Elemental Impurities - Certified Reference Materials for ICH Q3D, USP <232> and Ph.Eur. 5.20

Ingrid Hayenga, Product Manager Reference Materials, Merck

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ABOUT ELEMENTAL IMPURITIES

Metallic contamination in drug products, referred to as elemental impurities, may arise from several sources. The main source of contamination are equipment and utensils used in processing, holding, transferring and packaging, A second source can be residual metals used as process catalysts. Since elemental impurities pose a risk to patient health due to toxicological effects, element impurity levels should be controlled within acceptable limits in a drug product.[1]

POTENTIAL SOURCES OF ELEMENTAL IMPURITIES

- **Air and Water Media**

- **Manufacturing Equipment**

- **Container Closure and Packaging System**

- **Drug Compounds**

Excipients in Pharmaceutical Product

Elemental Impurities in Drug Products

EVOLUTION OF ICH Q3D GUIDELINES FOR ELEMENTAL IMPURITIES

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 2014 the first version of the ICH Q3D guideline for elemental impurities was published, categorizing the various elemental impurities in four different classes which were intended to facilitate decision during the risk assessment process. In 2019, a revision was done on the Cadmium Inhalation PDE (permitted daily exposure), published as ICH Q3D(R1) guideline. The current Q3D(R2) guideline has been published in April 2022 (step 4) and is now in the implementation status (step 5). It includes a correction of PDEs for Gold, Silver and Nickel; Gold and Silver monographs; and an addition of limits for elemental impurities by the cutaneous and transcutaneous route.

Class 1 Impurities

These 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

These impurities are generally considered routedependent 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 Impurities

These elements 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 per 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

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.

In January 2023 revision was closed regarding the revised ICH Q3D(R2) guideline with the new PDEs for Gold, Silver and Nickel as well as the additional limits for cutaneous and transcutaneous products. They will be incorporated in the USP-NF/PF general chapters on May 1st, 2024.

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.

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)	Cutaneous PDE (µg/day)	Cutaneous CTCL (µg/g) for sensitizers
As	1	15	15	2	30	
Cd	1	5	2	3	20	
Hg	1	30	3	1	30	
Pb	1	5	2	5	50	
Co	2A	50	5	3	50	35**
Ni	2A	200	20	6	200	35**
V	2A	100	10	1	100	
Tl	2B	8	8	8	7	

Au	2B	300 *(100)*	300 *(100)*	3	3000
Pd*	2B	100	10	1	100
Ir	2B	100	10	1	100
Os	2B	100	10	1	100
Rh	2B	100	10	1	100
Ru	2B	100	10	1	100
Se	2B	150	80	130	800
Ag	2B	150	15 *(10)*	7	150
Pt	2B	100	10	1	100
Li	3	550	250	25	2500
Sb	3	1200	90	20	900
Ba	3	1400	700	300	7000
Mo	3	3000	1500	10	15000
Cu	3	3000	300	30	3000
Sn	3	6000	600	60	6000
Cr	3	11000	1100	3	11000

Table 1. Permitted daily exposure (PDE) for elemental impurities
*There are insufficient data to set PDEs by any route of administration for iridium, osmium, rhodium and ruthenium. For these elements, the palladium PDE for the relevant route will apply.
**For elements with a cutaneous PDE and a CTCL, both limits need to be met. In case the results are conflicting, the lowest limit is applied..
All numbers in italic are the values from the former issue of ICH Q3D(R1) guideline, superseeded now by ICH Q3D(R2).

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

For the new ICH Q3D(R2) guideline being adapted by USP and Ph.Eur., we offer mixes with element concentration ratios according to oral, parenteral, inhalational and cutaneous permitted daily exposures (PDE) of drug products.

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

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

Element	Class	If intentionally added (all routes)	If not intentionally added			
			Oral	Parenteral	Inhalaion	Cutaneous
As	1	yes	yes	yes	yes	yes
Cd	1	yes	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes	yes

Co	2A	yes	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes	yes
V	2A	yes	yes	yes	yes	yes
Tl	2B	yes	no	no	no	no
Au	2B	yes	no	no	no	no
Pd	2B	yes	no	no	no	no
Ir	2B	yes	no	no	no	no
Os	2B	yes	no	no	no	no
Rh	2B	yes	no	no	no	no
Ru	2B	yes	no	no	no	no
Se	2B	yes	no	no	no	no
Ag	2B	yes	no	no	no	no
Pt	2B	yes	no	no	no	no
Li	3	yes	no	yes	yes	no
Sb	3	yes	no	yes	yes	no
Ba	3	yes	no	no	yes	no
Mo	3	yes	no	no	yes	no
Cu	3	yes	no	no	yes	no
Sn	3	yes	no	no	yes	no
Cr	3	yes	no	no	yes	no

Table 2. Elements to be considered in the risk assessment

		***Trace*CERT®**				***Trace*CERT®**				
Element	Class	Elemental Impurities Mix according to ICH Q3D oral				Elemental Impurities Mix according to ICH Q3D parenteral				
		Standard 1	Standard 2	Standard 4*	Standard 3	Standard 1	Standard 5**	Standard 2	Standard 6***	Sta 3
		Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat
		19041	**73108**	**75463**	**69729**	**89118**	77184	**89922**	**90088**	**073**
		in 12% HNO_3	in 10% HCl	in 7% HCl	in 5% HNO_3 & HF<0.5%	in 12% HNO_3	in 12% HNO_3	in 10% HCl	in 10% HCl	in 5 HN HF

As	1	15				15	15		
Cd	1	5				2	2		
Hg	1	1				3	3		
Pb	1	5				5	5		
Ni	2A	200				20	20		
V	2A	100				10	10		
Co	2A	50				5	5		
Se	2B	150				80	80		
Ag	2B	150				10	15		
Au	2B		100	300				100	300
Ir	2B		100	100				10	10
Os	2B		100	100				10	10
Pd	2B		100	100				10	10
Pt	2B		100	100				10	10
Rh	2B		100	100				10	10
Ru	2B		100	100				10	10
Tl	2B	8				8	8		
Cr	3				1100				11(
Cu	3				300				30
Mo	3				300				15(
Ba	3				140				70
Sb	3				120				9
Li	3				55				25
Sn	3				600				60

		***Trace*CERT®**				***Trace*CERT®**	
Element	Class	Elemental Impurities Mix according to ICH Q3D inhalation				Elemental Impurities Mix according to ICH Q3D cutaneous and transcutaneous	
		Standard 4	Standard 6*****	Standard 2	Standard 5****	Standard 1	Standard 2

		Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.	Cat. No.
		91496	78525	**93696**	**95419**	78524	96396
		in 12% HNO3	in 12% HNO3	in 10% HCl	in 10% HCl	in 12% HNO3	in 5% HNO3 & HF<0.5%
As	1	2	2			30	
Cd	1	3	3			20	
Hg	1	1	1			30	
Pb	1	5	5			50	
Ni	2A	5	6			200	
V	2A	1	1			100	
Co	2A	3	3			50	
Se	2B	130	130			800	
Ag	2B	7	7			150	
Au	2B			10	3		
Ir	2B			10	1		
Os	2B			10	1		
Pd	2B			10	1		
Pt	2B			10	1		
Rh	2B			10	1		
Ru	2B			10	1		
Tl	2B	8	8			8	
Cr	3						1100
Cu	3						300
Mo	3						1500
Ba	3						700
Sb	3						90
Li	3						250
Sn	3						600

Table 3. Suitable Multi-Element CRM Solutions according to ICH Q3D *Trace***CERT®**
all concentrations in mg/L
* 75463 will replace 73108
** 77184 will replace 89118
*** 90088 will replace 89922 and also covers cutaneous/transcutaneous application

**** 95419 will replace 93696
***** 78525 will replace 91496

***Trace*CERT® ICH Q3D mixes**
Unique level of accuracy and lot-specific value
Produced according to ISO 17034 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 list up to 70 trace impurities for the *Trace*CERT® products (auch hier CERT fett). All product documentation documents can be found on: **www.SigmaAldrich.com**
100 mL package size

Table 4. Features of the *Trace*CERT® CRMs

Materials

73108

Elemental Impurities according to ICH Q3D oral, Standard 2

*Trace*CERT®, (in 10% hydrochloric acid), applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

View

19041

Elemental Impurities according to ICH Q3D oral, Standard 1

*Trace*CERT®, (in 12% nitric acid), applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

View

69729

Elemental Impurities according to ICH Q3D oral, Standard 3

*Trace*CERT®, in nitric acid and hydrofluoric acid (5% nitric acid and <0.5% hydrofluoric acid), applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

View

89118

Elemental Impurities according to ICH Q3D parenteral, Standard 1

in 12% nitric acid), *Trace*CERT®, applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

ew

922

emental Impurities according to ICH Q3D parenteral, Standard 2

*Trace*CERT®, (in 10% hydrochloric acid), applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

View

07368

Elemental Impurities according to ICH Q3D parenteral, Standard 3

*Trace*CERT®, in nitric acid and hydrofluoric acid (5% nitric acid and <0.5% hydrofluoric acid), applicable for testing acc. to USP<232>, Ph.Eur. Gen. Chapter 5.20

View

93696

Elemental Impurities according to ICH Q3D inhalation, Standard 2