

USP<232>/<233>: New Regulations on Elemental Impurities in Drug Products

The FDA is requiring compliance of drug manufactures to meet the new standards for elemental impurities. These impurities include those that are naturally occurring or introduced to the product during the manufacturing process.

Prior to the introduction of USP 232 and 233 guidance on elemental impurities was found in ICH QD3. This document established the permitted daily exposure (PDE) for 24 toxic metals. The metals are separated into categories based on the level of toxicity. Class 1 elements are the most toxic. Class 2A elements have a high likelihood of exposure in drug products. Both Class 1 and 2A must be included in all risk assessments. Class 2B elements are less likely to appear in drug products. Class 3 elements have low oral toxicity. Class 2B and 3 do not need to be run during risk assessment unless the element is intentionally added during manufacture.

USP<232> runs in parallel with ICH Q3D. The new regulations incorporate the PDE, established by ICH Q3D, and scale the amount based on the maximum daily dose of the drug product. The list of elements and their daily dose PDE are organized below in *Table 1*.

Table 1. Elemental Impurities for Drug Products

Element	Class	Oral Daily Dose PDE (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)
Cadmium	1	5	2	2
Lead	1	5	5	5
Inorganic arsenic	1	15	15	2
Inorganic mercury	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5
Thallium	2B	8	8	8
Gold	2B	100	100	1
Iridium	2B	100	10	1
Osmium	2B	100	10	1
Palladium	2B	100	10	1
Platinum	2B	100	10	1
Rhodium	2B	100	10	1
Ruthenium	2B	100	10	1
Selenium	2B	150	80	130
Silver	2B	150	10	7
Chromium	3	11000	1100	3
Molybdenum	3	3000	1500	10
Copper	3	3000	300	30
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Tin	3	6000	600	60

In order to show compliance, one of three methods must be applied:

1. The daily dose PDE must be greater than or equal to the measured value of elemental impurities scaled by the maximum daily dose.

$$\text{Daily dose PDE} \geq \text{measured value} \times \text{max daily dose}$$

2. The separate amounts of each elemental impurity from drug product components are added together (Σ^M) and multiplied by the element concentration (C) in each component, the weight of component in each dose (W), and the number of units in the maximum daily dose (D).

$$\text{Daily dose PDE} \geq [\Sigma^M(C \times W)] \times D$$

3. For drug products with a daily dose of no more than 10g, if the individual components in a drug product fall below the values in *Table 2*, then no further calculation is necessary.

Table 2. Concentration Limits for Drug Products

Element	Components used in Oral Drug Products (µg/g)	Components used in Parenteral Drug Products (µg/g)	Components used in Inhalational Drug Products (µg/g)
Cadmium	0.5	0.2	0.2
Lead	0.5	0.5	0.5
Inorganic arsenic	1.5	1.5	0.2
Inorganic mercury	3	0.3	0.1
Cobalt	5	0.5	0.3
Vanadium	10	1	0.1
Nickel	20	2	0.5
Thallium	0.8	0.8	0.8
Gold	10	10	0.1
Iridium	10	1	0.1
Osmium	10	1	0.1
Palladium	10	1	0.1
Platinum	10	1	0.1
Rhodium	10	1	0.1
Ruthenium	10	1	0.1
Selenium	15	8	13
Silver	15	1	0.7
Chromium	1100	110	0.3
Molybdenum	300	1.50	1
Copper	300	30	3
Lithium	55	25	2.5
Antimony	120	9	2
Barium	140	70	30
Tin	600	60	6

USP<233> details recommended detection methods for analyzing elemental Impurities. The suggested techniques are inductively coupled plasma-atomic emission spectroscopy (ICP-AES), inductively coupled plasma-optical emission spectroscopy (ICP-OES), and inductively coupled plasma-mass spectrometry

(ICP-MS). The samples can be injected neat, or dissolved in aqueous or organic solvents. In cases where the sample is insoluble under these conditions, the sample can be broken down using closed vessel digestion. Alternative procedures may be developed however, they must be validated. The new procedures must pass criteria for accuracy, precision, specificity, detectability, and repeatability.

Jordi Labs offers method development, validation and testing for USP 232, 233 and 2232. We have been offering elemental impurities testing services for over 25 years and we excel at dealing with difficult sample matrices and provide quick execution.

References

1. USP Chapter <232> Elemental Impurities-Limits, USP 40
2. USP Chapter <233> Elemental Impurities- Procedures, USP 40-NF 35, Second Supplement
3. ICH Guideline Q3D on Elemental Impurities, Step 2b version, July 2013