FDA Guidance and Current Experience with New Drug Submissions

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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  - FDA Draft Guidance issued in **June 2016**: Elemental Impurities in Drug Products: Comments from stakeholders have now been addressed and final draft through clearance
  - recommendations for filing requirements and implementation timelines for new and existing drug products.
  - **January 2018** is implementation date for all products! Early implementation of USP<232>, ICH Q3D – do not need USP<231>
- Review and adopt training material developed by the ICH Q3D WG.

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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  - See FDA Draft Guidance: Elemental Impurities in Drug Products, Section III.E for more details.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.

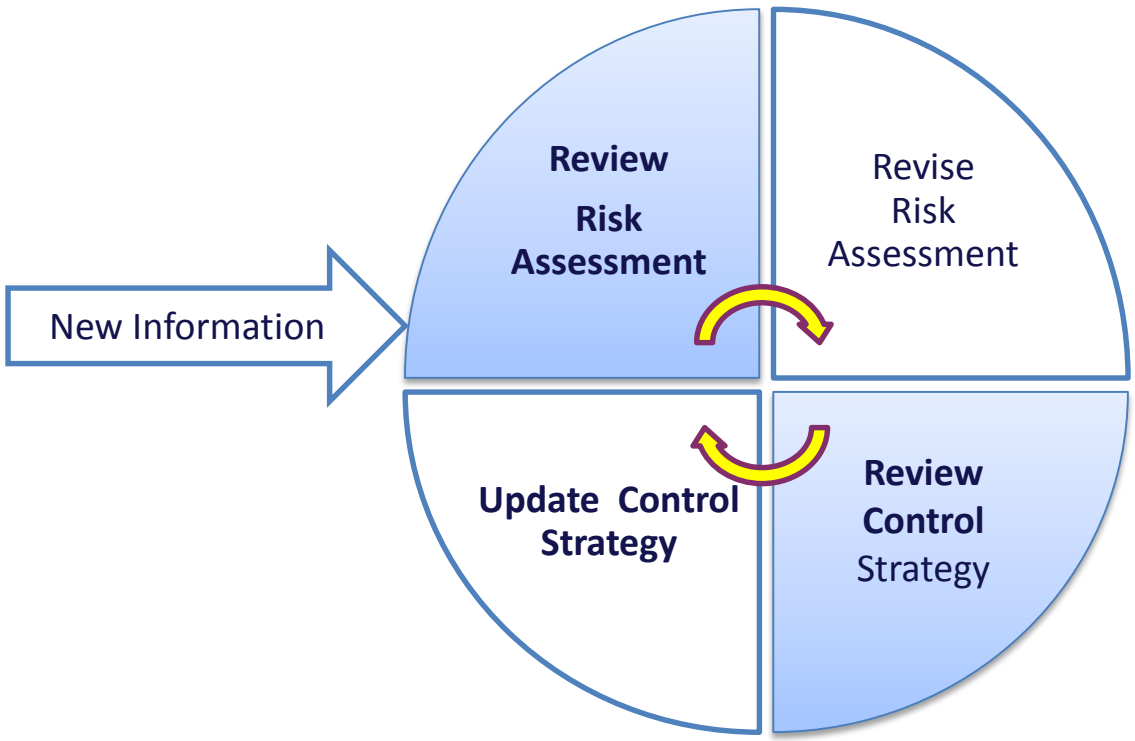
Risk assessment:
Potential considerations during review

- 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.

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.

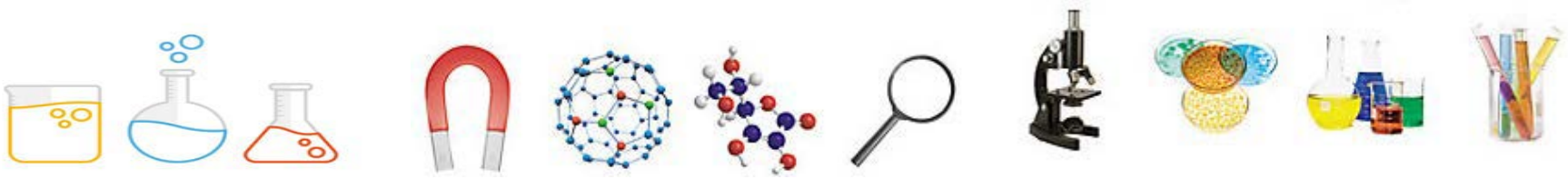
Method Validation

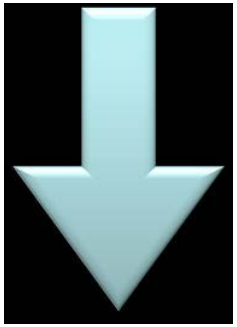
- “Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose.” [FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics, July, 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.
- Are the elemental impurities in the materials of interest consistently below control thresholds?

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 – New Drugs

- 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.)

- The sponsor was asked 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

Examples (contd.)

- NDA application for an orphan drug
- Drug substance is sourced from an ore from open-pit mines
- Drug product contains no additional ingredients
- EI-Z, Class 1 occurs naturally at levels that exceed parenteral PDE by 8-fold
- Additional Class 2A EIs exceed PDEs by 2-5 fold
- High doses (up to 10 g)
- Administered once or twice

Examples (contd.)

- Drug Substance Control:
- Source, one geographical location: defined
- Mineralogical composition: determined
- Reduction of EIs by purification: not feasible
- Controls in drug substance: established
- Batches: 3
- Verification of the analytical method resulted in re-validation

Examples (contd.)

- During review, the applicant was asked to provide a risk assessment for the EI-Z and detailed justification for exceeding the PDE specified in ICH Q3D. Include clinical use, and worst-case scenario of multiple doses, repeat administration to the same patient, and use in pediatrics.

Examples (contd.)

- The ICH Q3D PDEs have been set to ensure that exposure to an EI in a drug product, is safe based on daily exposure over a lifetime
- Safe Maximal Daily Parenteral Exposure (SMDPE) was calculated for children and adults for a maximal 10 g dose, dosing and elimination of the EI-Z

PDE = NO(A)EL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5]

See ICH Q3D, Appendix 1, modified factor approach

*Uncertainty factors: (WHO), 2005, Harmonization Project Document No. 2: Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment

Examples (contd.)

- Drug Product Control:
- Established EI controls after justification of levels of exposure that exceed PDEs
- Labeling:
- EI-Z risk exposure in pediatrics, pregnant and lactating women stated in the PI

Application was approved

THANK YOU FOR YOUR ATTENTION!

EI WG Members

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