BRIEFING

〈232〉 Elemental Impurities—Limits, *USP 37* page 162. The proposed revisions to 〈232〉 convey USP's review of and subsequent partial alignment with the International Conference on Harmonization (ICH) Q3D Step 2 limits. USP's proposed limits reflect a review of published toxicological data and studies, as well as expert review by toxicologists serving on the Elemental Impurities Expert Panel. This expert review has continued over time (see *Standards-Setting Record*) to adjust the limits in 〈232〉 to accommodate ICH decision making. Despite this consideration, some divergence remains, as reflected in the tables provided in 〈232〉. USP has notified ICH via a comment letter on the Q3D Step 2 document of these divergences (available at http://www.usp.org/usp-nf/key-issues/elemental-impurities). The General Chapters Chemical Analysis Expert Committee encourages comments only on the highlighted text in the proposed revision to 〈232〉. Comments made to other sections of 〈232〉 will be considered for future revisions. Following review of public comments on the highlighted text, USP expects the revisions to 〈232〉 (and *Elemental Impurities—Procedures* 〈233〉, published elsewhere in this issue of *PF*) to become official on August 1, 2015. As approved by the USP Council of Experts in December 2013, the *General Notices* provision making 〈232〉 applicable to *USP–NF* drug product monographs, section 5.60.30, will have an official date of December 1, 2015. This date reflects a delay of approximately 18 months from the date originally proposed in *PF* 39(1) [Jan.–Feb. 2013], which was deferred pending further deliberations by the Council at its September 2013 meeting. As part of the implementation of 〈232〉 (and 〈233〉), USP will remove all references to general chapter *Heavy Metals* 〈231〉 from monographs and general chapters in the *USP–NF* through its omission process. This omission is also scheduled for December 1, 2015, to align with the date of applicability of 〈232〉 (and *Elemental Contaminants in Dietary Supplements* 〈2232〉) under the *General Notices* provision. USP maintains a web page that provides further information on this important standard available at http://www.usp.org/usp-nf/key-issues/elemental-impurities.

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

(GCCA: K. Zaidi.) Correspondence Number—C139067

〈232〉 ELEMENTAL IMPURITIES—LIMITS

Official February 1, 2013

Change to read:

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 ▪and the container closure system).▪1S (*USP38*) 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-

based control strategy. Regardless of the approach used, compliance with the limits specified is required for all drug products ▪unless otherwise specified in an individual monograph or excluded in paragraph three of this introduction.▪ 1S (*USP38*)

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~~ ▪documented, and made available upon request.▪ 1S (*USP38*)

The limits indicated in this chapter are not required for articles intended only for veterinary use and conventional vaccines. ▪Requirements listed in this chapter also do not apply to total parenteral nutritions (TPNs) and dialysates.▪ 1S (*USP38*) Dietary supplements and their ingredients are addressed in *Elemental Contaminants in Dietary Supplements* 〈2232〉.

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 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 would apply to these products~~*~~Table 1.~~* ▪To account for the potential application of topical products to injured or broken skin, topical product permissible daily exposures (PDEs) will be the same as oral *Table 1*, except as indicated in the individual monograph. Mucosal will also use oral PDEs, except where otherwise stated in the individual monograph.▪ 1S (*USP38*) [NOTE—The routes of administration of drug products are defined in general chapter *Pharmaceutical Dosage Forms* 〈1151〉.]

Change to read:

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 NMT 100 mL must use the *Summation Option*.

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~~ may *1S (USP38)* be controlled through the individual ~~components used to produce the product~~ component option. *1S (USP38)* 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~~ 5.0 *1S (USP38)*	2.5	~~1.5~~ 3.4 *1S (USP38)*	0.25
Lead	~~5~~ 5.0 *1S (USP38)*	~~5~~ 5.0 *1S (USP38)*	~~5~~ 5.0 *1S (USP38)*	0.5
Inorganic arsenic[b]	~~1.5~~ 15 *1S (USP38)*	~~1.5~~ 15 *1S (USP38)*	~~1.5~~ 1.9 *1S (USP38)*	~~0.15~~ 1.5 *1S (USP38)*
Inorganic mercury[b]	15	1.5	~~1.5~~ 1.2 *1S (USP38)*	0.15
Iridium	100	10	1.5	1.0
Osmium	100	10	1.5	1.0
Palladium	100	10	~~1.5~~ 1.0 *1S (USP38)*	1.0
Platinum	100	10	1.5	1.0
Rhodium	100	10	1.5	1.0
Ruthenium	100	10	1.5	1.0
Chromium	—[c]	—[c]	~~25~~ 2.9 *1S (USP38)*	—[c]
Molybdenum	~~100~~ 180 *1S (USP38)*	~~10~~ 90 *1S (USP38)*	~~10~~ 7.6 *1S (USP38)*	~~1.0~~ 9.0 *1S (USP38)*
Nickel	~~500~~ 600 *1S (USP38)*	~~50~~ 60 *1S (USP38)*	~~1.5~~ 6.0 *1S (USP38)*	~~5.0~~ 6.0 *1S (USP38)*
Vanadium	~~100~~ 120 *1S (USP38)*	~~10~~ 12 *1S (USP38)*	~~30~~ 1.2 *1S (USP38)*	~~1.0~~ 1.2 *1S (USP38)*
Copper	~~1000~~ 1300 *1S (USP38)*	~~100~~ 130 *1S (USP38)*	~~100~~ 13 *1S (USP38)*	~~10~~ 13 *1S (USP38)*

[a] PDE = Permissible daily exposure based on a 50-kg person. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety factor against the standard weights of 60 or 70 kg that are often used in this type of calculation. It is

recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the metal was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.▪1S (*USP38*)

[b] See *Speciation* section.

[c] Not a safety concern. ▪Will be included in a future informational chapter.▪1S (*USP38*)

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:

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

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• (ERR 1-Oct-2013) 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.▪1S (*USP38*)

▪INDIVIDUAL COMPONENT OPTION

The Individual Component Option is available to LVP products only. An LVP may meet the requirements when each drug substance and excipient meets the limits provided in the LVP Component Limit column (*Table 1*). If all drug substances and excipients in a formulation meet the limits shown, 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.▪1S (*USP38*)

Change to read:

DRUG SUBSTANCE AND EXCIPIENTS

The ~~presence~~ ▪concentration▪1S (*USP38*) of elemental impurities in drug substances and

excipients must be controlled and, where present, ~~reported~~ documented. 1S (*USP38*) 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~~ 0.5 1S (*USP38*)	0.25	~~0.15~~ 0.34 1S (*USP38*)
Lead	0.5	0.5	0.5
Inorganic arsenic	~~0.15~~ 1.5 1S (*USP38*)	~~0.15~~ 1.5 1S (*USP38*)	~~0.15~~ 0.19 1S (*USP38*)
Inorganic mercury	1.5	0.15	~~0.15~~ 0.12 1S (*USP38*)
Iridium	10	1.0	0.15
Osmium	10	1.0	0.15
Palladium	10	1.0	~~0.15~~ 0.1 1S (*USP38*)
Platinum	10	1.0	0.15
Rhodium	10	1.0	0.15
Ruthenium	10	1.0	0.15
Chromium	—[a]	—[a]	~~2.5~~ 0.29 1S (*USP38*)
Molybdenum	~~10~~ 18 1S (*USP38*)	~~1.0~~ 9.0 1S (*USP38*)	~~1.0~~ 0.76 1S (*USP38*)
Nickel	~~50~~ 60 1S (*USP38*)	~~5.0~~ 6.0 1S (*USP38*)	~~0.15~~ 0.60 1S (*USP38*)
Vanadium	~~10~~ 12 1S (*USP38*)	~~1.0~~ 1.2 1S (*USP38*)	~~3.0~~ 0.12 1S (*USP38*)
Copper	~~100~~ 130 1S (*USP38*)	~~10~~ 13 1S (*USP38*)	~~10~~ 1.3 1S (*USP38*)

[a] Not a safety concern. Will be included in a future informational chapter. 1S (*USP38*)

Change to read:

ANALYTICAL TESTING

If, by process monitoring and supply-chain control, (ERR 1-Oct-2013) manufacturers can demonstrate the absence of impurities, then further testing ~~is~~ may (1S (*USP38*)) not be needed. When testing is done to demonstrate compliance, proceed as directed in general chapter *Elemental Impurities—Procedures* ⟨233⟩ and minimally include arsenic, cadmium, lead, and mercury in the *Target Element* evaluation.