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

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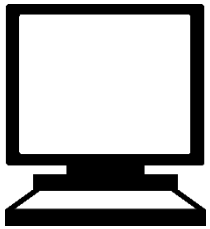
Disclaimer

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.



Pharmaceutical Quality

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

Drugs are no different.


FDA
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.


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

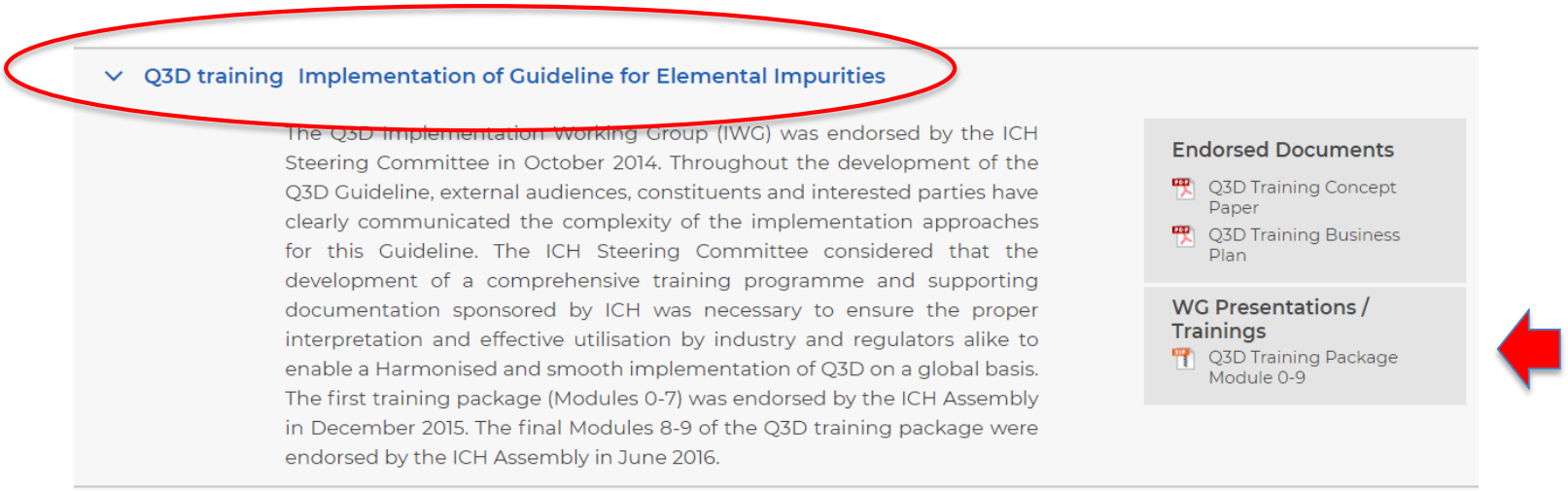
- By route of administration
- Based on permitted daily exposure (intake, not concentration)

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

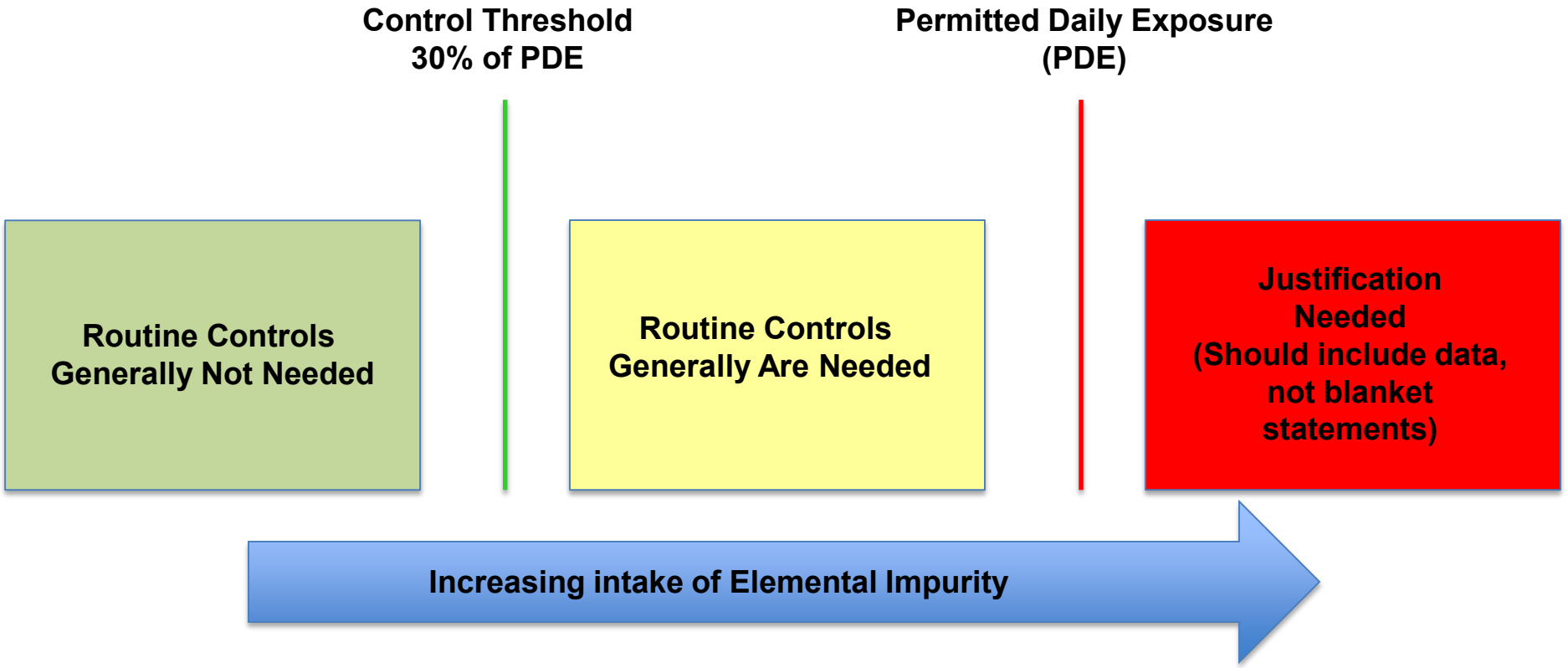


- FDA Guidance: “Elemental Impurities in Drug Products”
  https://www.fda.gov/media/98847/download

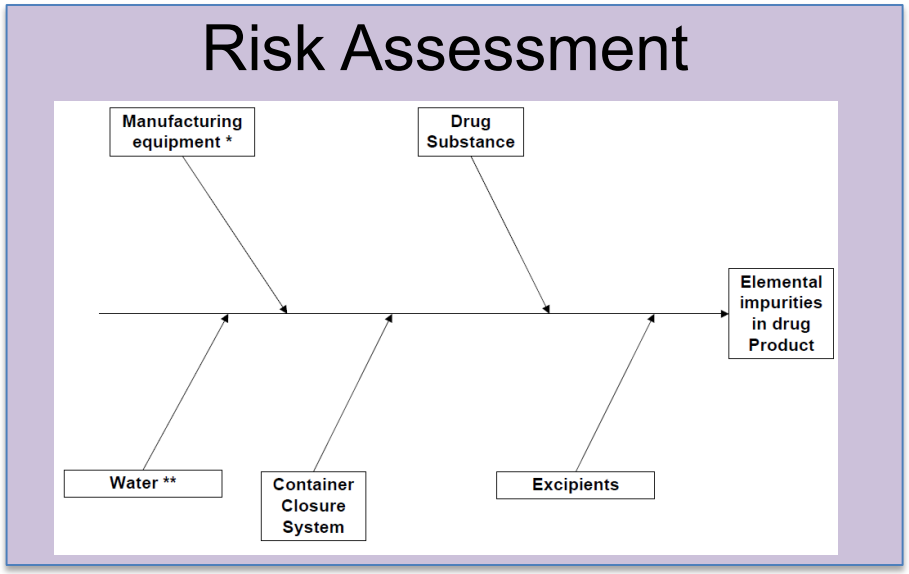
- USP <232> Elemental Impurities – Limits
- USP <233> Elemental Impurities – Procedures
  https://www.uspnf.com

Risk-based Approach to Testing

- Risk assessments used to determine the need for testing



To Test or Not To Test?



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

ICH Q3D, Section 7. www.ich.org

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.

Outline

- **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.

<u>Potential outlier situation</u>:

- 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:

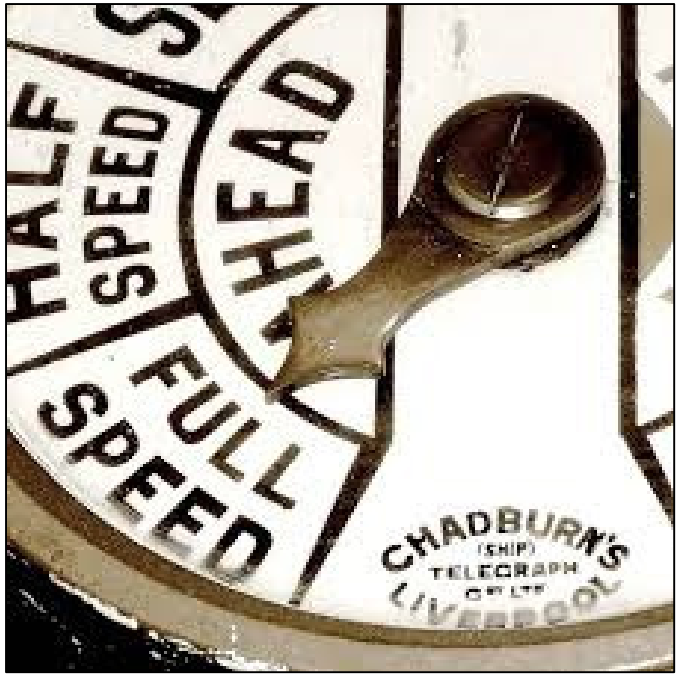
Option 1 Concentration Limit for EI (μg/g) X Actual Amount of Excipient (g) = Calculated Intake of EI (μg)

Calculated Intake of EI (μg) < Permitted Daily Exposure of EI (μg)

Outline

- **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 (μg/g) become intakes (μg/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

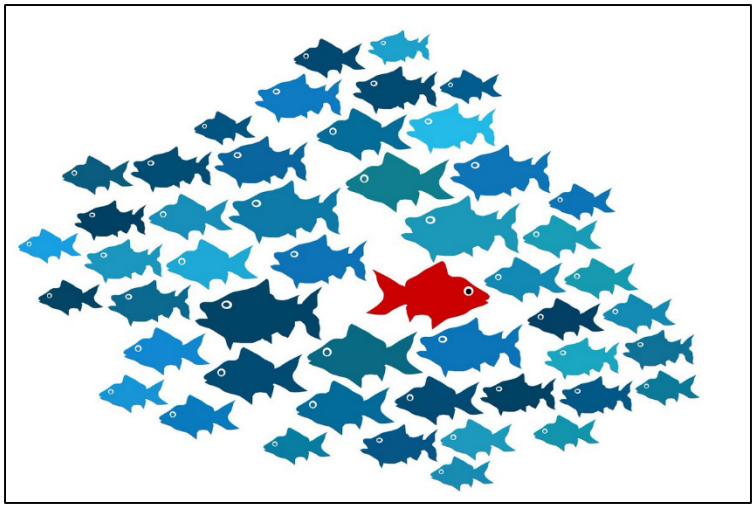
Variability includes:

- 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.

Outline

- **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