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

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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?

El 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  - FDA Draft Guidance: Elemental Impurities in Drug Products*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:
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.

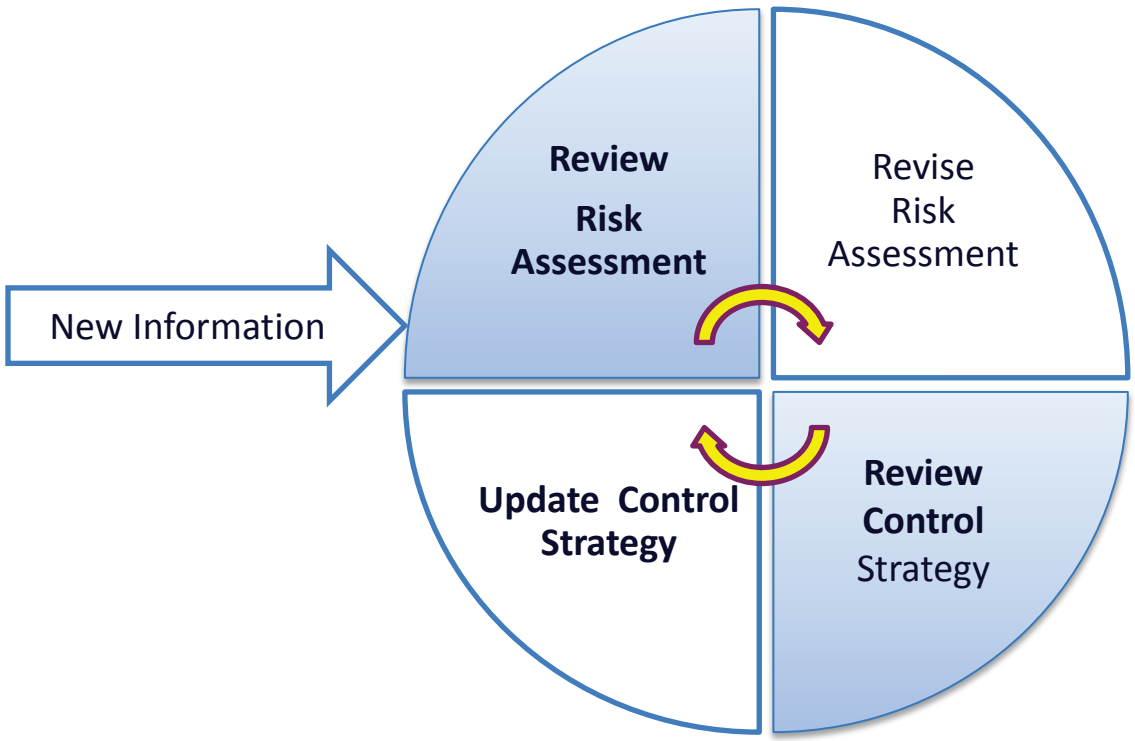
Q3D Table 5-1:
Elements considered in the risk assessment

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

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

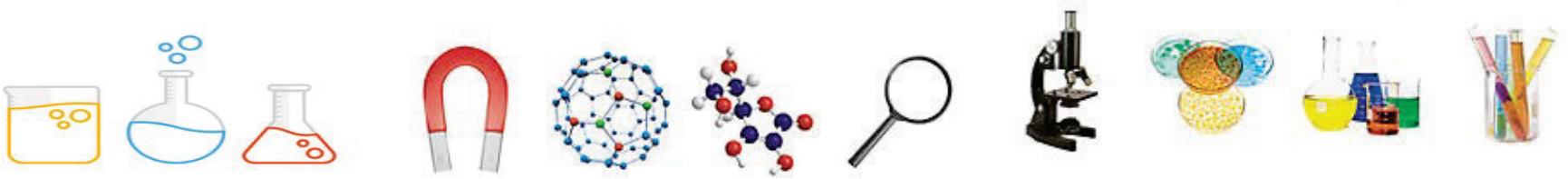
- FDA supports and encourages the early adoption of ICH Q3D and USP <232>/<233> before the implementation date.

- 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

Examples (contd.)

- FDA was asked whether a proposed EI-X was acceptable for an OTC product
- The sponsor requested a waiver of EI-X levels specified in <232> as use was intermittent and not considered a safety issue; no other information provided
- FDA analysis
  - EI-X was of concern to patients in a sensitive subpopulation
  - EI-X exceeded oral PDE by several multiples
  - Label did not indicate intermittent use only
  - Level of EI-X was at ~ 50% a level not known to be adverse
  - Conclusion: sponsor assessment was not adequate

Examples (contd.)

- Still unresolved, but based on usual approach for impurities:
  - Likely ask the sponsor to provide a rational as to why EI cannot be reduced to PDE
    - Reducing EI level to PDE – additional assessment toward revision of manufacturing and formulation processes
    - Future control plans?
  - If the EI cannot be reduced, provide a scientific justification to exceed the PDE; consider
    - Bioavailability in formulation
    - Provide information about risk in sensitive subpopulations
    - Risk mitigation (restrict use in sensitive subpopulations to medical need)
    - Provide data to support intermittent use claim
    - Label changes
    - Other

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)

U.S. FOOD & DRUG ADMINISTRATION

FDA
10903 New Hampshire Ave
Silver Spring, Maryland 20993