PHARMA & BIOPHARMA

Elemental Impurities

Certified Reference Materials for ICH Q3D, USP<232> & <2232> and Ph.Eur. 5.20

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Metallic contamination in drug products, referred to as elemental impurities, may arise from several sources. They may be added intentionally in synthesis, or may be present as contaminants, (e.g., through interactions with processing equipment or by being present in components of the drug product) and are consequently detectable in the drug product. Since elemental impurities pose a risk to patient health due to toxicological effects, element impurity levels should be controlled within acceptable limits in the drug product.[1]

Evolution of ICH Q3D guidelines

In 2009 the International Conference on Harmonization (ICH) proposed the development of a new harmonized guideline to provide a global policy for limiting metal impurities in drug products and ingredients. This approach should provide clear regulatory guidance on specification limits for elemental impurities worldwide and logically should have an impact on the work of the national regulatory bodies in having transparent and comparable results.

In a step 4 version of its "Guidelines for Element Impurities" document, the ICH categorized the various elemental impurities in four different classifications which were intended to facilitate decisions during the risk assessment process:

Class 1: impurities are significantly toxic to humans and have limited or no use in the manufacture of pharmaceuticals. They can be found as impurities from commonly used materials (e.g., mined excipients). All four elements require evaluation during the risk assessment across all potential sources of elemental impurities and routes of administration.

The class 1 elements are: As, Cd, Hg, Pb.

Class 2: impurities are generally considered route-dependent human toxicants. These impurities are further divided into two sub-classes, 2A and 2B, based on their relative likelihood of occurrence in the drug product.

- Class 2A elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources of elemental impurities and routes of administration (as indicated). The class 2A elements are: Co, Ni and V.
- Class 2B elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials. As a result, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product.

Class 2B elements are: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Class 3: includes elements which have relatively low toxicity at oral administration but may require a risk assessment if applied via inhalation or parenteral routes.

Class 3 elements are: Ba, Cr, Cu, Li, Mo, Sb and Sn.

Other elements: There are some elemental impurities for which Permitted Daily Exposures (PDEs) have not been established due to their low toxicities and/or differences in regional regulations. If they are present in a drug product, they are addressed by other guidelines and/or regional regulations.

These elements are: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

Evaluation of USP and EP

Up to 2010, the USP and EP proof of heavy metal contamination in drugs was obtained via a colorimetric analytical method based on the precipitation of a metal sulfide in a sample and comparing it to a lead standard (USP <231> and Ph.Eur. 2.4.8).

Based on the Guideline for Elemental Impurities (Q3D) which was published by the International Conference on Harmonization (ICH) in 2010, the USP proposed three new General Chapters covering impurity limits, analytical procedures in pharmaceutical products and raw materials, and elemental contaminants in dietary supplements.

- Chapter USP <232>, Ph.Eur. 5.20: Elemental Impurities in Pharmaceutical Products - Limits
- Chapter USP <233>: Elemental Impurities in Pharmaceutical Products – Procedures
- Chapter USP<2232>: Elemental Contaminants in Dietary Supplements

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In January 2015, the USP established January 1, 2018 as the new date of applicability for General Chapters <232>, <233> and <2232>. The implementation should align with limits and timelines set down by other pharmaceutical and medical agencies such as the ICH Q3D Step 4 Guidelines for Elemental Impurities announced on December 16, 2014.

The Pharmacopoeia Europe announced in July 2014 their strategy regarding elemental impurities and the implementation of the ICH Q3D. Nearly one year later, in April 2015, they published their policy on elemental impurities and timelines for revision of general and individual texts. In August of the same year, clarification was given for products outside the scope of ICH Q3D.

The implementation of the guideline compliances should start in June 2016 for products with new marketing authorization, either containing new active substances or already approved substances.

Marketed products, including new mutual recognition applications of already approved substances, should comply with the Guideline from December 2017.

The implementation of the General Test 5.20 and the General Method 2.4.20 replaced the EMA guideline on metal catalysts and metal reagents by the principles of the ICH. The publication was done in the Ph.Eur. Suppl. 9.3 (implementation date January 1, 2018), having no test for elemental impurities in the individual monographs except for substances of natural origin. Given the intrinsic nature of elemental impurities in these substances, they are among the major potential sources of elemental contamination in medicinal products. The Ph.Eur. Commission has also specifically recommended keeping the different tests for elements for which no PDE limits have been established, i.e., those identified as “other elements” in the ICH Q3D guideline in individual monographs.[2]

Analytical methods

Concerning new analytical methods, ICH Q3D does not include any recommendation on instrumental methods but the following analytical procedures are suggested in USP<233> dependent on the expected concentration of the elemental impurity in the product or component:

- Parts-per-million (ppm) concentrations
  ICP-OES or atomic absorption
- Parts-per-billion (ppb) concentrations
  ICP-MS

ICH Q3D limits for elemental impurities

For a total of 24 elements, toxicity limits are specified and defined as maximum PDE levels in mg/day for the four major drug delivery categories. **Table 1** lists the PDE values in µg/day, valid for drug products with an intake of ≤10 g/day.

Table 1. Permitted daily exposure (PDE) for elemental impurities

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
As	1	15	15	2
Cd	1	5	2	2
Hg	1	30	3	1
Pb	1	5	5	5
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rb	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Table 2 lists the elements to be considered in the risk assessment.

For the new adapted USP <232> and Ph.Eur.Suppl. 9.3 chapters, we offer three *Trace*CERT® element mixes with element ratio corresponding to the oral concentrations of the ICH Q3D guideline, mix I covers class 1, 2A and some of 2B elements; mix II covers the remaining 2B class elements; mix III covers all class 3 elements.

A second series of three mixes covers the parenteral concentration ratios.

All products with their element respective concentrations (mg/L) are listed in **Table 3**.

Table 4 lists the features of the *Trace*CERT® Certified Reference Material (CRM) solutions.

Table 2. Elements to be considered in the risk assessment

Element	Class	If Intentionally Added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
As	1	Yes	Yes	Yes	Yes
Cd	1	Yes	Yes	Yes	Yes
Hg	1	Yes	Yes	Yes	Yes
Pb	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
Rb	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	No	No
Sb	3	Yes	No	No	No
Ba	3	Yes	No	No	No
Mo	3	Yes	No	No	No
Cu	3	Yes	No	No	No
Sn	3	Yes	No	No	No
Cr	3	Yes	No	No	No

Table 4. Features of the TraceCERT® CRMs

*Trace*CERT® Solutions
Unique level of accuracy and lot-specific value
Produced according to ISO Guide 34 and analyzed in our ISO/IEC 17025 accredited lab; traceable to at least two independent references (NIST, BAM or SI unit kg)
Sophisticated packaging and comprehensive documentation including proper uncertainty calculation, expiry date and storage information
Packaged in opaque and gas-tight aluminum foil bags for extended stability. Certificates are included and list up to 70 trace impurities for the *Trace*CERT® products.
250 mL package size*

For more information and to view sample certificates, please visit
SigmaAldrich.com/inorganiccrm

References:

1. ICH Q3D limits from Step 4 version, December 16, 2014 Option 1
2. Thermo Fischer, the Medicine Maker, Edition 4 – August 2016100

Table 3. Suitable Multi-Element CRM Solutions according to ICH Q3D

Element	Class	*Trace*CERT® Elemental Impurities Mix according to ICH Q3D oral			*Trace*CERT® Elemental Impurities Mix according to ICH Q3D parenteral		
		Standard 1	Standard 2	Standard 3	Standard 1	Standard 2	Standard 3
		Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.
		19041	73108	69729	89118	89922	07368
		In 12% HNO_3	In 10% HCl	In 5% HNO_3 & HF<0.5%	In 12% HNO_3	In 10% HCl	In 5% HNO_3 & <0.5% HF
Ag	2B	150 mg/L			10 mg/L		
As	1	15 mg/L			15 mg/L		
Au	2B		100 mg/L			100 mg/L	
Ba	3			140 mg/L			70 mg/L
Cd	1	5 mg/L			2 mg/L		
Co	2A	50 mg/L			5 mg/L		
Cr	3			1100 mg/L			110 mg/L
Cu	3			300 mg/L			30 mg/L
Hg	1	30 mg/L			3 mg/L		
Ir	2B		100 mg/L			10 mg/L	
Li	3			55 mg/L			25 mg/L
Mo	3			300 mg/L			150 mg/L
Ni	2A	200 mg/L			20 mg/L		
Os	2B		100 mg/L			10 mg/L	
Pb	1	5 mg/L			5 mg/L		
Pd	2B		100 mg/L			10 mg/L	
Pt	2B		100 mg/L			10 mg/L	
Rh	2B		100 mg/L			10 mg/L	
Ru	2B		100 mg/L			10 mg/L	

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