

4th PQRI Workshop on ICH Q3D Elemental Impurities
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Implementation in the U.S. – FDA Perspectives

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

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's face and a blue garment.

Patients expect safe and effective medicine with every dose they take.



Pharmaceutical quality is
assuring *every* dose is safe and
effective, free of contamination
and defects.

A close-up photograph of a person's hands. The left hand holds an orange plastic pill container, tilted to pour three white, oval-shaped pills into the palm of the right hand. The container has a white label with some text and a yellow bar. The background is blurred, showing a person's arm in a blue sleeve.

**It is what gives patients confidence
in their *next* dose of medicine.**

Outline



➤ ICH Q3D Conceptual Overview

ICH Q3D: Conceptual Overview



Adds to the ICH Q3 Suite of Guidelines on Impurities

- Q3A: Impurities in New Drug Substances
- Q3B: Impurities in New Drug Products
- Q3C: Residual Solvents
- Q3D: Elemental Impurities

Limits based on toxicological safety assessment

- By route of administration
- Based on permitted daily exposure (intake, not concentration)

Enabled by modern, specific analytical methods

- ICP-AES (OES)
- ICP-MS

Useful References



- ICH Q3D Guideline
- ICH Q3D Training Modules:

<https://www.ich.org/page/quality-guidelines>

Q3D training Implementation of Guideline for Elemental Impurities

The Q3D Implementation Working Group (IWG) was endorsed by the ICH Steering Committee in October 2014. Throughout the development of the Q3D Guideline, external audiences, constituents and interested parties have clearly communicated the complexity of the implementation approaches for this Guideline. The ICH Steering Committee considered that the development of a comprehensive training programme and supporting documentation sponsored by ICH was necessary to ensure the proper interpretation and effective utilisation by industry and regulators alike to enable a Harmonised and smooth implementation of Q3D on a global basis. The first training package (Modules 0-7) was endorsed by the ICH Assembly in December 2015. The final Modules 8-9 of the Q3D training package were endorsed by the ICH Assembly in June 2016.

Endorsed Documents

- Q3D Training Concept Paper
- Q3D Training Business Plan

WG Presentations / Trainings

- Q3D Training Package Module 0-9

- FDA Guidance: “Elemental Impurities in Drug Products”

<https://www.fda.gov/media/98847/download>

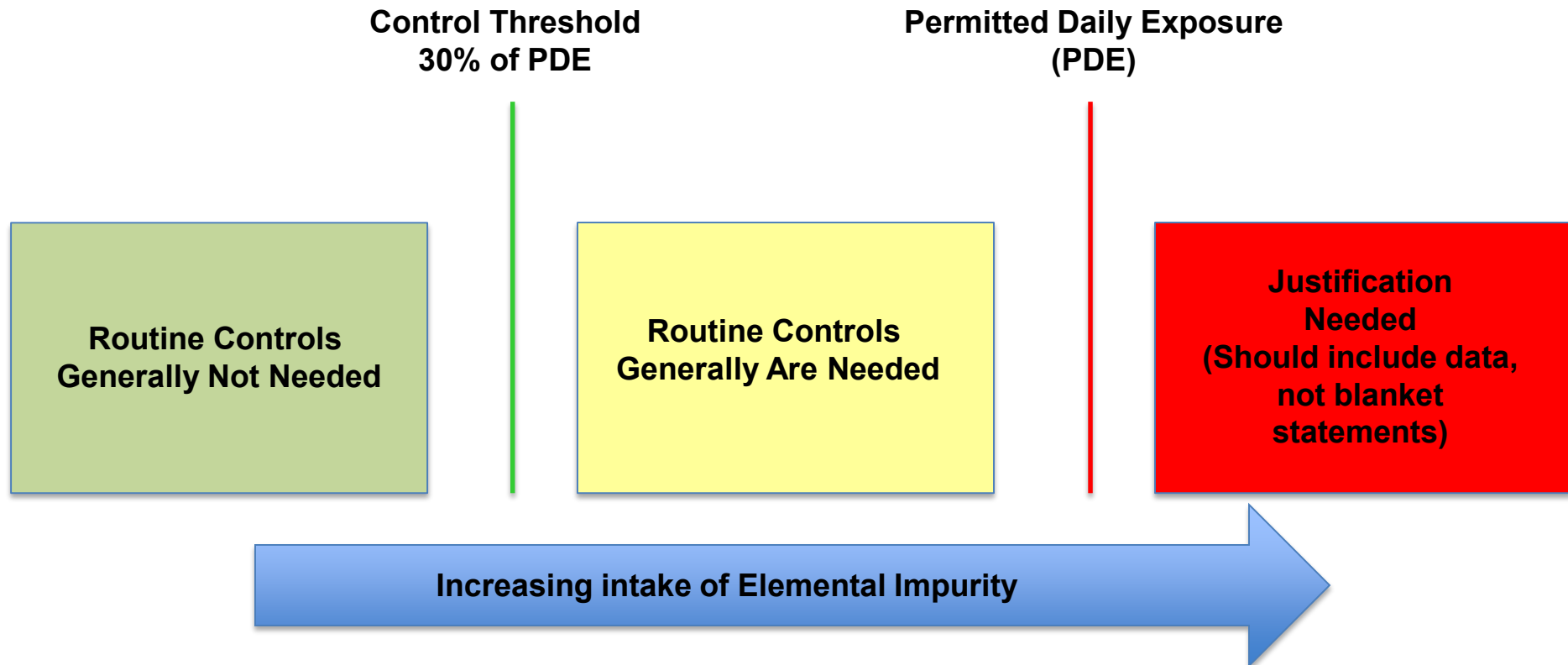
- USP <232> Elemental Impurities – Limits
- USP <233> Elemental Impurities – Procedures

<https://www.uspnf.com>

Risk-based Approach to Testing



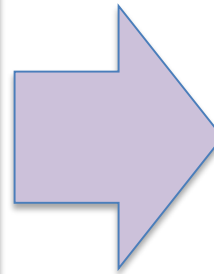
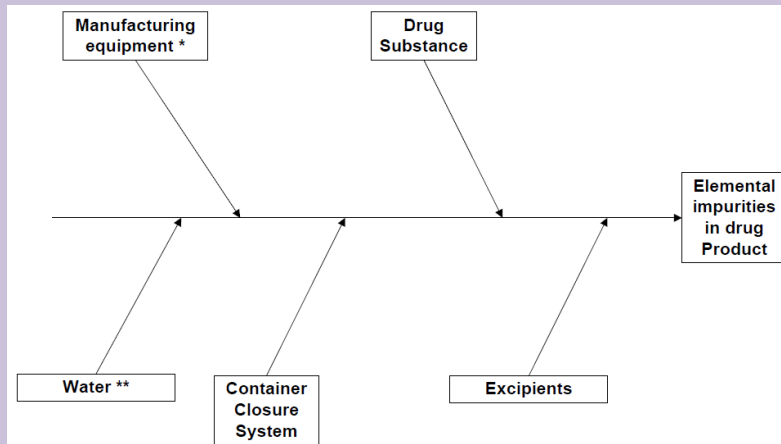
- Risk assessments used to determine the need for testing



To Test or Not To Test?



Risk Assessment



Additional controls are either:

- Needed
- Not needed

ICH Q3D, Section 5.6. www.ich.org

“If the total elemental impurity level from all sources in the drug product is expected to be **consistently less than 30% of the PDE**, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.”

“If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product.”

Calculation Options for Component Analysis In Risk Assessments



- Concentration limits used to determine the corresponding intake for a drug product
- Assumptions about the daily intake (mass) of the drug product at the maximum daily dose

Components can be
used in any proportion

Option 1: Assumes <10 g daily intake
Option 2a: Assumes some other specific
daily intake (e.g. 2.5 g/day)

Option 2b: Makes no assumptions – intake
is based on actual composition
of the formulation

Risk Assessment Information in the Regulatory Dossier



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.	

ICH Q3D Training Module 5, “Risk Assessment.” www.ich.org

The Risk Assessment Shows the Elemental Impurities Landscape of a Drug Product



- Elemental impurities are the responsibility of the finished product manufacturer.
- It is not the responsibility of suppliers of excipients or other components to “Meet Q3D.”
- The relationships between concentrations and the PDE/control threshold depend on the maximum daily dose and composition of the drug product.
- Communicate with component suppliers at an early stage, especially for formulations which are potentially problematic.

- **ICH Q3D Conceptual Overview**
- **Risk Assessments: Early Implementation Issues**

Early Implementation Issues: No Risk Assessment/EI Discussion



- Missing risk assessment or discussion of elemental impurities.
- Largely resolved with increasing awareness of ICH Q3D.

Potential outlier situation:

- Application was Tentatively Approved (or Drug Product Adequate) before ICH Q3D implementation
- Missing risk assessment is discovered just before approval
- If ICH Q3D package has not been submitted, reach out to the project managers handling the application.

Early Implementation Issues: The Incomplete/Perplexing Risk Assessment

- Missing elements
- Missing components
- Calculations of dubious value:

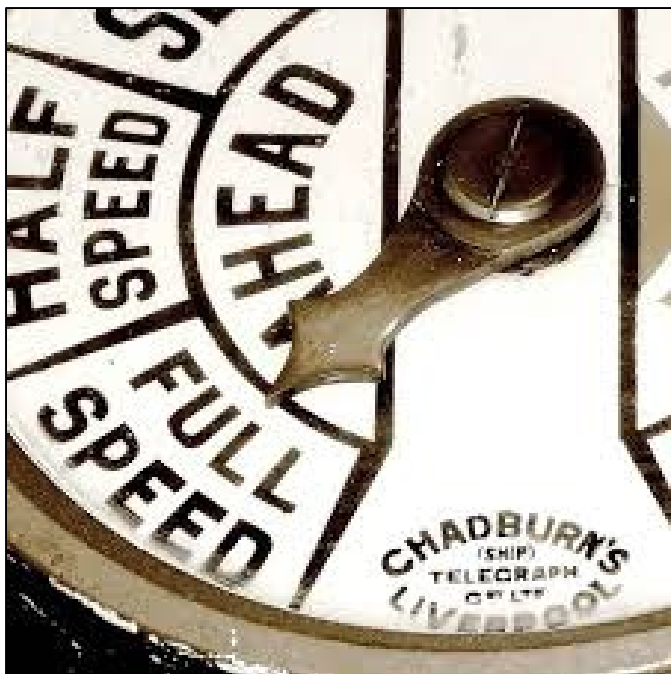


$$\begin{array}{ccccc}
 \text{Option 1} & & & & \\
 \text{Concentration} & & \text{Actual Amount} & & \text{Calculated} \\
 \text{Limit for EI} & \times & \text{of Excipient} & = & \text{Intake of EI} \\
 (\mu\text{g/g}) & & (\text{g}) & & (\mu\text{g})
 \end{array}$$

$$\begin{array}{ccc}
 \text{Calculated} & & \text{Permitted Daily} \\
 \text{Intake of EI} & < & \text{Exposure of EI} \\
 (\mu\text{g}) & & (\mu\text{g})
 \end{array}$$

- **ICH Q3D Conceptual Overview**
- **Risk Assessments: Early Implementation Issues**
- **Risk Assessments: Current Issues**

Post-Implementation: Current Issues



- Generally good uptake of the ICH Q3D risk assessment concept
- Some occasional bumps remain

Current Issues: The Confusing Risk Assessment



- Lack of summary discussion or explanation of the approach(es) used
- Reliance on tabulated data alone
- Inattention to detail:
 - Based on the wrong maximum daily dose
 - Inaccurate table captions and column headers
 - Incorrect units: concentrations ($\mu\text{g/g}$) become intakes ($\mu\text{g/day}$)



Current Issues: The Data-dump Risk Assessment



- Reliance on tabulated data alone
- A single table comparing expected values to control thresholds
- A massive appendix of vendor brochures and COAs without context
 - “Not detected”
 - “Negligible risk”
- No narrative interpretation or analysis

Current Issues: Risk Assessment and Variability



“If the total elemental impurity level from all sources in the drug product is expected to be **consistently less than 30% of the PDE...**”

-ICH Q3D, Section 5.6



Variability includes:

- Analytical method variability
- Variability in specific sources (component lots)
- Variability in the finished product

Current Issues: Risk Assessment and Variability

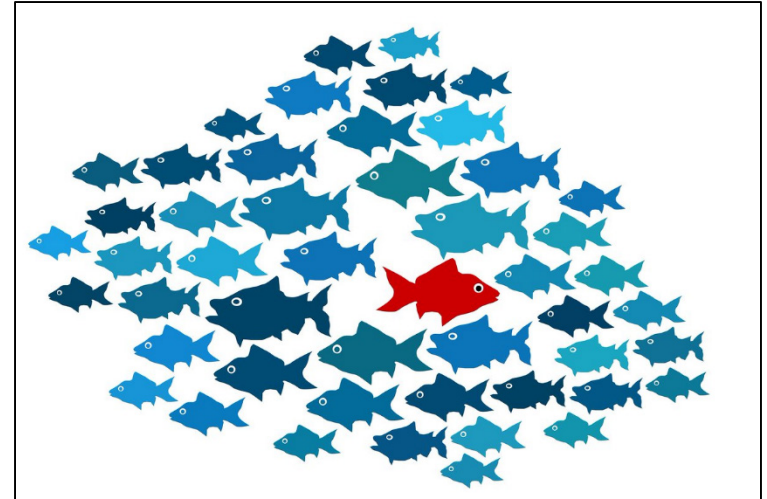


Example Scenario:

Vendor brochure for Component A states: Pb is <5 ppm

Is this value:

- The LOQ of a method that has never detected any Pb?
- A specification limit?
- The result of a one-time test performed on a single lot years ago?
- The maximum value based on years of testing?
- Confirmed by the Applicant?



Current Issues: The Option 3 “Risk Assessment”

Example scenario:

- Finished product testing of three exhibit batches shows results below the Control Threshold (30% of PDE.)
- No additional discussion provided.
- “No further testing is needed.”



Not a satisfactory risk assessment:

- No assessment of variability
- No situational awareness of pertinent elements or sources

Current Issues: Sound Risk Assessment, Wrong Conclusion



Example scenario:

- Risk assessment with Option 2b analysis shows all elements (except Pb) are below the Control Threshold.

- Pb is above Control Threshold but below PDE.
- Conclusion: No testing needed because $Pb < PDE$.

ICH Q3D, Section 5.6. www.ich.org

“If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product.”

- Either raw material controls or end-product controls.

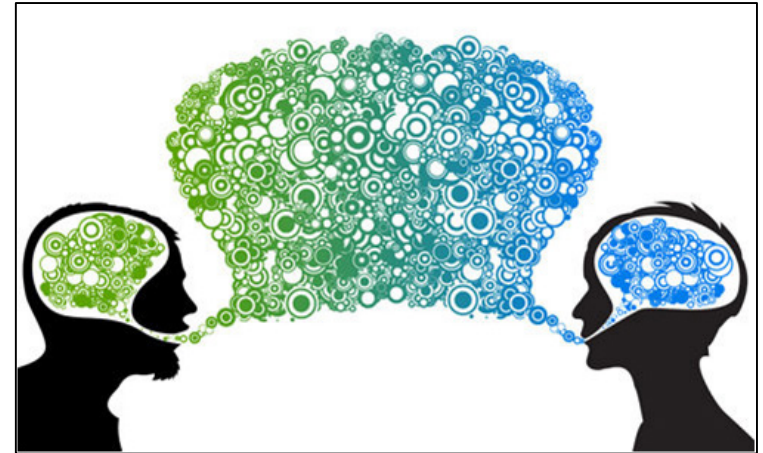
- **ICH Q3D Conceptual Overview**
- **Risk Assessments: Early Implementation Issues**
- **Risk Assessments: Current Issues**
- **Summary and Conclusions**

Summary and Conclusions

“...expected to be consistently less than 30% of the PDE.”














Effective communication is key

- Describe variability:
 - Why consistently less than 30% of PDE?
 - Basis for confidence?
- Tell a compelling story:
 - A good, clear explanation can be worth a lot of tabulated numbers
 - “Teach” the conclusion of the risk assessment.



Thank You!

ICH Q3D Training Modules: www.ich.org

-  Module 0 - Overview.pdf
-  Module 1 - Developing Acceptable Levels for Other Routes of Administration.pdf
-  Module 2 - Justification for Exceeding a PDE.pdf
-  Module 3 - Developing Acceptable Levels for EI not in Q3D.pdf
-  Module 4 - Considerations for Large Volume Parenterals.pdf
-  Module 5 - Risk Assessment.pdf
-  Module 6 - Controls on Elemental Impurities.pdf
-  Module 7 - Calculations Options.pdf
-  Module 8-1a - Case Study 1 for PQS_03Jul2018.pdf
-  Module 8-1b - Case Study 1 for Dossier_14Jul2016.pdf
-  Module 8-2 - Case Study 2 for PQS_August2016.pdf
-  Module 8-3 - Case Study 3 for PQS_14Jul2016.pdf
-  Module 9 - Consolidated FAQs final_14Jul2016.pdf