Module 0

Overview of Training Modules

ICH Q3D Elemental Impurities

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Principles for developing training materials

- Intended to provide clarity on key aspects of the guideline in order to facilitate a harmonized interpretation and implementation by industry and regulators in the ICH and non-ICH regions.
- Modular approach:
  - Overview (Module 0)
  - Modules 1-7 on key safety and quality topics
  - Module 8: Three case studies illustrating an approach to presenting the risk assessment
  - Module 9: Frequently Asked Questions
- Elaborate on key principles of the guideline
- Not intended to provide templates for addressing the Q3D recommendations.
- Training material does not provide additional guidance beyond Q3D.
Overview of the Guideline

- Main body, references and glossary (pages 1-17)
- Appendix 1: Method for Establishing Exposure Limits (pages 18-20)
- Appendix 2: Established Permitted daily exposures (PDEs) for Elemental Impurities by oral, parenteral and inhalation routes of administration (pages 21-22)
- Appendix 4: Illustrative Examples (pages 68-73)
# Table of Contents

1. Introduction
2. Scope
3. Safety Assessment of Potential Elemental Impurities
   - 3.1 Principles of the Safety Assessment
   - 3.2 Other Routes of Administration
   - 3.3 Justification for Elemental Impurity Levels Higher than an Established PDE
   - 3.4 Parenteral Products
4. Element Classification

- **Module 1**
- **Module 2**
- **Module 4: Large Volume Parenterals**
# Table of Contents

5. Risk Assessment and Control of Elemental Impurities  
6. Control of Elemental Impurities  
7. Converting between PDEs and Concentration Limits  
8. Speciation and other Considerations  
9. Analytical Procedures  
10. Lifecycle Management  

Appendix 1: Method for Establishing Exposure Limits

- Module 3: Acceptable exposures for elements without a PDE  
- Module 8: Case Studies  
- Module 9: Frequently Asked Questions
Training Modules

1. How to Apply Q3D Concepts to Routes of Administration, not addressed in Q3D
2. Justification for Elemental Impurity Levels Higher than an Established PDE
3. Application of Q3D concepts to determining safe levels of elements not included in Q3D
4. Large Volume Parenterals
5. Risk Assessment
6. Control of Elemental Impurities
7. Converting between PDEs and Concentrations
8. Case Studies
9. FAQs
Training Modules

1. How to Apply Q3D Concepts to Routes of Administration, not addressed in Q3D
2. Justification for Elemental Impurity Levels Higher than an Established PDE
3. Application of Q3D concepts to determining safe levels of elements not included in Q3D
4. Large Volume Parenterals
5. Risk Assessment
6. Control of Elemental Impurities
7. Converting between PDEs and Concentrations
8. Case Studies
9. FAQs
Q3D training module 0

Overview

Consolidated Workflow

1. Drug product assessment approach
   - Gather information on drug product and representative lots of drug product if necessary
   - Summarize available information to evaluate elemental impurity concentrations in the drug product
   - Compute percentile EI concentrations using Q3D software (compare with regulated concentrations)

2. Component assessment approach
   - Gather information on components of the drug product and representative lots of components if necessary
   - Summarize available information to evaluate elemental impurity concentrations in components of the drug product
   - Compute percentile EI concentrations using Q3D software (compare with regulated concentrations)

3. Output of the risk assessment
   - Elemental impurities excluded from the risk assessment (e.g., stable isotopes)
   - Elemental impurities that may be present below the control limit established in the drug product
   - Elemental impurities that may exceed the control limit but are below the FBE in the drug product
   - Elemental impurities that may exceed the FBE in the drug product

4. Define controls
   - Existing controls adequate
   - Define additional controls

5. Specification
   - Establish specification or appropriate component of drug product
   - Document control strategy

6. Risk Management
   - Control documented
   - Additional control should be considered across the product lifecycle
Control Strategy
Workflow

Product Risk Assessment

Drug product assessment approach
- Gather information on drug product, analyze representative lots of drug product if necessary
  - Summarize available information, tabulate elemental impurity concentrations in the drug product
    - Compute permissible EI concentrations using Options 3, compare with tabulated concentrations
  - Product independent information (e.g. equipment information, container closure information)

Component assessment approach
- Gather information on components of the drug product, analyze representative lots of components if necessary
  - Summarize available information, tabulate elemental impurity concentrations in components of the drug product
  - Compute permissible EI concentrations using Options 1, 2a or 2b, compare with tabulated concentrations

Output of the risk assessment
Control Strategy Workflow

Output of the risk assessment

- Elemental impurities excluded from the risk assessment (see Q3D: Table 5.1)
- Elemental impurities that may be present below the control threshold in the drug product
- Elemental impurities that may exceed the control threshold but are below the PDE in the drug product
- Elemental impurities that may exceed the PDE in the drug product

- Evaluate safety assessments and rationale to support levels higher than the PDE for specific elemental impurities
- Higher level justified?
  - No
  - Add upstream control and evaluate impact on EI levels
  - Yes
    - Upstream Control
    - Specification
      - Establish specification on drug product or appropriate component of drug product

- Define Additional controls

- Existing controls adequate

- Document elements of minimal concern. No further action required

Lifecycle Management
Control of elemental impurities should be considered across the product lifecycle
Q3D training module 0
Overview

Consolidated Workflow

Module 5

Module 7

Module 6

Lifecycle: Module 6
Module 9: Frequently Asked Questions

• Sources of FAQs
  o Public comments on Step 2b document
  o Constituents, referred to Q3D EWG through industry representatives
  o Other industry groups

• FAQs include
  o Common questions that could not be addressed in the Guideline
  o Questions related to how decisions were made during development of Q3D
  o Examples
    - Why are herbal products out of scope?
    - How did the EWG select the 24 elements (USP and EMA Guideline on Residual Catalysts have fewer elements in their documents).
    - Why is aluminum not included?