Elemental Impurities – Implementation of ICH Q3D
Challenges and Opportunities

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Agenda

- Overview of progress on ICH Q3D
- Challenges
- An approach to product risk assessments
- Considerations for pending implementation
- Conclusions
Overview of progress on ICH Q3D

- The primary content of the guideline was finalized June 2014
- Q3D Expert working group is finalizing two areas (Sept 2014)
  - Approach to evaluating large volume parenteral products, including enteral nutrition
  - Harmonized procedure on application of the guideline to currently marketed products
- Commitment to preparation of training materials (Dec 2014)
- Updates from Step 2b
  - Alignment of PDEs with USP <232> and ICH Q3D
  - Improved guidance on a standard process to evaluate less than daily dosing/intermittent dosing
  - Improved guidance on applying the approach to alternative routes of administration
  - Revision and simplification of the risk assessment process and examples
Challenges

Science and risk-based assessment

• Where to start?
• How much data/information is needed?
• What are the most significant potential sources of elemental impurities?
• Considering all potential sources of data - a significant undertaking

What will the Health Authority expectations be for the regulatory dossier

• Presentation of the risk assessment – level of detail
• How much data will be required to support risk assessment conclusions?
• Where should the information be presented in the CTD?

Current absence of a pharmacopeial analytical method common across ICH countries/regions
“During the risk assessment, the potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the drug product.”
Preliminary assessment approach

A pragmatic approach to initiating a science and risk-based product assessments

If present – more likely sources of elemental impurities

Proposal: Risk Assessments for these three to be prepared in a common document used across products

Lower Risk/Probability

Excipients (Mined vs. synthetic)

Drug Substance (Metal Catalysts)

Proposal: Risk Assessments for these three to be prepared separately for each product

Water (Water/Air/Facilities)

Packaging (Container Closure System)

Manufacturing (Equipment/Process)

Elemental impurities in Drug Product

Proposal: Risk Assessments for these three to be prepared separately for each product
Pharma Elemental Impurities

A proposed approach to product assessments

Assessments developed one time and applied to all products. Consideration for contributions of elemental impurities from these sources is only evaluated on an exception basis in the product specific assessment.

Note: This is one potential approach – others approaches are possible and are being applied.
General Assessments

Guiding principles

- GMP requirements and expectations provide a foundation for the assumptions included in the General Assessments.

- Each general assessment will describe the underlying controls within the quality system, current knowledge and data supporting the conclusions.

- General assessments are intended to be valid across all products.

- Departures from the assumptions in the general assessments will be documented in the product specific risk assessment (e.g. specific treatment of certain container closure systems).

- Change management processes ensure updating of assessments and evaluations.

- Periodic verification testing programs can be established to ensure sustained compliance.
General Assessment - Overview

**Potential contributions from facilities and utilities**

- Significant GMP elements
  - Facility design control
  - Facility qualification
  - Utility qualification
  - Engineering standards

- The potential elemental impurities that may come from water can be mitigated by:
  - Routine water quality monitoring program
  - Utility qualification
  - Using compendial grade water supplies

*The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process(es). (ICH Q3D Step 4)*
Potential contributions from manufacturing process and equipment

- Data from drug substance elemental impurity screening methods
  - Internal results show no significant elemental impurity contributions from manufacturing equipment across a wide variety of synthetic routes

- Drug substance manufacturing conditions have a higher potential to “extract” elemental impurities than do drug product processes

In general, the processes used to prepare a given drug substance are considerably more aggressive than processes used in preparing the drug product when assessed relative to the potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from drug product processing equipment would be expected to be lower than contributions observed for the drug substance. However, when this is not the case based on process knowledge or understanding, the applicant should consider the potential for incorporation of elemental impurities from the drug product manufacturing equipment in the risk assessment (e.g. hot melt extrusion). (ICH Q3D Step 4)
General Assessment - Overview

Potential Contributions from Container Closure Systems (Packaging)

- For solid oral dosage forms, contributions from container closure systems can be excluded from further consideration in the risk assessment (-ICH Q3D Step 2)

- For liquid and semi-solid dosage forms, leachable studies evaluate the impact of the CCS to the drug product

- Jenke, et.al., A Compilation of Metals and Trace Elements Extracted from Materials Relevant to Pharmaceutical Applications Such as Packaging Systems and Devices (PDA Journal of Pharmaceutical Science and Technology, October 2013)
General Assessment - Overview

Potential Contributions from Excipients

- Based on current data, excipients fall into two classes
  - Low potential for inclusion of elemental impurities
  - High potential for elemental impurities

- Internal data supports low risk for majority of excipients studied

- FDA-IPEC publication (manuscript in preparation) – blinded study of over 100 excipients

- General assessment (data rich assessment)
  - Low potential excipients – no further consideration in the product specific risk assessment
  - High potential excipients – defined and included in product specific assessment
Product Assessment Process

- If based on component evaluation and assessment
  - Follow process flow chart Parts 1 and 2

- If based on drug product analysis
  - Follow process flow chart Part 3
Product assessment process – Part 1

Component approach

1. Are the assumptions for the facility/utility common assessment valid for the product?
   - Yes: Document and transfer conclusions to product specific assessment.
   - No: Evaluate Differences, determine impact/potential transfer of elemental impurities to the drug product.

2. Are the assumptions for the manufacturing equipment common assessment valid for the product?
   - Yes: Complete assessment of excipients and drug substance used and add to specific product assessment tool.
   - No: Determine, calculate or predict potential concentration of identified elemental impurity and include in specific product assessment.

3. Are the assumptions for the container closure system common assessment valid for the product?
   - Yes: Continue product assessment and identify appropriate additional controls required (Part 2).
   - No: Is the total elemental impurity level < 30% of the PDE for identified element(s)?
     - Yes: Document and transfer conclusions to product specific assessment.
     - No: Determine, calculate or predict potential concentration of identified elemental impurity and include in specific product assessment.

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Conclusions from Product Assessment - Part 1

Determine source of impurity i.e. process, API, or excipient from information collected or further testing (of RM,...)

Can the impurity be controlled below the PDE in the drug product

Can the level of elemental impurity be justified (e.g. safety assessment, short term dosing)

Yes

No

Apply routine release analysis and specification at the appropriate point to ensure control

Can impurity be controlled < threshold for concern e.g. by changing source, synthesis etc.

Yes

No

Develop qualification strategy, consider product reformulation and request advice from regulatory authorities

Update product requirements using appropriate change control/change management processes

Document additional controls and justification in the product specific assessment and appropriate regulatory filing documents
Product Assessment Process – Part 3

Evaluation of drug products with limited component information

- Analyze NLT 3 representative batches of drug product (covering different RM suppliers, manufacturing lines and packaging material for potential elemental impurities. Assess the results vs PDEs.

- Are the observed levels of the elemental impurities below the control threshold?
  - No → Determine source of impurity i.e. process, API, or excipient from information collected or further testing.
  - Yes → Impurity can be controlled to < control threshold for by changing source, synthesis, in-coming material specification, etc.?
    - No → Impurity can be controlled at or below the PDE at the maximum daily dose of the DP.
    - Yes → Perform analysis on 1 batch/year on all impurities above LOQ.

- Establish specification to control the identified impurity(ies) either in materials, drug substance, or drug product

- Submit justification to regulatory authorities

- The level of elemental impurity can be justified?
  - Yes
  - No → Change of supplier, change of synthesis or reformulation of the product to reduce impurity.
Considerations for implementation

- Limited data available in the open literature to support elemental impurities in commonly used drug product components
  - Increasing availability of data as the guideline is implemented
  - Trade organizations are initiating collaborative work to develop/share additional information

- Desire to define the level of detail of the risk assessment to be included in the regulatory dossier

- Desire to establish a harmonized approach to document compliance with the requirements of ICH Q3D in regulatory submissions
Conclusion

- The implementation of ICH Q3D provides an opportunity to put into practice a risk- and science-based approach to the control of elemental impurities.

- ICH Q3D and USP <232> have modernized the approach to control of elemental impurities:
  - Safety limits based on the available toxicological data.
  - Based on the currently available component and evaluations – the implementation of the new standard is not in response to a health concern or a safety risk to patients (with few exceptions, observed elemental impurity limits are significantly below the control threshold).

- As experience is gained through implementation, more information and data will become available:
  - Higher risk materials will be identified (as well as potential controls).
  - The real risks of elemental impurity inclusion in drug products will become clearer, providing an ability to focus attention on the areas of greater risk.
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