Practical Implementation of ICH Q3D: Guidance on Elemental Impurities

SBIA Pharmaceutical Quality Symposium

July 20-21, 2016

John F. Kauffman, Ph.D.

CDER Office of Pharmaceutical Quality

Division of Pharmaceutical Analysis

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

Key Points

- Overview of Guideline
- Q3D Implementation Working Group is Developing Training Modules
- Data-based expectation: elemental impurity levels in drug products and components relatively low in most cases
- FDA Expectations for Implementation

The ICH Q3D Expert Working Group

- Broad membership supports harmonization
  - Toxicologists and Chemists
  - FDA, EMA, MHLW
  - EFTA, WHO, Health Canada, Chinese Taipei, China, Korea
  - Pharmacopeias: USP, Ph.Eur., JP
  - PhRMA, EFPIA, JPMA
  - IPEC, WSMI, IGPA, BIO
  - At the June 2014 meeting, approximately 24 representatives participated in the deliberations.

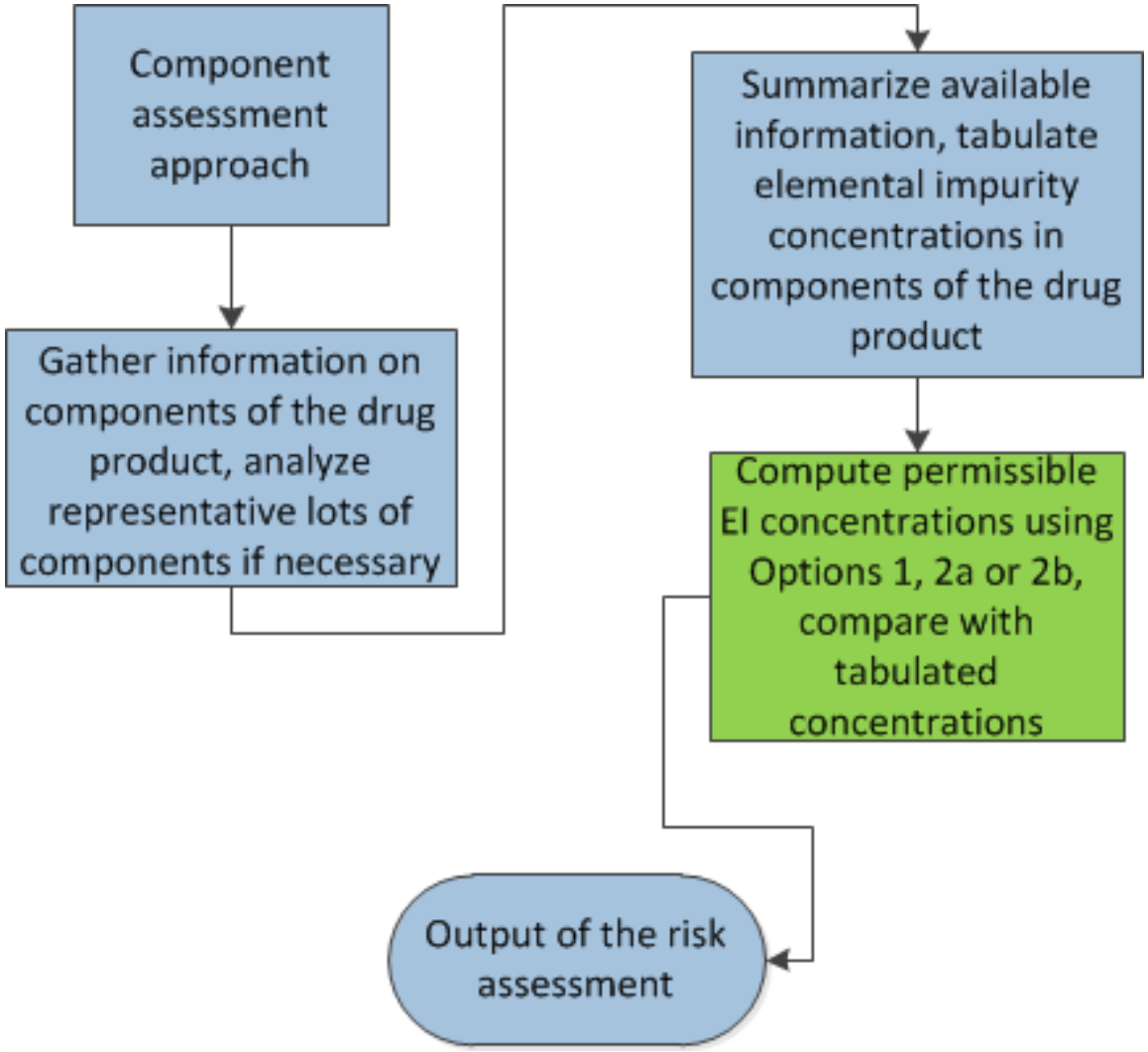
Overview of the Guideline

- 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 24 Elemental Impurities by oral, parenteral and inhalation routes of administration
- Appendix 3: Individual Safety Assessments for 24 elements (pages 23-67)
- Appendix 4: Illustrative Examples (pages 68-73)

Overview of the Guideline: Risk Assessment and Control

- Section 4: Classification of elements supports the risk assessment.
- Section 5: Assess levels of elemental impurities in a drug product in relation to the Q3D PDEs.
  - Several sources of information can support risk assessment.
  - "Control threshold" is defined as 30% of an element's PDE.
  - If an elemental impurity level is consistently below the control threshold in the drug product, existing controls are adequate.

Simplified Risk Assessment Process Flow

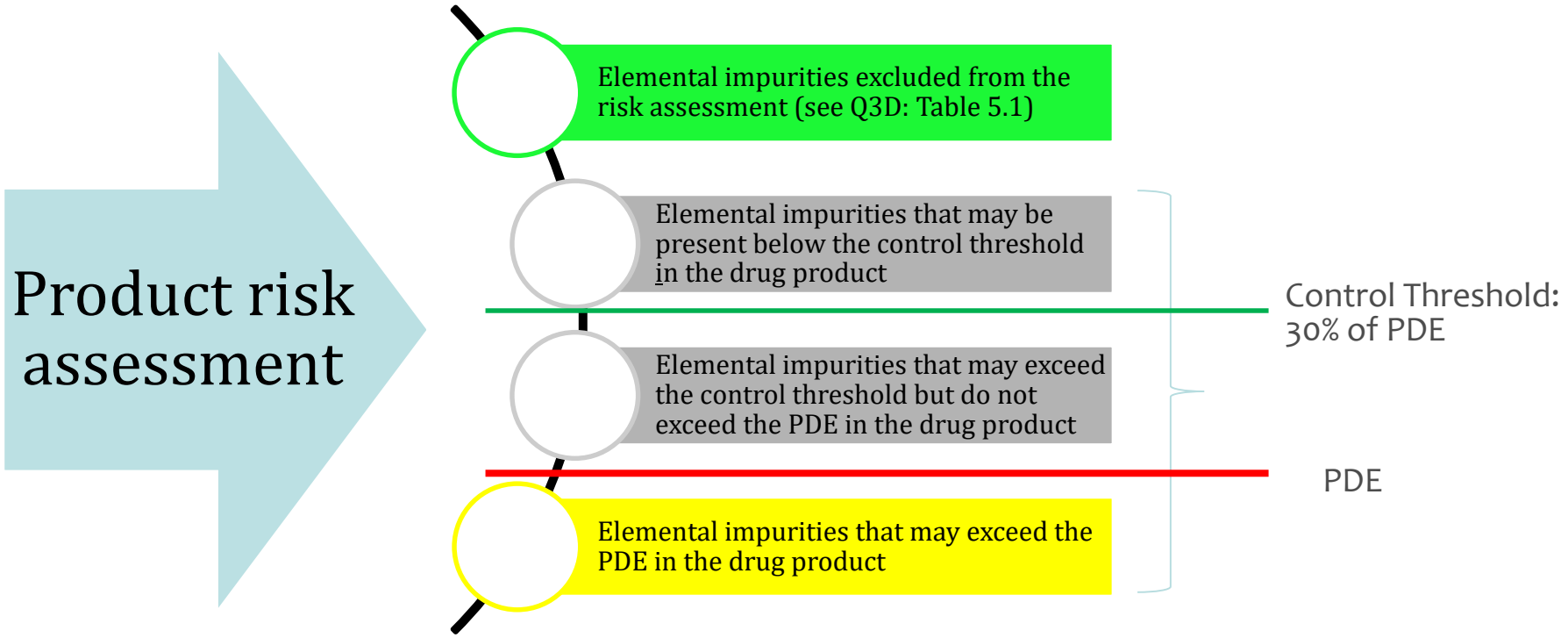


Q3D Table 5-1: Elements considered in the risk assessment

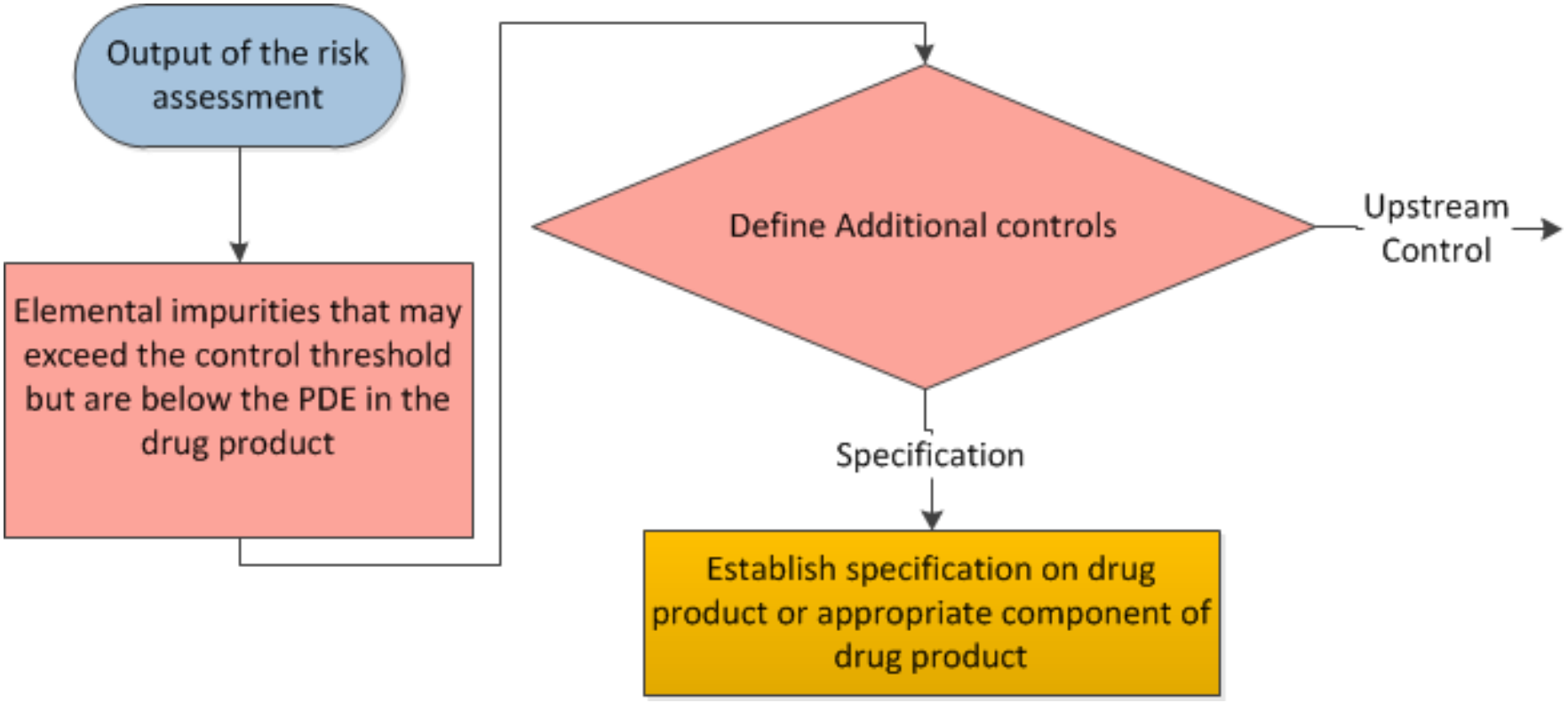
Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Reference this table in the summary of the risk assessment.

Risk Assessment Output



Simplified controls: Controls when an element is not consistently below the control threshold.



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

Toxicology

4. Large Volume Parenterals
5. Risk Assessment
6. Control of Elemental Impurities
7. Converting between PDEs and Concentrations
8. Case Studies
9. FAQs

Chemistry

Principles for Developing Q3D 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
- Does not provide additional guidance beyond Q3D
- Ten modules on key safety and quality topics
  - Modules 0-7 are available at WWW.ICH.ORG
  - Module 8&9 to appear soon
- Not intended to provide templates for addressing the Q3D recommendations.

Related Standards and Guidance

- 2008, EMA issued a Guideline on Residual Catalysts and Reagents
  - ICH Q3D replaces this guideline
- USP <232> and <233> for compendial products
  - Implementation Date: January 1 2018
  - Harmonized table of elements, classification scheme and PDEs
  - Risk-based approach to control of elemental impurities
  - Scope is nearly identical to Q3D

FDA Division of Pharmaceutical Analysis Studies of Elemental Impurities

- Lead Survey, 2007: Reg. Tox. Pharm. (2007) 48, 128
- Elemental Impurities in Drug Products Survey-2010
- Small Volume Parenterals, 2013 (With ONDP)
- Excipient Survey, 2015 (Published, OpenAccess)
  - DOI: 10.1002/jps.24650
  - Google "Journal of Pharmaceutical Sciences Elemental Impurities"
  - Complete data set available in Supplementary Material

Summary of Studies: No Surprises

- Most products have low levels of elemental impurities
- Q3D/<232> Class 2B elements are only present when intentionally added
  - Critical for Risk Assessment!
- Highly refined excipients have low levels of elemental impurities
  - Cellulose based materials
  - Lactose

Summary of Studies: No Surprises – Cont'd

- Some excipients have elevated levels of elemental impurities **relative to refined excipients**
  - E.g., mined excipients and products primarily composed of mined excipients
  - Levels may still be low compared to Table A.2.2 concentrations
  - The risk assessment reveals which materials make significant contributions
- Relatively high risk
  - high dose mass, e.g., large volume parenterals
  - intentionally added reagents and catalysts
  - unrefined naturally sourced materials

FDA Draft Guidance: Elemental Impurities in Drug Products

- **Recommendations and Timelines** for risk assessment and documentation of risk assessment
- New NDA and ANDA applications submitted after June 1, 2016 should follow the recommendations of Q3D.
  - Consistent with the EMA implementation timeline
- For existing marketed products, manufactures should follow the recommendations of Q3D and/or comply with USP <232> by January 1, 2018.
  - Consistent with USP implementation timeline for <232> and <233>.

See http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm509432.pdf , or search FDA Guidance Elemental Impurities for details.

Thank You For Your Attention!

Please evaluate this session:

surveymonkey.com/r/PQS-D2S12