Add the following:

■⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

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. Due to the ubiquitous nature of As, Cd, Pb, and Hg, they (at the minimum) must be considered in the risk-based control strategy. 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.

The limits indicated in this chapter are not required for articles intended only for veterinary use and conventional vaccines. Dietary supplements and their ingredients are addressed in *Elemental Contaminants in Dietary Supplements* ⟨2232⟩.[1]

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 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. The other two routes of administration, mucosal and topical, are considered to be the same as oral for the purpose of this standard, and the PDEs described in *Table 1* would apply to these products. [NOTE—The routes of administration of drug products are defined in general chapter *Pharmaceutical Dosage Forms* ⟨1151⟩.]

DRUG PRODUCTS

The limits described in the second through fourth columns of *Table 1* are the base daily dose PDEs of the elemental impurities of interest for a drug product taken by the patient according to indicated routes of administration. 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

When the daily dose of an injection is greater than 100 mL (large volume parenteral (LVP)), the amount of elemental impurities present in the 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 fifth column of *Table 1*.

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)	LVP Component Limit (µg/g)
Cadmium	25	2.5	1.5	0.25
Lead	5	5	5	0.5
Inorganic arsenic[b]	1.5	1.5	1.5	0.15
Inorganic mercury[b]	15	1.5	1.5	0.15
Iridium	100	10	1.5	1.0
Osmium	100	10	1.5	1.0
Palladium	100	10	1.5	1.0
Platinum	100	10	1.5	1.0
Rhodium	100	10	1.5	1.0
Ruthenium	100	10	1.5	1.0
Chromium	*	*	25	*
Molybdenum	100	10	250	1.0
Nickel	500	50	1.5	5.0

[a] PDE = Permissible daily exposure based on a 50-kg person.
[b] See *Speciation* section.
* Not a safety concern.

[1] This dietary supplement chapter is still under revision and will appear online in *PF* 38(3) [May–June 2012].

Table 1. Elemental Impurities for Drug Products *(Continued)*

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)	LVP Component Limit (µg/g)
Vanadium	100	10	30	1.0
Copper	1000	100	70	25

[a] PDE = Permissible daily exposure based on a 50-kg person.
[b] See *Speciation* section.
* Not a safety concern.

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 using the following equation:

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

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/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 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 2* 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 2. Default Concentration Limits for Drug Substances and Excipients

Element	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Parenteral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Inhalational Drug Products with a Maximum Daily Dose of ≤10 g/day
Cadmium	2.5	0.25	0.15
Lead	0.5	0.5	0.5
Inorganic arsenic	0.15	0.15	0.15
Inorganic mercury	1.5	0.15	0.15
Iridium	10	1.0	0.15
Osmium	10	1.0	0.15
Palladium	10	1.0	0.15
Platinum	10	1.0	0.15
Rhodium	10	1.0	0.15
Ruthenium	100	10	1.5
Chromium	*	*	2.5
Molybdenum	10	1.0	25
Nickel	50	5.0	0.15
Vanadium	100	10	30
Copper	100	10	7

* Not a safety concern.

ANALYTICAL TESTING

If, by validated processes and supply-chain control, manufacturers can demonstrate the absence of impurities, then further testing is not needed. When testing is done to demonstrate compliance, proceed as directed in general chapter *Elemental Impurities—Procedures* ⟨233⟩, and minimally include As, Cd, Pd, and Hg in the *Target Element* evaluation.■2S (*USP35*)