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⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

INTRODUCTION

This chapter specifies limits for the amounts of elemental impurities in drug products. Regardless of the approach used, compliance with the limits specified is required for all drug products unless otherwise specified in an individual monograph or specifically excluded in this *Introduction*.

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard. Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment.

This chapter does not apply to the following:

- Radiopharmaceuticals
- Articles intended only for veterinary use
- Vaccines
- Cell metabolites
- DNA products
- Allergenic extracts
- Cells, whole blood, cellular blood components, or blood derivatives, including plasma and plasma derivatives
- Products based on genes (gene therapy)
- Cells (cell therapy)
- Tissue (tissue engineering)
- Dialysate solutions not intended for systemic circulation
- Total parenteral nutrition (TPN)
- Elements that are intentionally included in the drug product for therapeutic benefit
- Dietary supplements and their ingredients, which are addressed in *Elemental Contaminants in Dietary Supplements ⟨2232⟩*

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. However, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data, or if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using *Table 2* in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally sourced materials, must be considered in the risk assessment.

SPECIATION

The determination of the oxidation state, organic complex, or combination is termed “speciation”. Each of the elemental impurities has the potential to be present in differing oxidation or complexation states. However, arsenic and mercury are of particular concern because of the differing toxicities of their inorganic and complexed organic forms.

The arsenic limits are based on the inorganic (most toxic) form. Arsenic can be measured using a total-arsenic procedure under the assumption that all arsenic contained in the material under test is in the inorganic form. Where the limit is exceeded using a total-arsenic procedure, it may be possible to show, via a procedure that quantifies the different forms, that the inorganic form meets the specification.

The mercury limits are based upon the inorganic (2^+) oxidation state. The methyl mercury form (most toxic) is rarely an issue for pharmaceuticals. Thus, the limit was established assuming the most common (mercuric) inorganic form. Limits for articles that have the potential to contain methyl mercury (e.g., materials derived from fish) are to be provided in the monograph.

Change to read:

ROUTES OF ▲ADMINISTRATION▲ (USP 1-MAY-2024)

The elements included in the tables below have been placed into three classes, based on their toxicity and likelihood of occurrence in the drug product. The classification scheme is intended to focus the risk assessment on those elements that are the most toxic but also have a reasonable probability of inclusion in the drug product (see *Table 2*).

The toxicity of an elemental impurity is related to its extent of exposure (bioavailability). The extent of exposure has been determined for each of the elemental impurities of interest for ▲the following▲ (USP 1-May-2024) routes of administration: oral, parenteral, inhalational ▲, and cutaneous and transcutaneous.▲ (USP 1-May-2024) These limits are based on chronic exposure. ▲For other routes of administration,▲ (USP 1-May-2024) consider the oral permitted daily exposures (PDEs) in *Table 1* as a starting point in developing specific PDEs for other routes of administration, except where otherwise stated in the individual monograph.

[NOTE—The routes of administration of drug products are defined in *Pharmaceutical Dosage Forms* ⟨1151⟩.]

Change to read:

DRUG PRODUCTS

The limits described in the third through ▲sixth▲ (USP 1-May-2024) columns of *Table 1* are the base daily dose PDEs of the elemental impurities of interest for a drug product taken by a patient according to the indicated routes of administration.

Parenteral Products

Parenteral drug products with maximum daily volumes up to 2 L may use the maximum daily volume to calculate permitted concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 L (e.g., saline, dextrose, and solutions for irrigation), a 2-L volume may be used to calculate permitted concentrations from PDEs.

▲Permitted Daily Exposures

The information in *Table 1* applies to oral, parenteral, inhalation, and cutaneous and transcutaneous drug products (referred to as cutaneous product) whether intended for local or systemic effects. This table does not apply to products intended for mucosal administration. Products not covered by *Table 1* should be assessed following the principles described for other routes of administration. For cutaneous products, an additional limit is provided for elements that have been demonstrated to be sensitizers (i.e., cobalt and nickel). The cutaneous and transcutaneous concentration limit (CTCL) was added because sensitization interactions have a concentration effect (not simply related to the total amount of the sensitizing element). The current limits for the stated routes of exposure for each element are provided in *Table 1*.▲ (USP 1-May-2024)

Table 1. Permitted Daily Exposures for Elemental Impurities

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)	▲Cutaneous Products▲ (USP 1-May-2024)	
					▲PDE (µg/day)	CTCL for Sensitizers (µg/g)▲ (USP 1-May-2024)
Cadmium	1	5	2	3	▲20	—▲ (USP 1-May-2024)
Lead	1	5	5	5	▲50	—▲ (USP 1-May-2024)
Arsenic	1	15	15	2	▲30	—▲ (USP 1-May-2024)
Mercury	1	30	3	1	▲30	—▲ (USP 1-May-2024)
Cobalt	2A	50	5	3	▲50	35[a]▲ (USP 1-May-2024)

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)	▲Cutaneous Products▲ (USP 1-May-2024)	
					▲PDE (µg/day)	CTCL for Sensitizers (µg/g)▲ (USP 1-May-2024)
Vanadium	2A	100	10	1	▲100	—▲ (USP 1-May-2024)
Nickel	2A	200	20	▲6	200	35[a]▲ (USP 1-May-2024)
Thallium	2B	8	8	8	▲8	—▲ (USP 1-May-2024)
Gold	2B	▲300	300	3	3000	—▲ (USP 1-May-2024)
Palladium	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Iridium	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Osmium	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Rhodium	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Ruthenium	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Selenium	2B	150	80	130	▲800	—▲ (USP 1-May-2024)
Silver	2B	150	▲15▲ (USP 1-May-2024)	7	▲150	—▲ (USP 1-May-2024)
Platinum	2B	100	10	1	▲100	—▲ (USP 1-May-2024)
Lithium	3	550	250	25	▲2500	—▲ (USP 1-May-2024)
Antimony	3	1200	90	20	▲900	—▲ (USP 1-May-2024)
Barium	3	1400	700	300	▲7000	—▲ (USP 1-May-2024)

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)	▲ Cutaneous Products▲ (USP 1-May-2024)	
					▲PDE (µg/day)	CTCL for Sensitizers (µg/g)▲ (USP 1-May-2024)
Molybdenum	3	3000	1500	10	▲15,000	—▲ (USP 1-May-2024)
Copper	3	3000	300	30	▲3000	—▲ (USP 1-May-2024)
Tin	3	6000	600	60	▲6000	—▲ (USP 1-May-2024)
Chromium	3	11000	1100	3	▲11,000	—▲ (USP 1-May-2024)

[a] 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. Using cobalt as an example, based on the PDE and a 1-g maximum daily dose of drug product, the calculated cutaneous concentration is 50 µg/g, which exceeds the CTCL of 35 µg/g. In this situation, the CTCL should be used.

Recommendations for Elements to Be Considered in the Risk Assessment

Table 2 identifies elemental impurities for inclusion in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 2. Elements to Be Considered in the Risk Assessment

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added▲[a]▲ (USP 1-May-2024)			
			Oral	Parenteral	Inhalation	▲Cutaneous▲ (USP 1-May-2024)
Cadmium	1	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Lead	1	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Arsenic	1	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Mercury	1	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Cobalt	2A	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Vanadium	2A	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)
Nickel	2A	Yes	Yes	Yes	Yes	▲Yes▲ (USP 1-May-2024)

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added[a] (USP 1-May-2024)			
			Oral	Parenteral	Inhalation	Cutaneous (USP 1-May-2024)
Thallium	2B	Yes	No	No	No	No (USP 1-May-2024)
Gold	2B	Yes	No	No	No	No (USP 1-May-2024)
Palladium	2B	Yes	No	No	No	No (USP 1-May-2024)
Iridium	2B	Yes	No	No	No	No (USP 1-May-2024)
Osmium	2B	Yes	No	No	No	No (USP 1-May-2024)
Rhodium	2B	Yes	No	No	No	No (USP 1-May-2024)
Ruthenium	2B	Yes	No	No	No	No (USP 1-May-2024)
Selenium	2B	Yes	No	No	No	No (USP 1-May-2024)
Silver	2B	Yes	No	No	No	No (USP 1-May-2024)
Platinum	2B	Yes	No	No	No	No (USP 1-May-2024)
Lithium	3	Yes	No	Yes	Yes	No (USP 1-May-2024)
Antimony	3	Yes	No	Yes	Yes	No (USP 1-May-2024)
Barium	3	Yes	No	No	Yes	No (USP 1-May-2024)
Molybdenum	3	Yes	No	No	Yes	No (USP 1-May-2024)
Copper	3	Yes	No	Yes	Yes	No (USP 1-May-2024)
Tin	3	Yes	No	No	Yes	No (USP 1-May-2024)

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added[▲a▲] (USP 1-May-2024)			
			Oral	Parenteral	Inhalation	▲Cutaneous▲ (USP 1-May-2024)
Chromium	3	Yes	No	No	Yes	▲No▲ (USP 1-May-2024)

▲[a] This also applies to materials for which the element is intrinsically associated with (e.g., as can be found in naturally occurring materials).▲ (USP 1-May-2024)

Options for Demonstrating Compliance

DRUG PRODUCT ANALYSIS OPTION

The results obtained from the analysis of a typical dosage unit, scaled to a maximum daily dose, are compared with the daily dose PDE.

$$\text{Daily dose PDE} \geq \text{measured value } (\mu g/g) \times \text{maximum daily dose } (g/\text{day})$$

The measured amount of each impurity is not more than the daily dose PDE, unless otherwise stated in the individual monograph.

SUMMATION OPTION

Separately, add the amounts of each elemental impurity (in µg/g) present in each of the components of the drug product:

$$\text{Daily dose PDE} \geq \left[\Sigma_1^M \left(C_M \times W_M\right)\right] \times D_D$$

M = each ingredient used to manufacture a dosage unit

C_M = element concentration in component (drug substance or excipient) (µg/g)

W_M = weight of component in a dosage unit (g/dosage unit)

D_D = number of units in the maximum daily dose (unit/day)

The result of the summation of each impurity is not more than the daily dose PDE, unless otherwise stated in the individual monograph. Before products can be evaluated using this option, the manufacturer must ensure that additional elemental impurities cannot be inadvertently added through the manufacturing process or via the container–closure system over the shelf life of the product.

INDIVIDUAL COMPONENT OPTION

For drug products with a daily dose of not more than 10 g, if all drug substances and excipients in a formulation meet the concentration limits shown in *Table 3*, then these components may be used in any proportion. No further calculation is necessary. Although elemental impurities derived from the manufacturing process or the container–closure system are not specifically provided for in the *Individual Component Option*, it is expected that the drug product manufacturer will ensure that these sources do not contribute significantly to the total content of elemental impurities.

Change to read:

DRUG SUBSTANCE AND EXCIPIENTS

The acceptable levels of elemental impurities depend on the material's ultimate use. Therefore, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance manufacturers or excipient manufacturers, who may provide test data, or, if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using *Table 2* in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally sourced materials, must be considered in the risk assessment.

The values provided in *Table 3* are example concentration limits for components (drug substances and excipients) of drug products dosed at a maximum daily dose of 10 g/day. These values serve as default concentration limits to aid discussions between drug product manufacturers and the suppliers of the components of their drug products. [Note—Individual components may need to be limited at levels different from those in the table depending on monograph-specific mitigating factors.]

Table 3. Permitted Concentrations of Elemental Impurities for Individual Component Option ▲(based on a maximum 10-g dose)▲ (USP 1-May-2024)

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)	▲Cutaneous Concentration (µg/g)	CTCL for Sensitizers (µg/g)▲ (USP 1-May-2024)
Cadmium	1	0.5	0.2	0.3	▲2	—▲ (USP 1-May-2024)
Lead	1	0.5	0.5	0.5	▲5	—▲ (USP 1-May-2024)
Arsenic	1	1.5	1.5	0.2	▲3	—▲ (USP 1-May-2024)
Mercury	1	3	0.3	0.1	▲3	—▲ (USP 1-May-2024)
Cobalt	2A	5	0.5	0.3	▲5[a]	35▲ (USP 1-May-2024)
Vanadium	2A	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Nickel	2A	20	2	▲0.6	20[a]	35▲ (USP 1-May-2024)
Thallium	2B	0.8	0.8	0.8	▲0.8	—▲ (USP 1-May-2024)
Gold	2B	▲30	30	0.3	300	—▲ (USP 1-May-2024)
Palladium	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Iridium	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Osmium	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Rhodium	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Ruthenium	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)
Selenium	2B	15	8	13	▲80	—▲ (USP 1-May-2024)
Silver	2B	15	▲1.5▲ (USP 1-May-2024)	0.7	▲15	—▲ (USP 1-May-2024)
Platinum	2B	10	1	0.1	▲10	—▲ (USP 1-May-2024)

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)	▲Cutaneous Concentration (µg/g)	CTCL for Sensitizers (µg/g)▲ (USP 1-May-2024)
Lithium	3	55	25	2.5	▲250	—▲ (USP 1-May-2024)
Antimony	3	120	9	2	▲90	—▲ (USP 1-May-2024)
Barium	3	140	70	30	▲700	—▲ (USP 1-May-2024)
Molybdenum	3	300	150	1	▲1500	—▲ (USP 1-May-2024)
Copper	3	300	30	3	▲300	—▲ (USP 1-May-2024)
Tin	3	600	60	6	▲600	—▲ (USP 1-May-2024)
Chromium	3	1100	110	0.3	▲1100	—▲ (USP 1-May-2024)

[a] For elements with a cutaneous PDE and a CTCL, both limits need to be met. If the results are conflicting, the lowest limit is applied. Using cobalt as an example, based on a 10-g maximum daily dose of the drug product, the calculated cutaneous concentration is 5 µg/g; based on a 1-g maximum daily dose of drug product, the calculated cutaneous concentration is 50 µg/g, which exceeds the CTCL of 35 µg/g. In this situation, the CTCL should be used.

ANALYTICAL TESTING

If, by process monitoring and supply chain control, manufacturers can demonstrate compliance, then further testing may not be needed. When testing is done to demonstrate compliance, proceed as directed in *Elemental Impurities—Procedures ⟨233⟩*.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<232> ELEMENTAL IMPURITIES--LIMITS	Edmond Biba Senior Scientific Liaison	GCCA2020 General Chapters - Chemical Analysis 2020

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