution S4 (Alkali Extraction): 20-g material/50mL 0.01N NaOH

Industry Challenges for EI Compliance: Some Recommendations for consideration.

- Harmonize EI list or cite USP <232> Elemental Impurities in <661.1>
- Establish PDEs Al, Ca, Ge, Mn, Ti, Zn, Zr to ICH Q3D and USP <232>
- Do away with specification limits applied to S3 and S4 extraction solutions and allow for dose-based permitted concentrations to be applied
- Include allowances for analysis of drug product stability samples at or beyond expiry to demonstrate material does not contribute EIs above specific PDE

Industry Challenges for EI Compliance: Total Parenteral Nutrition Solutions

Characteristics of TPN Solutions

- Parenteral source of carbohydrates, electrolytes, amino acids, lipids for patients that are not capable of ingesting food. Replaces normal food intake.
- Large volume parenterals, up to several liters.
- Administered through a bed-side metering pump
- Contain solutes in percent range. Represent very high “dissolved solids” test articles for ICP mass spectrometry, often with inorganic constituents (salts)

EI Analysis of TPN Solutions: Analytical challenges

- High unit volumes (often in excess of 2-L) for almost ALL TPN product formulations.
- High dissolved solids in TPN formulations which frequently includes inorganic salts
- Even analysis of the individual components at the formulation concentrations are a challenge when applying 2-L dose
- ICP mass spectrometry has limited tolerance for dissolved solids. In general, the dissolved solids in a test solution is a few tenths of a percent.

Working concentrations for control threshold (30% of permitted concentration) spikes, 2000mL Dose, at various nominal sample dilutions:

Class	Element	Parenteral PDE, µg/Day	Permitted Conc., µg/mL	Control Threshold, µg/mL	Spiking Conc. (DF=10), µg/L	Spiking Conc. (DF=50), µg/L	Spiking Conc. (DF=100), µg/L	Spiking Conc. (DF=200), µg/L
1	Cd	2	0.001	0.0003	0.03	0.006	0.003	0.0015
1	Pb	5	0.0025	0.00075	0.075	0.015	0.0075	0.00375
1	As	15	0.0075	0.00225	0.225	0.045	0.0225	0.01125
1	Hg	3	0.0015	0.00045	0.045	0.009	0.0045	0.00225
2A	Co	5	0.0025	0.00075	0.075	0.015	0.0075	0.00375
2A	V	10	0.005	0.0015	0.15	0.03	0.015	0.0075
2A	Ni	20	0.01	0.003	0.3	0.06	0.03	0.015
3	Li	250	0.125	0.0375	3.75	0.75	0.375	0.1875
3	Sb	90	0.045	0.0135	1.35	0.27	0.135	0.0675
3	Cu	300	0.15	0.045	4.5	0.9	0.45	0.225

EI Analysis of TPN Solutions:
Some recommendations for consideration.

- Apply adjustment to PDEs for infrequent/short duration dosing of TPNs per Q3D section 3.3?
- Even though packaged unit volume may be 2-L or more, does that reflect actual daily dosing in practice?
- If current Q3D PDEs are based upon EI consumption through typical food/water intake and the TPNs substitute ingested food…..should PDEs be applied that take this into account?
- ICH Q3D is specific for drug products. Should a separate EI guideline for TPN solutions be implemented?

Questions?