<232> Elemental Impurities - Limits

This General Chapter specifies limits for the amounts of elemental impurities in 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 chapter *Elemental Impurities in Dietary Supplements <2232>*. For articles that are designated "For Veterinary Use Only", or for which veterinary administration is intended, the 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.

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., through 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 determining how to assure compliance with this standard. Regardless of the approach used, compliance with the limits specified is required for all drug products.

LIMITS OF ELEMENTAL IMPURITIES

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, few have markedly differing toxicities. Two that are of concern are arsenic and mercury. Arsenic may 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, compliance with the limit of inorganic arsenic shall be demonstrated on the basis of a speciation procedure. Methylmercury determination is not necessary when the content for total mercury is less than the limit. Specific monographs may provide exceptions for articles that have the potential to contain methylmercury.

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. [Note: The routes of administration of drug products are defined in General Chapter *Pharmaceutical Dosage Forms <1151>*.]

Table 1. Exposure Factor

	Exposure Factor
Oral (solids and liquids)	1
Parenteral (Injectables and implants)	0.1
Topicals and Dermal	1
Mucosal (ophthalmics, 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 and are subject to modification due to routes of exposure. Pediatric and other special population shall comply with the limits proscribed for an adult patient daily dose. 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)
Inorganic Arsenic[b]	15	0.15
Cadmium	5	0.05
Lead	10	0.1
Inorganic Mercury	15	0.15
Chromium	250	2.5
Copper	2500	25
Manganese	2500	25
Molybdenum	250	2.5
Nickel	250	2.5
Palladium	100	1.0
Platinum	100	1.0
Vanadium	250	2.5
Osmium	100 (Combination not to exceed)	1.0 (Combination not to exceed)
Rhodium		
Ruthenium		
Iridium		

[a] PDE = permitted daily exposure based on a 50 Kg 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.

Modified Daily Dose PDE = Daily Dose PDE x 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.*

Modified Daily Dose PDE > measured value x (maximum daily dose)

The measured amount of each impurity must be less than the *Modified Daily Dose PDE,* unless otherwise stated in the individual monograph.

Summation Option

Separately add the amounts of each elemental impurity (in µg/day) present in each of the components of the drug product using the following equation:

$$\textit{Modified Daily Dose PDE} > (\sum\nolimits_{m}^{1}(C_M \times W_M)) \times D_D$$

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 must be less than 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 to customers. The acceptable levels for these impurities are dependent upon their ultimate use. Therefore, the drug product manufacturer must determine the acceptable level of elemental impurities in the drug substances and excipients used to produce their products.

ANALYTICAL TESTING

This chapter allows for the use of control strategies to ensure compliance to the standard. If testing is done to demonstrate compliance, see General Chapter *Elemental Impurities—Procedures <233>.*