Impact of New ICH Q3D and USP <232> Guidelines for Elemental Impurities Analyses

Content

Background

It is recommended in current ICH Q3D and USP <232> guidelines to include the container closure system used for storage of a drug product in the risk assessment concerning elemental impurities [1], [2].
SCHOTT pharma services has unique expertise in the characterization of container closure systems and of drug container interaction for the pharmaceutical industry.

Why should the amounts of elemental impurities be controlled in drug products?

For protection of public health for all patient populations by establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern: "Because elemental impurities do not provide any therapeutic benefit to the patient, their levels to the drug product in the drug product should be controlled" [1].

Regulatory requirements

Expanded testing of heavy metals in primary pharmaceutical packaging has already become mandatory [1], [2]:
"This Guideline (ICH Q3D) has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Switzerland, Japan, USA and Canada." [1].

- EMA deadlines for elemental impurities ICH Q3D: June 2016 for new drugs and December 2017 as transition for marketed drugs
- USP deadline for elemental impurities:
  "As of January 1, 2018: "All new and existing NDAs and ANDAs for drug products with an official USP monograph are required to meet the requirements in USP General Chapters <232> and <233> for the control of elemental impurities." [6]

Key points of ICH Q3D

Structure of ICH Q3D

The ICH Q3D guideline is split into 3 parts [1]:

1) Evaluation of toxicity data for potential elemental impurities
2) Establishment of a Permitted Daily Exposure[1] (PDE) for each element of toxicological concern: PDEs were established for different routes of administrations: oral, parenteral and inhalation.
3) Application of a risk based approach to control elemental impurities in drug products

[1] *Note: "In some cases lower levels of elemental impurities may be warranted e.g. due to other requirements from pharmaceutical quality perspective" [1]*

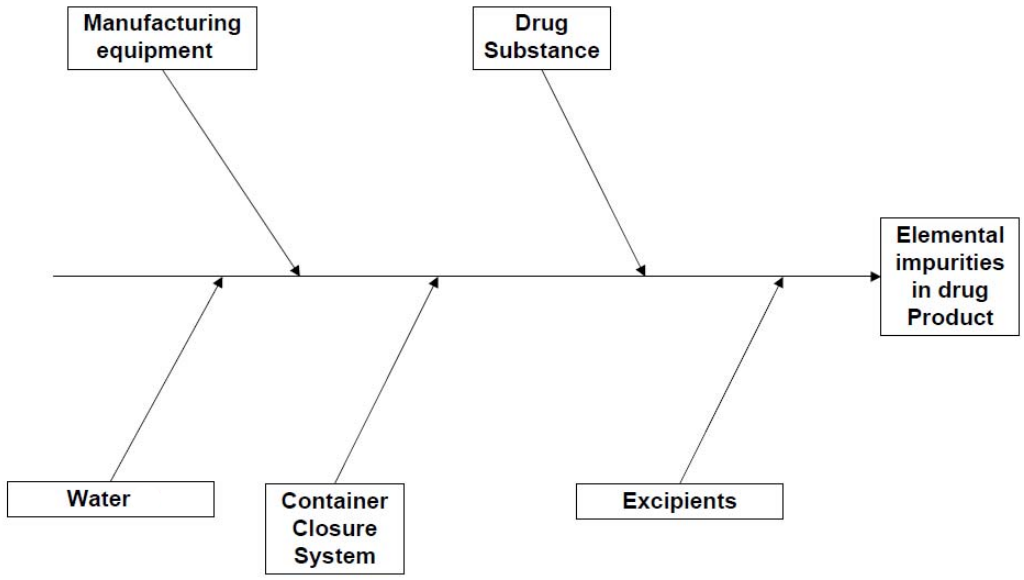
Scope

"The ICH Q3D guideline applies to drug products as new finished drug products and new drug products containing existing drug substances, e.g. drug products containing purified proteins and polypeptides [1].

Sources for elemental impurities

Several sources for elemental impurities in drug products are known as shown in Fig. 1. One source of elemental impurities is residual catalysts that were added intentionally in synthesis or leached into the drug solution due to interaction with drug contact materials like the container closure system or processing equipment or impurities being present in ingredients of the drug product [1].

Fig.1: Diagram with example of typical sources for elemental impurities (diagram from ICH Q3D [1])



Elemental classification

24 elements of ICH Q3D have been assigned into 3 different classes based on their toxicity and likelihood of occurrence in the drug products and 10 other elements are addressed by other guidelines or due to quality considerations as described in Table 1.

Class 1: The "class 1A" elements As, Cd, Hg and Pb are human toxicants present in drug products as impurities from commonly used materials. Their use in pharmaceutical manufacturing is limited. A risk assessment is required for all potential sources and for all routes of administration due to the unique nature of these elements.

Class 2: "Class 2" elements are generally regarded as toxicants depending on the route of administration.

Class 2A: The "class 2A" elements Co, Ni and V have a relatively high probability of occurrence in the drug product. A risk assessment is required for all potential sources and for all routes of administration.

Class 2B: The "class 2B" elements Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl have a reduced probability of occurrence in the drug product because they are rare and their potential for co-isolation with other materials is low. If "Class 2B" elements are not intentionally added during the manufacturing of drug substances, excipients or other components of the drug product, they might be excluded from a risk assessment.

Class 3: The "class 3" elements Ba, Cr, Cu, Li, Mo, Sb, and Sn are assessed with relatively low toxicities for the oral administration route, but need to be considered, if they are intentionally added. For inhalation and parenteral routes they should also be taken into account within a risk assessment, unless the route specific Permitted Daily Exposure (PDE) is above 500 µg/day, or if they are intentionally added.

Other elements: The "other" elements Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn are not addressed in the ICH Q3D guideline because PDEs have not been established due to their low inherent toxicity and / or differences in regional regulations. Some of these elements are addressed by other or regional guidelines or due to quality requirements for the final drug product (e.g. W impurities in therapeutic protein solutions or Al for patients with compromised renal and Mn, Zn with compromised hepatic function).

Table 1: Elemental impurities with classification from ICH Q3D_*STEP4* and USP <232> (see [1], [2] for details)

	Elements Tested	Required to be included in Risk Assessment
Class 1	Cd, Pb, As, Hg	Yes
Class 2A	Co, V, Ni	Yes
Class 2B	Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt	Yes, if added intentionally
Class 3	Li, Sb, Ba, Mo, Cu, Sn, Cr	Yes, if parenteral administration (Li, Sb, Cu) Yes, if inhalation or if added intentionally
Other elements	Al, B, Ca, Fe, K, Mg, Mn, Na, W, Zn	Not addressed in ICH Q3D, but in other regional guidelines and due to quality considerations (e.g. W impurities in therapeutic proteins)
Additional	Si	Not addressed in ICH Q3D, but recommended by SCHOTT pharma services for glass containers

Additional: The "additional" element Si is recommended by SCHOTT pharma services to be analyzed for drug products stored in glass containers and for testing purposes of primary glass packaging, respectively. This allows an assessment of the overall corrosive attack of the glass container in contact with the drug product, particularly useful within storage stability studies concerning glass delamination [4], [5].

Key points of USP <232> and <233>

General chapter USP <232>

The general chapter of USP <232> specifies limits for the amounts of elemental impurities in drug products. As elemental impurities catalysts and environmental contaminants can occur in drug substances, excipients, or drug products. The elements As, Cd, Pb, and Hg must be included in the risk evaluation due to their omnipresent nature.

Elements

For 24 elements specific Permitted Daily Exposure (PDE) limitation values are given in USP <232> and ICH Q3D for different routes for administration [2], [1].

Demonstration of Compliance

Minimum requirements for analytical testing: "When testing is done to demonstrate compliance, proceed as directed in *Elemental Impurities-Procedures* <233> and minimally include arsenic, cadmium, lead, and mercury in the *Target Elements* evaluation" [2], [3].

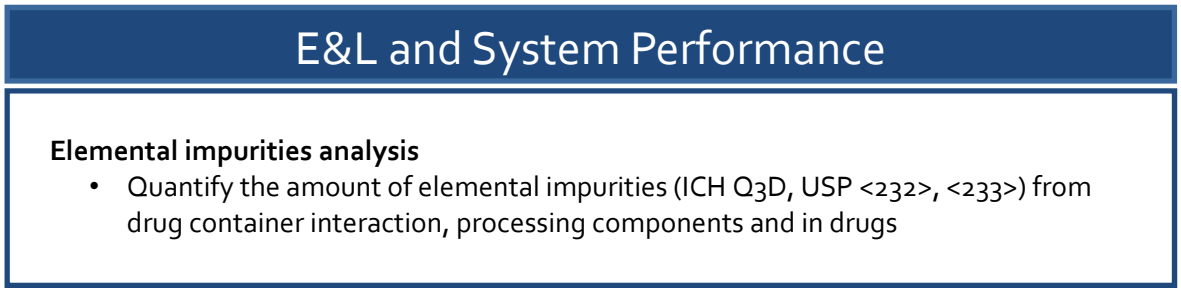
Procedures in USP <233>

The chapter of USP <233> describes analytical procedures for evaluation of the levels of elemental impurities [3]. For "procedure 2" Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is recommended as suitable method for quantification of the amounts of elemental impurities.

Offering SCHOTT pharma services for Elemental Impurities

SCHOTT pharma services has implemented appropriate methods for the determination of elemental impurities with elemental detection at lowest concentrations in the low µg/L range based on High Resolution Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS). This method is especially applied for screening of extractable elemental impurities from the container closure system as well as for determination of leachable elemental impurities that have migrated into the drug solution. SCHOTT pharma services is very experienced in adapting the HR-ICP-MS method for different drug products. A typical study requires 50-100 mL of blank drug solution and 20 – 50 mL of solution stored in the final container form. The quantification of elemental impurities in drug products can be offered to be conducted with validated methods. For assessment of the drug product ↔ container and drug product ↔ preparation materials interactions methods for determination of extractable and leachable elemental impurities are offered as described in Fig. 2:

Fig. 2: SCHOTT pharma services offering for assessment of elemental impurities from drug product ↔ container and drug product ↔ processing materials interactions



About SCHOTT pharma services

SCHOTT pharma services are an established solution provider for pharmaceutical industry supporting more than 100 customers worldwide from laboratories in Europe and USA. The laboratories are accredited according to DIN EN ISO 17025. A high level of quality management is verified through regular reviews by quality auditors.

SCHOTT has more than 35 years experience with the testing of pharmaceutical glass and polymer packaging. Tests are conducted for all kind of primary contact materials (containers, filters, tubing) and closure systems (elastomers) according to current EP, USP and JP regulatory guidelines and ICH recommendations (e.g. USP <1660>, <1663>, <1664>, <232>, EP 3.2., ICH Q3D, JP 7.01).

SCHOTT is one of the world's leading suppliers of parenteral packaging for the pharmaceutical industry with three product groups: pharmaceutical tubing, pharmaceutical packaging, and contract analytical testing. It is widely recognized as a pioneer and a proven expert in glass and materials technology with more than 130 years of experience. The company operates Europe's most advanced research center for special glass, the Otto Schott Research Center in Mainz, Germany and its US branch in Duryea, PA. SCHOTT employs more than 600 individuals in the field of application-oriented research. The unique combination of specialized analytics and our expertise in materials, products, and processes enables SCHOTT pharma services to support pharmaceutical companies by finding solutions to the most challenging packaging requirements.

References

[1] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, ICH harmonized guideline, guideline for elemental impurities Q3D, Current *Step 4* version, dated 16 December 2014

[2] U.S. Pharmacopeial Convention (USP), USP 41 Chemical Tests / <232> Elemental Impurities – Limits

[3] U.S. Pharmacopeial Convention (USP), USP 41 Chemical Tests / <233> Elemental Impurities – Procedures

[4] SCHOTT pharma services, Haines, D; Scheumann, V; Rothhaar, U; Glass Flakes, "Pre-Testing stops a big problem before it even starts", Contract Pharma, June 2013, 92-97

[5] U.S. Pharmacopeial Convention (USP), USP <1660> Durability of Glass Containers, "Evaluation of the Inner Surface Durability of Glass Containers"

[6] www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm590075.htm *accessed 07 March 2018*

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