SBIA-DMF Drug Substance Workshop

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Evaluation of Elemental Impurities in Drug Substances

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PURPOSE

The elemental impurities pose toxicological concerns and do not provide any therapeutic benefit to the patient. The levels of elemental impurities in drug products should be controlled within acceptable limits.

The drug substance is one of the components in a drug product, and a major source of elemental impurities. FDA requires DMF holders to provide a risk assessment of elemental impurities for the manufacturing process of a drug substance.

The purpose of this poster is to discuss the risk assessment for elemental impurities including catalysts and environmental contaminants that may present in a drug substance.

GUIDANCE

ICH guidance for industry Q3D *Elemental Impurities* contains recommendations for manufacturers of human drugs and biologics on applying a risk-based approach to control elemental impurities and Permitted Daily Exposures (PDEs).

USP introduced new limits and analytical procedures for elemental impurities in General Chapters <232> and <233>.

Element Classification in ICHQ3D: 24 Elements of ICHQ3D are classified into 3 categories based on their toxicity and 10 other elements are addressed by other guidelines.

- ***Class 1***: Human toxicants. Must be controlled in all dosage form
- ***Class 2***: Generally regarded as toxicants depending on route of administration

  Class 2A: Relatively high probability of occurrence. Must be controlled in all dosage form

  Class 2B: Reduced probability of occurrence.
- ***Class 3***: Relatively low toxicities by oral route but need to be considered if they are intentionally added.
- ***Other elements***: low inherent toxicity, or addressed by other guidelines and/or regional regulations.

Elements not covered by ICH Q3D:

- Atypical Drug substances from mined/ore sources, excipient, food additive or cosmetic ingredients registered as API, such as Lanthanum Carbonate, Potassium Chloride, etc.
- Catalysts not included in ICH Q3D

How to assess elemental impurities in a drug substance

- Elements need to be evaluated (Table 5.1 in ICH Q3D)
- PDEs per Route of Administration: Oral, Parenteral and Inhalation (Table A.2.1 in ICH Q3D)
- Converting PDEs to allowable concentration limits (Section 7)

$$Concentration\ (\mu g/g) = \frac{PDE\ (\mu g/g)}{Daily\ amount\ of\ drug\ product\ (g/day)}$$

  If the Maximum Daily Dose of a drug substance is higher than 10g/day, the firm should to use Maximum Daily Dose (MDD) instead of Option 1.

  Drug substance is one of the components of the drug product. The DMF holder should work with the ANDA applicants to determine appropriate limits for elemental impurities.
- Methods (USP<233> ICP-OES or ICP-MS). Method details, LOD/LOQ and batch data should be reported. LOQ should be less than 30% of specification limit.
- If the level of an element impurity is higher than 30% of the limit in the batch data, the element should be controlled in DS specification.

Example 1: Risk Assessment of Elemental Impurities according to ICHQ3D

Drug Product: Ampicillin for Injection
Drug Substance: Ampicillin Sodium
Maximum Daily Dosage: 12g/day of Ampicillin (12.75g/day of Ampicillin Sodium)
Route of Administration: Injection (IV, IM)
Intentionally added elements: No

Element	Class	Parenteral PDE (µg/day)	Limit (µg/g or ppm)
Cd	1	2	0.16
Pb	1	5	0.39
As	1	15	1.2
Hg	1	3	0.24
Co	2A	5	0.39
V	2A	10	0.78
Ni	2A	20	1.6
Li	3	250	19.6
Sb	3	90	7.1
Cu	3	300	23.5

WHERE TO GET MORE INFORMATION & LINKS.

Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on March 4th.

ICH Q3D Website: https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf

How to control elemental impurities not covered by ICH Q3D

- Case-by-case
- Other elements in ICHQ3D: PDEs are not established in ICH Q3D due to low risk unless specific quality considerations apply.
- Mineral-sourced drug substances: There are some elemental impurities from natural contamination and the levels may vary widely depending on the geographic location of the ore.
- PDEs should be derivatized on case-by-case basis by following the method described in ICH Q3D Appendix 1.
  - ✓ The proposed limit can be justified if the observed levels do not exceed the levels observed in the batches of Referenced Listed Drug (RLD).
  - ✓ The proposed limit can also be qualified with scientific literature or toxicity studies. Please provide the reports for Pharm/Tox assessment by the agency.

Example 2: Drug Substance with Elemental Impurities Outside ICH Q3D

Drug Product: Lanthanum Carbonate Chewable tablet
Drug Substance: Lanthanum Carbonate

Maximum Daily Dosage: 3g of element lanthanum/day, ~6g of Lanthanum Carbonate Pentahydrate

- Elemental impurities should be treated like “related substances” and routinely controlled in drug substance specification.
- Control strategies:
  - a) 24 Elements described in ICHQ3D
  - b) Lanthanum belongs to the rare earth elements. Due to the similarity in ionic radius between adjacent lanthanide elements, it is difficult to separate them from each other in naturally occurring ores and other mixtures. These lanthanides should be controlled.
  - c) All possible elements should be controlled at starting material or drug substance specifications. The proposed limits should not exceed the level observed in RLD. Or justified with scientific literatures or toxicity studies.
  - d) The omission of an element can be justified by test results. The method details and validation should be provided. Method should be sensitive. The LOQ should be less than 30% of proposed limit.
  - e) Control of starting material - Lanthanum Oxide. The geographic location of the ore should be provided. If the starting material source/ore location changes, all possible impurities in the starting material batches should be tested.

CONCLUSION(S)

This poster talks about the risk assessment for elemental impurities covered by ICH Q3D, and other elemental impurities outside ICH Q3D in every primary DMF. It also provides the recommended methods for risk assessment and control strategies for elemental impurities in a drug substance.

U.S. FOOD & DRUG ADMINISTRATION

Evaluation of Elemental Impurities in Drug Substances

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Purpose

- Elemental impurities pose toxicological concerns.
- The drug substance is one of the components in a drug product, and a major source of elemental impurities.
- How to perform the risk assessment of elemental impurities.

Guidance

ICH Guidance for Industry Q3D

"Guideline for Elemental Impurities"

***USP* General Chapters**

<232> Elemental Impurities - Limits

<233> Elemental Impurities - Procedures

Element Classification in ICH Q3D

Class	Element	Comment
Class 1	As, Cd, Hg and Pb	Human toxicants. Must controlled in all dosage forms of a DP.
Class 2		Elements are generally regarded as toxicants depending on route of administration.
Class 2A	Co, Ni and V	Relatively high probability. Must controlled in all DP dosage forms.
Class 2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl	Reduced probability of occurrence in the DP
Class 3	Ba, Cr, Cu, Li, Mo, Sb and Sn	Relatively low toxicities for the oral route of administration.

How to Assess Elemental Impurities in a Drug Substance

- Elements need to be evaluated (*Table 5.1* in ICH Q3D)
- PDEs per Route of Administration (*Table A.2.1* in ICH Q3D)
- Converting PDEs to allowable concentration limits (Section 7 of ICH Q3D)

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ amount\ of\ drug\ product(g / day)}$$

Option 1, 10g/day

MDD of DS (MDD>10g/day)

Analytical Methods

- Methods (USP<233> ICP-OES or ICP-MS)
- Method details, LOD/LOQ and batch data should be reported.

LOQ ≤ 30% of Limit

- When should an elemental impurity be controlled in DS specification?

Level ≥ 30% of Limit

Example 1 Risk Assessment of Elemental Impurities According to ICHQ3D

- ***Drug Product***: Ampicillin for Injection
- ***Drug Substance***: Ampicillin Sodium
- ***Maximum Daily Dose***:

  12g/day of Ampicillin

  12.75g/day of Ampicillin Sodium
- ***Route of Administration***: Injection (IV, IM)
- ***Intentionally added elements***: No

Example 1: Con't

Element	Class	Parenteral PDE (µg/day)	Limit (µg/day or ppm)
Cd	1	2	0.16
Pb	1	5	0.39
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Co	2A	5	0.39
V	2A	10	0.78
Ni	2A	20	1.6
Li	3	250	19.6
Sb	3	90	7.1
Cu	3	300	23.5

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{MDD\ 12.75\ g/day}$$

Elements not Covered by ICH Q3D

- Other elemental impurities mentioned in ICH Q3D (Al, B, Ca, F, K, Mg, Mn, Na, W, Zn)
- Atypical drug substances
- Catalysts not included in ICH Q3D

How to Control Elemental Impurities Not Covered by ICH Q3D

- Case-by-case basis
- General principles in Q3D apply
- PDEs should be derived using the method in ICH Q3D Appendix 1
- Justification of limits
  a) Justify by testing RLD batches.
  b) Justify by comprehensive summary of scientific literature or Pharm/Tox studies.

Example 2, Elemental impurities not Covered by ICH Q3D

Drug Product: Lanthanum Carbonate Chewable tablet

Drug Substance: Lanthanum Carbonate

Maximum Daily Dose: 3g/day as element lanthanum, ~6g/day of Lanthanum Carbonate Pentahydrate

Elemental impurities should be treated like "related substances" and routinely controlled in drug substance specification.

Example 2, Elemental impurities not Covered by ICH Q3D

- 24 Elements in ICH Q3D
- Lanthanides
- All possible elements
- Justification of the omission of an element
- Control of the starting material

Conclusions

- The risk assessment for elemental impurities covered by ICH Q3D and other elemental impurities outside ICH Q3D in every primary DMF.

- The control strategies for elemental impurities in a drug substance.

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on *March 4th*

- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.