

BRIEFING

〈 232 〉 **Elemental Impurities—Limits**, page 197 of *PF* 36(1) [Jan–Feb 2010]. This revision to general chapter [Elemental Impurities](#) 〈 232 〉 is based on comments received during the public comment period. The Expert Panel on elemental impurities has reviewed these comments and is proposing revisions both to 〈 232 〉 and its accompanying general chapter [Elemental Impurities—Procedures](#) 〈 233 〉. Although these proposed changes do not materially impact the scientific content of these chapters, they are being published in *PF* to assure that the chapter requirements are clear to all users and to seek any final input.

The Permissible Daily Exposure (PDE) limits presented in the proposed new general chapter 〈 232 〉 are consistent with the current early deliberations of the International Congress on Harmonization (ICH) Q3D expert working party on metal impurities. Changes by ICH Q3D to the PDE limits for the elements contained in this chapter will be managed as proposed changes to the chapter via existing USP revision processes, with corresponding changes to the implementation times if the limits decrease. The addition of elements to this chapter based on additions made by ICH Q3D will be managed similarly. However, any elements (and their accompanying PDE) included in the final ICH document that are less toxic than those included in chapter 〈 232 〉 will be incorporated in a future informational general chapter rather than in 〈 232 〉.

The previously published *PF* 36(1) revision to the *General Notices and Requirements* pertaining to the *Elemental Impurities* chapters (section 5.60.30) was deferred from USP 34–NF 29. Any change in the implementation date will be reflected in a *General Notices* revision. This proposal will be included on the official ballot when chapters 〈 232 〉 and 〈 233 〉 are considered for approval by the Expert Committee.

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Comment deadline: July 31, 2011

Add the following:

■ 〈 232 〉 **ELEMENTAL IMPURITIES—LIMITS**

INTRODUCTION

The objective of this chapter is to set limits on the amounts of elemental impurities in pharmaceuticals. The chapter applies to drug substances, drug products (including natural source and rDNA biologics), and excipients. Dietary supplements and their ingredients are addressed in chapter *Elemental Impurities in Dietary Supplements* 〈 2232 〉. For articles that are designated “For Veterinary Use Only,” higher or lower levels for the permissible daily exposure and concentration limit may be justified in exceptional cases, based on the actual daily dose, actual target species, relevant toxicological data, and consumer safety considerations.

Elemental impurities addressed in this chapter are classified as shown in *Table 1*.

Table 1. Elemental Impurity Classes

Class	Assessment
Class 1	Elements should be essentially absent
	Known or strongly suspected human toxicants
	Environmental hazards

Class	Assessment
Class 2	Elements should be limited
	Elements with less toxicity than Class 1
	Elements deliberately added to an article

Class 1 Elemental Impurities

Compliance with the limits specified for Class 1 elemental impurities is required for all drug products, regardless of the likelihood of the presence of impurities. The presence of unexpected elemental contaminants, as well as that of impurities likely to be present, should be considered in determining compliance and planning the risk-based extent of testing.

Class 2 Elemental Impurities

In general, for Class 2 elemental impurities, the testing of drug substances, excipients, and drug products for elemental impurities need be conducted only when these elements are added during the manufacture of the article.

LIMITS OF ELEMENTAL IMPURITIES

Class 1

Class 1 elemental impurities ([Table 2](#)), because of their unacceptable toxicities or deleterious environmental effects, should not be present in a drug substance, excipient, or drug product. However, if their presence is unavoidable, their levels should be restricted as shown in [Table 2](#), unless otherwise stated in the individual monograph.

Class 2

Class 2 elemental impurities ([Table 3](#)) should be limited in drug substances, excipients, and drug products because of their inherent toxicities.

Table 2. Class 1 Elemental Impurities

Element	Component Limit (µg/g)	Oral Daily Dose PDE[*] (µg/day)	Parenteral Component Limit (µg/g)	Parenteral Daily Dose PDE (µg/day)
Arsenic	1.5	15	0.15	1.5
Cadmium	0.5	5	0.05	0.5
Lead	1	10	0.1	1
Mercury	1.5	15	0.15	1.5

^{*} Permitted daily exposure.

Table 3. Class 2 Elemental Impurities

Element	Component Limit (µg/g)	Oral Daily Dose PDE[*] (µg/day)	Parenteral Component Limit (µg/g)	Parenteral Daily Dose PDE (µg/day)
Chromium	25	250	2.5	25
Copper	250	2500	25	250
Manganese	250	2500	25	250

^{*} Permitted daily exposure.

Element	Component Limit (µg/g)	Oral Daily Dose PDE* (µg/day)	Parenteral Component Limit (µg/g)	Parenteral Daily Dose PDE (µg/day)
Molybdenum	25	250	2.5	25
Nickel	25	250	2.5	25
Palladium	10	100	1.0	10
Platinum	10	100	1.0	10
Vanadium	25	250	2.5	25
Osmium	10 (combination not to exceed)	100 (combination not to exceed)	1.0 (combination not to exceed)	10 (combination not to exceed)
Rhodium				
Ruthenium				
Iridium				

* Permitted daily exposure.

OPTIONS FOR DESCRIBING LIMITS OF ELEMENTAL IMPURITIES

Three options are available when applying limits of elemental impurities for orally dosed products. Parenteral products are covered separately (see *Parenteral Products* section below).

Drug Product Analysis Option

This option is generally applicable. The results obtained from the analysis of a typical dosage unit, scaled to a maximum daily dose, are compared to the Daily Dose PDE, as shown in [Table 2](#) and [Table 3](#).

$$\text{Daily Dose PDE} \geq \text{measured value} \times (\text{maximum daily dose})$$

Individual Component Option

For drug products with a maximum daily dose of NMT 10 g, the product meets the requirements when each drug substance and excipient meets the limits provided in the Component Limit column ([Table 2](#) and [Table 3](#)). If all drug substances and excipients in a formulation meet the limits shown in the Component Limit, these components may be used in any proportion. No further calculation is necessary.

Summation Option

This option can be used for drug products that are administered in doses other than 10 g/day or products in which any component of a product exceeds the applicable Component Limit. The Daily Dose PDE, as shown in [Table 2](#) and [Table 3](#), can be used to calculate the concentration of elemental impurities allowed in a drug product. Apply this option by separately adding the amounts of each elemental impurity (in µg/day) present in each of the components of the drug product, using the following equation:

$$\text{Result} = S \sum_m (C_M \times W_M)$$

m = each ingredient used to manufacture the dosage form

C_M = element concentration in that component (µg/g)

W_M = weight of component in a dosage form (g)

The sum of the quantities of each element/day should be less than that shown by the Daily Dose PDE in [Table 2](#) and [Table 3](#) for that element.

Examples

Consider an example of the application of the *Individual Component Option* and the *Summation Option* to the arsenic concentration in a drug product. The Daily Dose PDE is 15 µg/day, and the Component Limit is 1.5 µg/g (ppm). The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of arsenic are shown in [Table 4](#).

Table 4

Component	Amount in Formulation (g)	Arsenic Content (µg/g)	Daily Exposure (µg/day)
Drug substance	0.3	3.0	0.9
Excipient 1	0.9	1.0	0.9
Excipient 2	3.8	2.0	7.6
Drug product	5.0	—	9.4

Excipient 2 and the drug substance do not meet the Component Limit, but Excipient 1 does. Thus, the *Individual Component Option* cannot be used. However, under the *Summation Option*, the drug product meets the Daily Dose PDE limit of 15 µg/day and thus conforms to the acceptance criteria in this chapter.

Consider another example where the maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of arsenic are shown in [Table 5](#).

Table 5

Component	Amount in Formulation (g)	Arsenic Content (µg/g)	Daily Exposure (µg/day)
Drug substance	0.3	5.0	1.5
Excipient 1	0.9	5.0	4.5
Excipient 2	3.8	5.0	19.0
Drug product	5.0	—	25.0

In this example, the drug product exceeds the limits in [Table 2](#), using both the *Individual Component Option* and the *Summation Option*. The manufacturer can test the drug product by using the *Drug Product Analysis Option*. If the level of arsenic in the formulation exceeds the Daily Dose PDE, the product fails to meet the impurity limits as described in this chapter.

Parenteral Products

Because of the presumption of 100% bioavailability of the elemental impurity during parenteral administration, versus the presumed 10% bioavailability via the oral route, the Parenteral Component Limit and the Parenteral Daily Dose PDE ([Table 2](#) and [Table 3](#)) are 10% of those for the oral route of introduction. To evaluate the limits for elemental impurities, one can apply the three options described above, using the Parenteral Component Limit instead of the Component Limit, and using the Parenteral Daily Dose PDE instead of the Oral Daily Dose PDE.

ANALYTICAL PROCEDURES

For a presentation of the alternatives for testing, see the chapter *Elemental Impurities—Procedures* (233). The validation necessary will vary depending on the situation. For all three options described in Chapter <232> in the section *Options for Describing Limits of Elemental Impurities*, it may be appropriate to use the section *Limit Procedure Validation* in Chapter <233>. However, for the *Summation Option* in Chapter <232>, acceptable levels of validation must be determined on a case-by-case basis. Validation of a procedure using the *Quantitative Procedure Validation* in Chapter <233> is acceptable for all options under all circumstances, and it is generally preferred. The determination of the level of validation necessary is at the discretion of the manufacturer and the competent regulatory authority.

INTRODUCTION

This general chapter specifies limits for the amounts of elemental impurities in drug products. 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). 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. Regardless of the approach used, compliance with the limits specified is required for all drug products.

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in this chapter or in the individual monographs. However, elemental impurity levels present in drug substances and excipients must be known and reported.

Dietary supplements and their ingredients are addressed in *Elemental Contaminants in Dietary Supplements* (2232). For articles that are designated “For Veterinary Use Only”, or for which veterinary administration is intended, the permissible daily exposures (PDE) presented in this chapter are applicable. However, higher or lower PDE and concentration limits may be appropriate based on the daily dose, target species, relevant toxicological data, or consumer safety impact.

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.

ROUTES OF EXPOSURE

The toxicity of an elemental impurity is related to its extent of exposure (bioavailability). The *Exposure Factor* in [Table 1](#) is used to modify the PDEs presented in [Table 2](#), column 2, based on the route of administration, assuming 100% bioavailability for the parenteral and inhalational routes. These limits are based on chronic exposure but exclude potential genotoxic effects. When carcinogenicity is suspected (e.g., arsenic in inhalation products), the limits should be modified. [NOTE—The routes of administration of drug products are defined in general chapter *Pharmaceutical Dosage Forms* (1151).]

Table 1. Exposure Factor

Route of Administration	Exposure Factor
Oral (solids and liquids)	1
Parenteral (Injectables, implants, and ophthalmics)	0.1
Topicals and Dermal	1
Mucosal (nasal, otic, rectal, vaginal, urethral, others)	1
Inhalational (aerosols, inhalers, and gases)	0.1

DRUG PRODUCTS

The limits described in the second column of [Table 2](#) are the base daily dose PDEs of the elemental impurities of interest for a drug product taken by an adult patient according to indicated routes of administration. Exceptions for pediatric or other special populations that lower the PDE should be reflected in the limits in the appropriate monographs. Parenterals with an intended maximum dose of greater than 10 mL and not more than 100 mL must use the *Summation Option* described below.

Large Volume Parenterals

The amount of elemental impurities present in a Large Volume Parenteral (LVP – daily dose greater than 100 mL) drug product must be controlled through the individual components used to produce the product. The amounts of elemental impurities present in each component used in an LVP are less than the values included in the third column of [Table 2](#).

Table 2. Elemental Impurities for Drug Products

Element	Daily Dose PDE ^a (µg/day)	LVP Component Limit (µg/g)
Cadmium	5	0.05
Lead	10	0.1
Inorganic arsenic ^b	15	0.15
Inorganic Mercury ^b	15	0.15
Iridium	100	1.0
Osmium	100	1.0
Palladium	100	1.0
Platinum	100	1.0

^a PDE = Permissible Daily Exposure based on a 50Kg person.

^b See *Speciation* section.

Element	Daily Dose PDE ^a (µg/day)	LVP Component Limit (µg/g)
Rhodium	100	1.0
Ruthenium	100	1.0
Chromium	250	2.5
Molybdenum	250	2.5
Nickel	250	2.5
Vanadium	250	2.5
Copper	2500	25
Manganese	2500	25

^a PDE = Permissible Daily Exposure based on a 50Kg person.

^b See *Speciation* section.

Modified Daily Dose PDE

The *Modified Daily Dose PDE* is the maximum exposure to an impurity that a patient should experience from the maximum daily dose of a drug product. The *Modified Daily Dose PDE* is calculated by multiplying the *Daily Dose PDE* values in [Table 2](#) by the *Exposure Factor* from [Table 1](#) for the elements in question.

$$\text{Modified Daily Dose PDE} = \text{Daily Dose PDE} \times \text{Exposure Factor}$$

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 *Modified Daily Dose PDE*.

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

The measured amount of each impurity is NMT the *Modified 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 using the following equation:

$$\text{Modified Daily Dose PDE} \geq [S^M_1(C_M \times W_M)] \times D_D$$

where

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/unit). [NOTE—unit = 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 *Modified Daily Dose PDE*, unless otherwise stated in the individual monograph. Before products can be evaluated using this option, the manufacturer must validate that additional elemental impurities cannot be inadvertently added through the manufacturing process.

DRUG SUBSTANCE AND EXCIPIENTS

The presence of elemental impurities in drug substances and excipients must be controlled and, where present, reported. 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 values provided in [Table 3](#) represent 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. Default concentration limits for drug substances and excipients

Element	Concentration limits ($\mu\text{g/g}$) for Table 1 Exposure Factor 1 Drug Products with a Maximum Daily dose of ≤ 10 g/day	Concentration limits ($\mu\text{g/g}$) for Table 1 Exposure Factor 0.1 Drug Products with a Maximum Daily dose of ≤ 10 g/day
Cadmium	0.5	0.05
Lead	1	0.1
Inorganic Arsenic	1.5	0.15
Inorganic Mercury	1.5	0.15
Iridium	10	1
Osmium	10	1
Palladium	10	1
Platinum	10	1
Rhodium	10	1
Ruthenium	10	1
Chromium	25	2.5
Molybdenum	25	2.5
Nickel	25	2.5
Vanadium	25	2.5
Copper	250	25
Manganese	250	25

ANALYTICAL TESTING

If, by validated processes and supply-chain control, manufacturers can demonstrate the absence of impurities, then further testing is not needed. If testing is done to demonstrate compliance, see general chapter [Elemental Impurities](#)

[—Procedures](#) [〈 233 〉](#).

■1S (USP35)

Auxiliary Information - Please [check for your question in the FAQs](#) before [contacting USP](#).