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

• Brief History of Revision to Control of Elemental Impurities

• High Degree of Harmonization in 2016

• Data-based expectation: elemental impurity levels in drug products and components relatively low in most cases

• Q3D Implementation Working Group is Developing Training Modules
  – Modules reviewed by regulatory authorities from ICH regions and beyond

• FDA Expectations for Implementation: Elemental Impurities Implementation Working Group
The ICH Q3D Expert Working Group

- Broad membership supports harmonization
  - Toxicologists and Chemists
  - FDA, PhRMA, EMA, EFPIA, MHLW, JPMA
  - EFTA, WHO, Health Canada
  - Pharmacopeias: USP, Ph.Eur., JP
  - IPEC, WSMI, IGPA, BIO
  - Chinese Taipei, China, Korea
  - At the June 2014 meeting, approximately 24 representatives participated in the deliberations.
Timeline

• 1995, USP published a stimuli article identifying issues with <231>

• 1998, EMA began drafting a guideline on Specification Limits for Residues of Metal Catalysts

• 2000, USP published stimuli proposing ICPMS as an alternative to <231>
  - Numerous stakeholder meetings from 2000 to 2008

• 2008, EMA issued a Guideline on Residual Catalysts and Reagents
  - Implemented for new products in September, 2008
  - Implementation for existing products scheduled for September, 2013
  - July 2013, EMA deferred implementation of Residual Catalyst Guideline to existing products until Q3D is finalized.
Timeline

- 2008, USP initiated development of <232> and <233>
  - Proposed PDEs for 31 elements in a Stimuli Article, PF 34(5), 2008
  - Finalized in November, 2012, PDEs for 15 elements
  - Implementation originally scheduled for May 2014
  - May 2013, USP deferred implementation of <232> and <233> to allow Q3D to complete its work.
  - <232> and <233> became official on 01-Dec-2015
Timeline

- 2010, ICH convened Q3D to develop harmonized limits for elemental impurities in pharmaceuticals
- June 2013, ICH Q3D reached step 2
- September 2014, ICH Q3D reached step 4
  - Approved by the ICH Steering Committee in November, 2014
  - Published on the ICH Website on 16 December, 2014
- Proposed Revision to <232> published in PF 42(2), Mar-Apr 2016
  - Harmonized table of elements, classification scheme and PDEs
  - Risk-based approach to control of elemental impurities
  - Scope is nearly identical to Q3D
FDA Division of Pharmaceutical Analysis
Studies of Elemental Impurities

- Small Volume Parenterals, 2013 (With ONDP)
- Elemental Impurities in Drug Products Survey-2010
- Lead Survey, 2007 (Published)
- Excipient Survey, 2015 (Published, OpenAccess)
  - DOI: 10.1002/jps.24650
  - Google “Journal of Pharmaceutical Sciences Elemental Impurities”
  - Complete data set available in Supplementary Material
Summary of Studies: No Surprises

• Most products have low levels of elemental impurities

• Q3D/<232> Class 2B elements are only present when intentionally added
  – Critical for Risk Assessment!

• Highly refined excipients have low levels of elemental impurities
  – Cellulose based materials
  – Lactose
Summary of Studies: No Surprises – Cont’d

• Some excipients have elevated levels of elemental impurities relative to refined excipients
  - E.g., mined excipients and products primarily composed of mined excipients
  - Levels may still be low compared to Table A.2.2 concentrations
  - The risk assessment reveals which materials make significant contributions

• Relatively high risk
  - high dose mass, e.g., large volume parentericals
  - intentionally added reagents and catalysts
  - unrefined naturally sourced materials
Principles for developing Q3D training materials

- Intended to provide clarity on key aspects of the guideline in order to facilitate a harmonized interpretation and implementation by industry and regulators in the ICH and non-ICH regions
- Does not provide additional guidance beyond Q3D
- Elaborate on key principles of the guideline
- Modular approach:
  - Seven modules on key safety and quality topics
    - Available at WWW.ICH.ORG
  - Module 8: Case studies illustrating an approach to presenting the risk assessment
  - Module 9: Frequently Asked Questions
- Not intended to provide templates for addressing the Q3D recommendations.
# Training Modules

1. How to Apply Q3D Concepts to Routes of Administration, not addressed in Q3D
2. Justification for Elemental Impurity Levels Higher than an Established PDE
3. Application of Q3D concepts to determining safe levels of elements not included in Q3D
4. Large Volume Parenterals
5. Risk Assessment
6. Control of Elemental Impurities
7. Converting between PDEs and Concentrations
8. Case Studies
9. FAQs
Q3D Table 5-1: Elements considered in the risk assessment

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<th>If intentionally added (all routes)</th>
<th>If not intentionally added</th>
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Reference this table in the summary of the risk assessment.
Determine appropriate controls

From Risk Assessment to Controls (In Module 5 & 6)

1. Elemental impurities excluded from the risk assessment (see Q3D Table 5.1)
2. Elemental impurities that may be present, but are below the control threshold in the drug product
3. Elemental impurities that may exceed the control threshold, but are below the PDE in the drug product
4. Elemental impurities that may exceed the PDE in the drug product

Product risk assessment
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.
  - recommendations for filing requirements for new and existing drug products.

- Review and adopt training material currently under development by the ICH Q3D WG.

- Timeline of implementation for new and existing products.
Timeline considerations

- **Recommendations** of the EI WG
  - After June 1, 2016: applicants should follow the recommendations of Q3D for new drug products
    - ~18 months after Q3D published on the ICH website
    - Consistent with the EMA implementation timeline
  - January 1, 2018: Manufacturers should follow the recommendations of Q3D and/or comply with USP <232>.
    - ~36 months after Q3D published on the ICH website
    - Consistent with USP implementation timeline for <232> and <233>. 
Method Validation

• “The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose” [ICH Q2(R1)]

• “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 Analytical Procedures and Methods Validation for Drugs and Biologics, July, 2015]

  - “In addition, a risk-based approach on the need for revalidation of existing analytical methods may need to be considered when the manufacturing process changes during the product’s life cycle.”
Method Validation

- 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.

- 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.

- The analytical procedures should be validated with this goal in mind.
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.
THANK YOU FOR YOUR ATTENTION!