Drug Development & Delivery

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Elemental Impurities: Implications for Manufacturers of Drug Products, APIs & Excipients

By: Ulrich Reichert, PhD, Head of Pharma & Food Materials, Regulatory Management, Merck KGaA, Darmstadt, Germany

Introduction

The International Conference on Harmonization (ICH) finalized the ICH Q3D Guideline for elemental impurities in December 2014.[1] Regulators are now implementing the requirements worldwide, with some start dates already in place as of June 2016.

ICH Q3D is the most comprehensive guideline for limits and risk assessment approaches for elemental impurities in final drug products to date; however, it does not specify limit for the major components of drug products. This brings excipients in particular under scrutiny, being they, unlike APIs, lack established daily doses.[2] Given this, how can drug product manufacturers assess risk of elemental impurity to comply with ICH Q3D?

Classes of Elements

ICH Q3D classifies 24 elements based on toxicity and likelihood of occurrence in final drug products. Figure 1 summarizes the elements included in each class, noting when risk assessment is required.

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
Ag	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

Figure 1. Elements to be considered in risk assessments[1]

Risk Assessments

Risk assessments should consider all potential sources of elemental impurities, including water, starting materials, manufacturing equipment, process materials, and packaging materials (Figure 2).

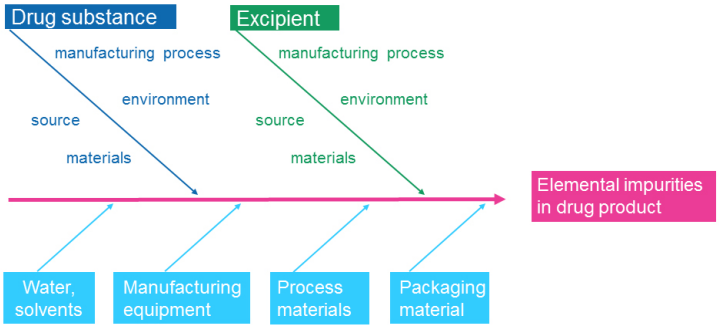

Figure 2. Drug manufacturer's perspective of possible sources of elemental impurities

Drug Product Assessment & Component Assessment Approach

ICH Q3D recommends two established approaches for impurity assessment:

The *drug product assessment approach* is to analyze the final product and provide a mandatory risk management strategy. Data alone is not considered sufficient.

The *component assessment approach* assesses individual components, then compares the combined elemental level with the PDE. A control strategy is established if necessary. This approach benefits from supplier information regarding specific components. Figure 3 compares the approaches.

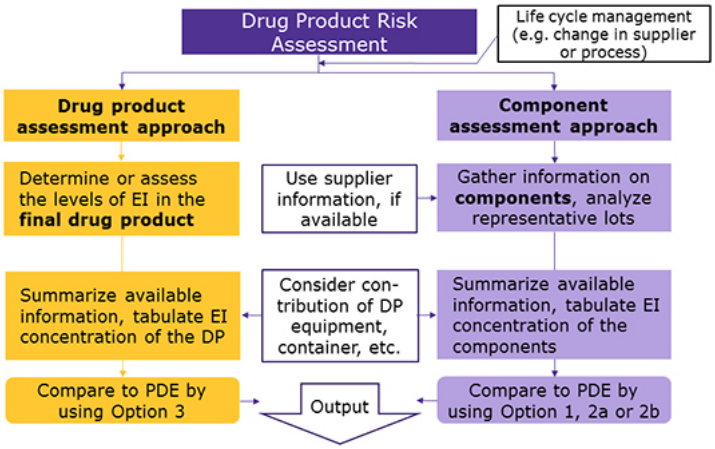

Figure 3. Product and component assessment approach[3]

Control Strategy

ICH Q3D provides PDE limits in µg/day for elemental impurities. However, concentration limits in µg/g are more useful for evaluating sample impurity content.

Chapter 7 of ICH Q3D offers Options for translating:

-Option 1 assumes daily intake of the drug product is 10 g or less
-Option 2A uses an actual maximum daily intake (versus assuming 10 g)
-Option 2B sums known component impurity levels
-Option 3 measures the concentration of elements in the final drug product

Drug Products

Of the 24 elements considered, a number will not likely be present and need only be documented as such. Other elements, such as those in Class 1 and Class 2A, must be in all risk assessments.

The control threshold helps determine which elements are at risk of exceeding the PDE. For elements consistently below the control threshold – 30% of the PDE – existing controls are considered adequate. Elements that surpass the control threshold need to be controlled, whether by upstream controls or by source purification. A rationale for higher levels of exposure (eg, short-term usage, a life-threatening disease) may justify surpassing the threshold.

Excipients

Because excipients do not have a daily dose, there is no established concentration limit in line with ICH Q3D to which excipient manufacturers can refer. Acceptable limits for these components are therefore left to drug product manufacturers and their suppliers. To support negotiations, Option 1 (10 g daily dosage) is a useful default concentration limit. Figure 4 illustrates this approach.

- Latitude Pharmaceuticals, Inc.
- LifeSciencePR
- Lyophilization Technology, Inc.
- Metrics Contract Services
- Minnesota Rubber & Plastics
- Multisorb Technologies
- Nemera
- Noble
- Patheon
- Pfanstiehl, Inc.
- PharmaCircle
- Pion, Inc.
- Polymer Conversions, Inc.
- PYRAMID Laboratories
- REVOX Sterilization Solutions
- SHL
- Terumo
- UPM Pharmaceuticals, Inc.
- Vetter Pharma International
- West Pharmaceutical Services

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INTERPHEX
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New York, NY

PDA Annual Meeting
April 3-5
Anaheim, CA

RDD (Respiratory Drug Delivery)
April 25-28
Nice, France

AAPS National Biotechnology Meeting
May 1-3
San Diego, CA

Innovation Networking Summit & Table-top Exhibition
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CPhI North America & Informex
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BIO 2017
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San Diego, CA

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Universe of Prefilled Syringes & Injection Devices Europe
November 7-8
Nienna, Austria

AAPS
November 12-17
San Diego, CA

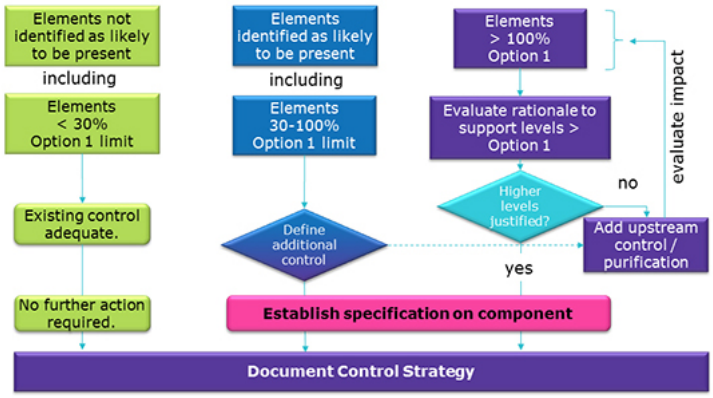

Figure 4. Control strategy for components, based on the Option 1 limit as the default[4]

Elements Intentionally Added

Intentionally added metals or elements should be considered in every risk assessment. This requires information about which elements have been added, relevant production steps, and the purge potential of subsequent steps.

Elements Not Intentionally Added

Figure 5 illustrates an approach to evaluating the results of a multi-element analysis of a pharmaceutical substance. The y-axis depicts the concentration of the individual elements, the guideline limit, and the respective control threshold. The guideline limit is dependent on route of synthesis and the maximum daily dose of the drug product.

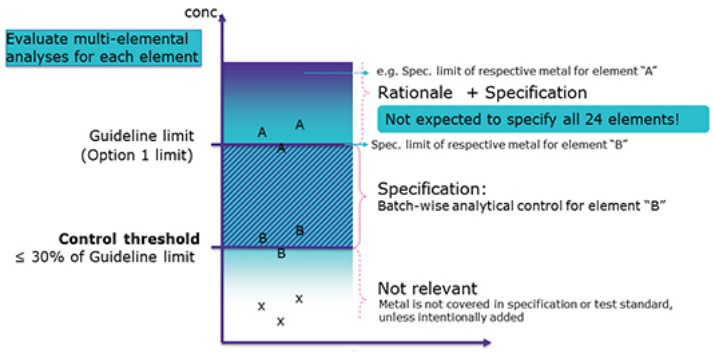

Figure 5. Control strategy for elements not intentionally added[4]

If metal X is consistently below the control threshold, the metal can be excluded from the specification, unless other risk factors require its control. If metal B is higher than the control threshold, but below the guideline limit, the element should be subject to analytical control and covered in the specification. A pharmaceutical substance with element results higher than the Option 1 limit may be used in final drug products, but a rationale is appropriate.

Conclusion

The component assessment approach allows drug product manufacturers to assess elemental impurity risk in compliance with ICH Q3D. For standardizing impurity limits across components, manufacturers and excipient suppliers may find the Option 1 limit useful as the default concentration limit. This approach permits manufacturers and suppliers to obtain crucial impurity information for components with indeterminate impurity limits, particularly excipients.

References

1. ICH. 2014. ICH Harmonized Guideline Q3D, Guideline for Elemental Impurities, Step 4.
2. Teasdale A, et al. Implementation of ICH Q3D elemental impurities guideline: challenges and opportunities. Pharm Tech. 2015;39(3):36-49.
3. ICH. 2016. ICH Q3D Training Package Module 5.
4. Reichert U. Elemental impurities: ICH Q3D finalized. Pharm Ind. 2016;78(5):670-676.

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