

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

BRIEFING

⟨232⟩ Elemental Impurities—Limits. This proposed new general test chapter is the first of two being developed to replace the general test chapter *Heavy Metals* ⟨231⟩; the second chapter is *Elemental Impurities—Procedures* ⟨233⟩. The term *elemental impurities* is used here as an alternative to the term *heavy metals*. The limits presented in this chapter are based on in-depth review of the toxicological literature and discussions involving several experts in metal toxicology. These limits, based on documented toxicity and regulatory recommendations, focus on the four most toxic and best-understood metals: lead, mercury, arsenic, and cadmium. The chapter also provides limits of metal catalysts that can be added in the production of a drug substance or excipient. The metal catalyst limits are the same as those published by the European Medicines Agency (EMA),* with the exception of iron and zinc, which because of their low toxicity were not included. The chapter also describes three separate options for determination of compliance with limits. These options are similar to those presented in the chapter *Residual Solvents* ⟨467⟩.

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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.

* See page 6 at <http://www.emea.europa.eu/pdfs/human/swp/444600enfin.pdf>.

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 elemental impurities (*Table 3*) should be limited in drug substances, excipients, and drug products because of their inherent toxicities.

Class 2

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
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 $\mu\text{g}/\text{day}$) present in each of the components of the drug product, using the following equation:

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

m = each ingredient used to manufacture the dosage form

C_M = element concentration in that component ($\mu\text{g}/\text{g}$)

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 $\mu\text{g}/\text{day}$, and the Component Limit is 1.5 $\mu\text{g}/\text{g}$ (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 ($\mu\text{g}/\text{g}$)	Daily Exposure ($\mu\text{g}/\text{day}$)
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.▲^{USP34}