BRIEFING

⟨232⟩ Elemental Impurities—Limits, *USP 39* page 268. This chapter is being revised to address comments received and to further align this chapter with ICH Q3D. USP's Elemental Impurities Expert Panel approved a recommendation to the General Chapters—Chemical Analysis Expert Committee that this chapter be revised to align with the ICH Q3D Step 4 document to the greatest extent possible. Therefore, this revision is being proposed to include additional elements and their specific limits in this chapter. Additional changes are made to provide clarity on the topic of risk assessment. Stakeholders are encouraged to comment only on the revised text.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

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⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

Change to read:

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*.■1S (*USP40*)

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. ~~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.~~

~~The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or non-recombinant origins), their derivatives,~~

and products of which they are components (e.g., conjugates) are within the scope of this chapter, as are drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides.

This chapter does not apply to radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This chapter does not apply to products based on genes (gene therapy), cells (cell therapy), and tissue (tissue engineering).

▪This chapter does not apply to:

- 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 nutritions (TPNs)
- 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⟩

▪1S (*USP40*)

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. However, elemental impurity levels present in drug substances and excipients must be known, documented, and made available upon request. ▪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.▪1S (*USP40*)

~~This chapter does not apply to articles intended only for veterinary use. Requirements listed in this chapter also do not apply to total parenteral nutritions (TPNs) and dialysates. Dietary supplements and their ingredients are addressed in *Elemental Contaminants in Dietary Supplements* ⟨2232⟩.~~

▪▪1S (*USP40*)

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 EXPOSURE

▪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*).▪1S (*USP40*)

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 three routes of administration: oral, parenteral, and inhalational. These limits are based on chronic exposure. Consider the oral permissible 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 ~~second~~ ■third■1S (USP40) through ~~fourth~~ ■fifth■1S (USP40) 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 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 permissible 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, ~~TPNs,~~ ■■1S (USP40) and solutions for irrigation), a 2-L volume may be used to calculate permissible concentrations from PDEs.

~~**Table 1. Elemental Impurities for Drug Products**~~

~~**Element**~~	~~**Oral Daily Dose PDE[a] (µg/day)**~~	~~**Parenteral Daily Dose PDE (µg/day)**~~	~~**Inhalational Daily Dose PDE (µg/day)**~~
~~Cadmium~~	~~5~~	~~2~~	~~2~~
~~Lead~~	~~5~~	~~5~~	~~5~~
~~Inorganic arsenic[a]~~	~~15~~	~~15~~	~~2~~
~~Inorganic mercury[a]~~	~~30~~	~~3~~	~~1~~
~~Iridium~~	~~100~~	~~10~~	~~1~~
~~Osmium~~	~~100~~	~~10~~	~~1~~
~~Palladium~~	~~100~~	~~10~~	~~1~~
~~Platinum~~	~~100~~	~~10~~	~~1~~
~~Rhodium~~	~~100~~	~~10~~	~~1~~
~~Ruthenium~~	~~100~~	~~10~~	~~1~~
~~Chromium~~	~~11000~~	~~1100~~	~~3~~
~~Molybdenum~~	~~3000~~	~~1500~~	~~10~~
~~Nickel~~	~~200~~	~~20~~	~~5~~
~~Vanadium~~	~~100~~	~~10~~	~~1~~
~~Copper~~	~~3000~~	~~300~~	~~30~~

~~[a] See *Speciation* section.~~

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Table 1: Permitted Daily Exposures for Elemental Impurities

Element	**Class**	**Oral PDE (µg/day)**	**Parenteral PDE (µg/day)**	**Inhalation PDE (µg/day)**
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Hg	1	30	3	1
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
Rh	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

Recommendations for Elements to be Considered in the Risk Assessment

The following *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		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
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
Rh	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	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

■1S (*USP40*)

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 to the *Daily Dose PDE*.

Daily Dose PDE ≥ measured value (µg/g) × maximum daily dose (g/day)

The measured amount of each impurity is NMT 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:

$$\textit{Daily Dose PDE} \geq [\Sigma^{M}_{1}(C_M \times W_M)] \times D_D$$

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 NMT 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 NMT 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. While 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 concentration of elemental impurities in drug substances and excipients must be controlled and, where present, documented.. The acceptable levels for these impurities depend on the material's ultimate use. Therefore, drug product manufacturers must determine the acceptable level of elemental impurities in the drug substances and excipients used to produce their products.~~

▪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.▪1S (*USP40*)

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 2. Example Concentration Limits for Components of Drug Products with a 10-g Maximum Daily Dose**~~

Element	Concentration Limits (µg/g) (ERR 1-Jun-2015) for Components Used in Oral Drug Products	Concentration Limits (µg/g) (ERR 1-Jun-2015) for Components Used in Parenteral Drug Products	Concentration Limits (µg/g) (ERR 1-Jun-2015) for Components Used in Inhalation Drug Products
Cadmium	0.5	0.2	0.2
Lead	0.5	0.5	0.5
Inorganic arsenic[a]	1.5	1.5	0.2
Inorganic mercury[a]	3	0.3	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
Chromium	1100	110	0.3
Molybdenum	300	150	1
Nickel	20	2	0.5
Vanadium	10	1	0.1
Copper	300	30	3
[a] See *Speciation* section.			

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Table 3: Permitted Concentrations of Elemental Impurities for Individual Component Option

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

■1S (*USP40*)

Change to read:

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⟩. ~~and minimally include arsenic, cadmium, lead, and mercury in the *Target Elements* evaluation.~~■■1S (*USP40*)