FDA Guidance on Elemental Impurities in Drug Products

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Outline

- Elemental Impurities: Basics
- ICH Q3D and USP <232>: Notable Differences
- ICH Q3D and USP <232>, <233> Implementation: FDA Expectations and Timelines
- FDA/CDER viewpoint on recent USP proposals

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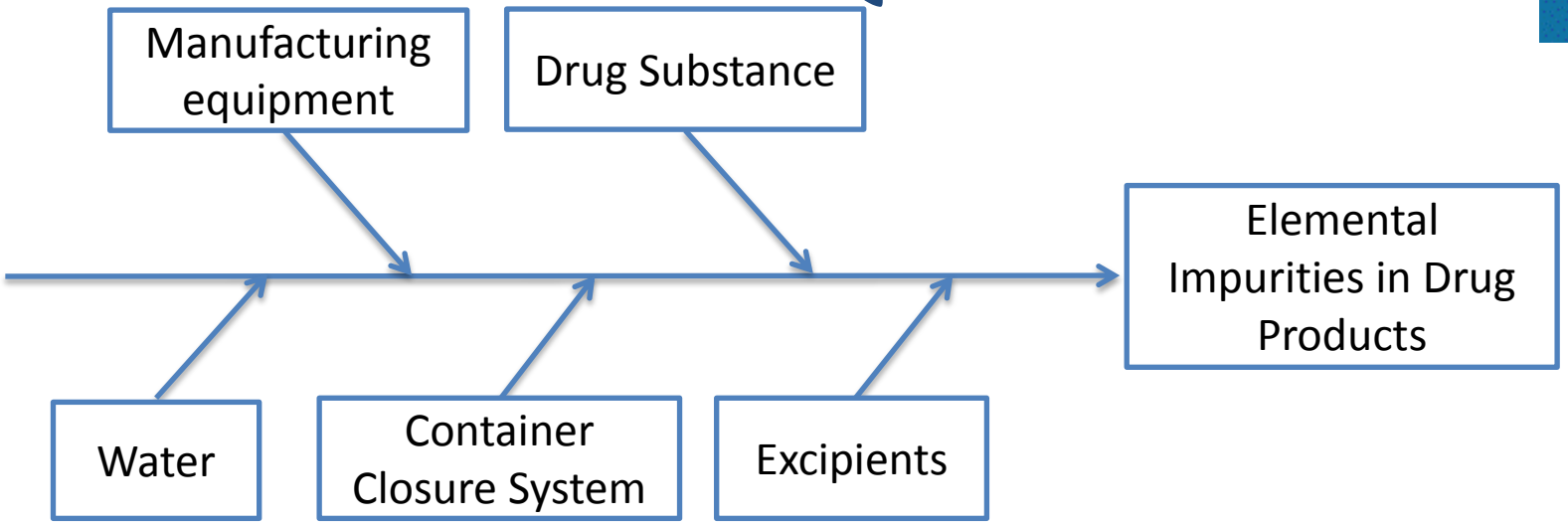
Elemental Impurities - Basics

ICH Q3D



- Establishes Permitted Daily Exposures (PDEs) for 24 elements for Oral, Inhalation and Parenteral Routes. Concepts can be applied to other routes.
- Concepts can be used for other routes of administration.
- Training modules provide further guidance on calculations and risk assessment.
- Four calculation options for converting PDEs to concentrations
  - **Options 1 and 2a** include calculations based on individual component contributions.
  - **Excipient CoA and evaluations can provide valuable information to overall risk assessment and control strategy.**

USP <232>, <233>

- Applicable to all articles that are the subject of a USP or NF monograph (official articles)
- Establishes Permitted Daily Exposures (PDEs)
- Provides analytical methods and validation criteria
- Made applicable through USP General Notices Section ***5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements*** (similar to Residual Solvents)

Notable Differences between ICH Q3D and USP Elemental Impurities Chapters

Notable Differences between ICH Q3D and USP <232>, <233>:

ICH Q3D	USP <232>, <233>
Guideline	Enforceable standards
Includes 24 elements	Currently includes 15 elements (Not included: Ti, Au, Se, Co, Ba, Sn, Li, Sb, Ag) ***Upcoming revision to include all 24 elements***
Analytical methods not provided (delegated to pharmacopeias)	Provides analytical methods and validation criteria
Includes Total Parenteral Nutrition (TPN) products	Excludes Total Parenteral Nutrition (TPN) products

FDA Draft Guidance on Elemental Impurities in Drug Products

Filing/Documentation Recommendations for Risk Assessment

Product type	Documentation
New NDA/ANDA*	Summary of risk assessment in CTD Module P.2 Pharmaceutical Development
Approved NDA/ANDA*	Summary of risk assessment in next annual report
Products not approved as NDA or ANDA (for example non-application OTC products)	Include risk assessment in the documentation maintained at the manufacturing site for agency review

* State in cover letter regarding the inclusion of risk assessment. Maintain in Pharmaceutical Quality System complete and detailed risk assessment document to support dossier summary.

Implementation timelines

ICH Q3D will be effective for existing products

- New NDA/ANDA effective June 01, 2016
- Existing products effective January 01, 2018

USP <232>, <233>

- On January 1, 2018
  - <231> Heavy Metals will be deleted
  - <232> Elemental Impurities- Limits, and, <233> Elemental Impurities- Procedures will reach official implementation date

Early Adoption

FDA supports and encourages early adoption of ICH Q3D and USP General Chapters <232> and <233> prior to implementation date:

- ICH Q3D and General Chapters <232> and <233> provide significant improvements over existing approaches
- If adopted, compendial products are not expected to demonstrate compliance with General Chapter <231>

FDA/CDER viewpoint on Validation of Analytical Methods

- USP <233> describes two procedures (ICP-MS and ICP-OES) and provides validation criteria for analytical methods.
- Any selected method must be demonstrated to be suitable for intended purpose (See 21 CFR 211.194(a)(2)).
- If methods other than ICP-MS and ICP-OES are used cross-validation with the ICP methods is not required.
- FDA participates in the Pharmacopeial Discussion Group for harmonization between USP, EP and JP

Other Considerations

- Lower limits may be needed for certain products based on safety concerns.
- If a product has challenges to meet ICH Q3D and/or USP <232>, <233>
  - For NDA/ANDA: Contact the respective review division
  - For FDA Monograph OTC products: Contact the Division of Non-Prescription Drug Products
- Inter-disciplinary review will be conducted to assess the impact on patient safety.

FDA Viewpoint on Recent USP Stimuli Articles

FDA/CDER Viewpoint on the Exclusion of Total Parenteral Nutrition Products from <232>

USP *Stimuli Article* in PF 41.4, and 42.2 revisions to <232>:

- USP excludes TPNs from <232> but ICH Q3D includes TPNs.
- Stimuli Article in PF 41.4 explains the reasons behind USP's decision to exclude TPNs from the scope of <232>.
- ***Important to note that FDA intends to apply the ICH Q3D guidelines to TPNs.***

FDA/CDER Viewpoint on USP Plans for Element-Specific General Chapters

USP *Stimuli Article* in PF 42.4:

- CDER supports USP's plans for element specific chapters as outlined in this Stimuli Article.
  - Rely on <233> Elemental Impurities -- Procedures for the analytical testing procedures rather than using the procedures in element specific chapters.
  - Align the specific elemental impurities limits with <232> unless there is a known quality- or safety-reason to maintain a specific elemental impurity limit.
- We recommend that USP engage in a careful study of the impact of revisions by experts (including FDA, USP and Industry) to determine which monographs qualify for an exception from the <232> limits.
- Also evaluate other USP General Chapters that refer to the element-specific chapters.

Element-specific Limits in Individual Monographs: Thorough evaluation by experts is recommended.

References

- FDA Guidance on Elemental Impurities in Drug Products http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM509432.pdf
- ICH Q3D training modules http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html#3-5
- Recording of ICH Q3D Regional Workshop held at FDA in August 2016 http://www.fda.gov/Drugs/NewsEvents/ucm498553.htm
- http://www.usp.org/usp-nf/key-issues/elemental-impurities

Thank You!