

**General Chapter/Section:** <232> Elemental Impurities - Limits

**Expert Committee(s):** General Chapters—Chemical Analysis

**No. of Commenters:** 18

**Editorial changes suggested by commenters have been reviewed by the Expert Committee. Some of these changes as approved by the Expert Committee have been incorporated in the chapter. Where they have not been incorporated, the Expert Committee's response is indicated below.**

**Comment Summary #1:** The commenter suggested alignment of this chapter with ICH Q3D (pending) and EMA guidelines to avoid confusion.

**Response:** Comment incorporated. To the extent possible, the chapter has been aligned with the pending ICH Q3D document and the current EMEA guideline.

**Comment Summary #2:** The commenter requested that USP provide five years following publication of the final, official chapters for implementation of the new requirements because these new requirements will not only impact the pharmaceutical industry, but also impact external manufacturers of active ingredients, excipient manufacturers, instrument manufacturers, contract laboratories, and the FDA.

**Response:** Comment not incorporated. Notifications that the heavy metals chapter would be changing began more than five years ago, with the publication of proposed General Chapters <232> and <233> for public comment. There will be a delayed implementation date and an additional period of time between when the chapters are posted on the USP web site and the time that they are published as official, giving the industry an additional period of time during which to prepare. Given the globalization of the supply chain and a series of recent issues regarding elemental impurity contamination in drugs and dietary supplements, patient safety dictates the setting of acceptable levels for the elements specified, presentation of sensitive and specific methodology to allow the appropriate quantification, and a timely implementation period.

**Comment Summary #3:** The commenter requested clearly stating the intent of the chapter because the first and last sentences in the first paragraph (*Introduction*) clearly indicate that the limits in the chapter apply to drug products, yet the second sentence in the second paragraph implies that there is also a responsibility to detect and report impurities levels in components.

**Response:** Comment not incorporated. No change to the text was deemed necessary. The text is consistent in that compliance to the limits indicated in the chapter is only expected for a drug product, but it is important that the presence and the amount of each elemental impurity is known to the manufacturer and customers of a component of a drug product.

**Comment Summary #4:** The commenter requested clarifying that General Chapter <232> is only intended to apply to drug products, so that other industries should not extrapolate these requirements to their own products.

**Response:** Comment not incorporated. This chapter indicates the application to drug products and the exclusion of dietary supplements. Additionally, the General Notices of the *USP-NF* indicates the scope of the Pharmacopeia.

**Comment Summary #5:** The commenter requested clarifying the text under *Drug Substance and Excipients* section that states that the presence of elemental impurities in drug substances and excipients must be reported to indicate where and to whom should this should be reported.

**Response:** Comment not incorporated. A more complete description is not possible due to variable customer needs and regulatory requirements.

**Comment Summary #6:** The commenter requested adding the following footnote after the *Large Volume Parenterals* subsection heading to reference the ICH definition. This footnote will link this chapter with the other USP General Chapter ~1/ Injections:

Footnote: \*ICH Q3D defines a large volume parenteral as an injection for which the total daily dose is greater than 100 mL.

**Response:** Comment not incorporated because the chapter already contains this definition.

**Comment Summary #7:** The commenter requested including text similar to the statement in USP General Chapter <467> Residual Solvents, Table 2 because the average adult weight exceeds 50 kg in United States.

**Response:** Comment not incorporated. Average weight is a fixed number that is used by Toxicologists to arrive at a uniform Permissible Daily Exposure.

**Comment Summary #8:** The commenter requested allowing higher PDEs and concentration limits in cases of short-term use (30 days or less), or for products for life-saving indications. ICH Q3C Guideline for Residual Solvents considers this approach as well. Such higher PDE's and concentration limits are justified on a case by case basis.

**Response:** Comment not incorporated. USP monographs do not indicate nor do they consider typical dosing strengths, intervals, or durations. Such considerations may be discussed with the appropriate regulatory body as a rationale for relief from this standard.

**Comment Summary #9:** The commenter suggested differentiating between chronic and short term use because this would result in PDEs and concentration limits based on a safer and sounder scientific ground and make implementation of the monograph easier. Products for chronic use and/or large quantities administered (e.g., solutions for parenteral nutrition) make compliance with limits based on toxicological considerations unfeasible due to limitations of the technologies.

**Response:** Comment not incorporated—see the answer to Comment #8 above. Note also that solutions for parenteral nutrition are specifically addressed by the large volume

parenteral section of the chapter and the limits are well within the capabilities of current measurement technologies.

**Comment Summary #10:** The commenter requested assigning an exposure factor for Topicals and Dermals of greater than 1 because this route of administration has a much lower potential for exposure than do Oral and Mucosal routes.

**Response:** Comment not incorporated. Exposure factors have been removed from General Chapter <232>, but the discussion surrounding the appropriate limits for topical administration has been extensive and continues in the Expert Panel. If changes are indicated at a later date, then a revision will be considered.

**Comment Summary #11:** The commenter indicated concerns with the inclusion of the additional routes of administration in the chapter, beyond “Oral” and “Parenteral” and requested that further details be provided regarding inclusion of “Inhalation”, “Mucosal”, and “Topicals and Dermals”, and the rationale for the proposed “Exposure Factor”.

**Response:** See the response to Comment #10 above.

**Comment Summary #12:** The commenter requested changing the title of Table 3 from “default limits” to “suggested minimum limit” as the intention of this listing is to aid in discussions between drug product and drug substance/excipient manufacturers,

**Response:** Comment not incorporated. Table 3 has been revised and renumbered as Table 2. Limits listed in Table 2 are based on the assumption of 10 g daily dose and can vary depending on the daily dose. Most drug products have a maximum daily exposure much lower than these values. The table is intended to serve as a starting point for further discussions between drug substance / excipient manufacturers and the drug product manufacturer. This table was added in response to the comments received from the drug substance/excipient manufacturers.

**Comment Summary #13:** The commenter requested deleting Table 3 because its inclusion will give suppliers of these materials a false sense of the true requirements.

**Response:** Comment not incorporated—see the response to Comment #12 above.

**Comment Summary #14:** The commenter requested that USP harmonize with the Ph. Eur. and ICH Q3D in relation to EMA cumulative sub-class limit for group 1B (Ir, Os, Rh, Ru – the total parenteral PDE not to exceed 10 µg/day). If conducted as a limit test, the testing limits for each of the four members of the sub-class would need to be 25% of the additive class limit, in order to determine if the required cumulative limit was being met.

**Response:** Comment incorporated—see the response to Comment #1 above.

**Comment Summary #15:** The commenter requested that the Chromium in Table 2 be footnoted to specify the limit as Chromium (+6), and *Speciation* section be updated to include a discussion of the oxidation states of Chromium.

**Response:** Comment not incorporated. The oxidation state of Chromium was thoroughly discussed by the Expert Panel and the need for speciation of Chromium was

considered to be unnecessary due to the extremely rapid conversion rate of Chromium (VI) to Chromium (III) *in vivo*. The USP Expert Committee willing to consider a future revision if data support tighter limits.

**Comment Summary #16:** The commenter requested removing the following text: "Exceptions for pediatric or special populations that lower the PDE should be reflected in the limits in the appropriate monographs." The interpretation and application of this caveat is unclear, and will introduce the analytical challenges unique to LVP's.

**Response:** Comment incorporated.

**Comment Summary # 17:** The commenter requested that the *Drug Product Analysis* option also be permitted for parenterals with an intended maximum dose of greater than 10 mL and not more than 100 mL.

**Response:** Comment not incorporated. The Expert Committee incorporated this approach to reduce the testing burden on the parenterals manufacturing industry. As volumes of injections increase, the limit concentrations associated with the PDE become increasingly lower and more difficult to meet. To further aid the industry, USP will include a limit of elemental impurities in either the *Water for Injection* or the *Sterile Water for Injection*. With these limits, a manufacturer can be assured that the water will not contribute a significant amount of impurities to the total, which would then be discounted. A user would therefore only be expected to ensure control of the active and other inactive ingredients that would be present.

**Comment Summary # 18:** The commenter requested clarifying the *Speciation* section by adding the word "specific" to the last sentence right before monograph to clarify that this statement is referring to a specific article.

**Response:** Comment not incorporated. Adding the word "specific" would not add additional clarity.

**Comment Summary #19:** The commenter requested removing the reference to special or pediatric populations because the statement is not specific and could lead to compliance issues due to differences in opinions of what products the statement would apply to and what an acceptable limit(s) would be.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter requested adding PDEs for children and neonates to the chapter.

**Response:** Comment not incorporated because special populations are not addressed in <232>.

**Comment Summary #21:** The commenter requested replacing "validated processes" with "process monitoring" in the *Analytical testing* section.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter requested using the Institute of Medicines (IOM) published guidelines on Tolerable Upper Intake Level (UL) as the oral daily dose

PDE, and calculating the parenteral daily dose PDE by multiplying the UL for each element by the IOM estimates of the lowest oral absorption of that element.

**Response:** Comment not incorporated. Limits were established by a team of toxicologists, who considered a variety of information in making their determinations. The IOM guidelines were one of the sources used in their deliberations.

**Comment Summary #23:** The commenter requested adding other elements such as aluminum, fluoride, and iodine to the Tables.

**Response:** Comment not incorporated. Attempts were made to harmonize with the EMA and ICH, wherever possible. Additional metals are currently in discussion in several forums. As a consensus is formed, the USP will reconsider their inclusion in General Chapter <232>. An informational chapter, <1232>, is contemplated to provide recommended limits for other, less-toxic elemental impurities.

**Comment Summary #24:** The commenter requested mentioning that individuals with organ system dysfunction, especially liver and kidney, can experience toxicity with exposures significantly below the stated PDEs.

**Response:** Comment not incorporated. Not every special population can be accommodated with a general standard and therefore, special populations are not delineated in General Chapter <232>.

**Comment Summary #25:** The commenter requested including the elemental impurities classification back in the chapter and adjusting the testing requirements accordingly.

**Response:** Comment not incorporated. These classifications were deemed unnecessary in a quality-focused chapter.

**Comment Summary #26:** The commenter requested an elaboration of the statement “risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard” to allow development of not-likely-to-be-present arguments (and no routine release testing), and skip testing for present metals that are shown to be adequately controlled.

**Response:** Comment not incorporated. Discussions regarding appropriate risk-based strategies must be conducted with the appropriate regulatory body. All drug products should comply with the requirements when tested.

**Comment Summary #27:** The commenter indicated that the limit of 0.50 ppm for Cadmium in Calcium Carbonate is much lower than the levels found in the natural carbonate deposits. The introduction of this proposed limit would eliminate the ability to supply this mineral ingredient to the pharmaceutical and dietary supplements market worldwide. Therefore, it is suggested changing the individual monographs to allow for higher limits of impurities found in some mineral excipients/dietary supplements.

**Response:** The specific limit included in General Chapter <232> is 25 µg/day for oral delivery, 2.5 µg/day for parenteral delivery, and 1.5 µg/day for inhalation delivery. The PDE limits must be adjusted by the maximum daily dose to determine the limit in terms of concentration (ppm). When considered in this manner, it is likely that the drug

product in question would be found to be in compliance. However, exceptions to monograph requirements can be made via the appropriate regulatory channels.

**Comment Summary # 28:** The commenter requested replacing the language addressing veterinary products in the chapter with the following: “Articles intended for veterinary use are exempt from complying with the requirements in this Chapter, unless specific safety concerns are identified by the appropriate regulatory Agency.”

**Response:** Comment incorporated.

**Comment Summary #29:** The commenter requested that USP exclude natural mineral excipients that conform to *USP* and *NF* monographs from calculations of total elemental impurities in drug products because trace metals inherent in mineral structures are not process residues, and are not subject to control or removal in the way that residues would be. In addition, these trace elements in natural mineral excipients do not pose any risk to human health.

**Response:** Comment not incorporated. The source of a given Elemental Impurity does not change its toxicity. Because these limits are directly linked to safety, material-specific limits will not be included in the general chapter, but monograph specific exemptions may be considered by the appropriate Expert Committees.

**Comment Summary # 30:** The commenter requested that USP justify the elemental impurity limits proposed in this Chapter, and their application to natural mineral excipients, with health and safety data and a subsequent risk-based analysis that shows such application is warranted.

**Response:** Comment not incorporated. Limits were established by a team of toxicologists, who used a variety of data to make their determinations. The justification for the various limits was provided in a Stimuli to the Revision Process article and will be further elaborated through the ICH Q3D process.

**Comment Summary #31:** The commenter requested that USP provide guidance on how to reconcile the requirements in this chapter with existing specifications for As and Pb in current NF monographs.

**Response:** Comment not incorporated. The USP will work to reconcile requirements on a case-by-case basis. Monograph-specific acceptance criteria supersede the general chapter requirements.

**Comment Summary #32:** The commenter requested limiting the application of General Chapters <232> and <233> to new drug products only to avoid significant turmoil in the pharmaceutical industry.

**Response:** Comment not incorporated. USP standards are applicable to all monographs to which they apply independent of the date of regulatory approval.

**Comment Summary #33:** The commenter requested adding the component option for demonstrating compliance back in the chapter.

**Response:** Comment not incorporated. In earlier presentations of the chapter, the level of confusion caused by the inclusion of the component option led to its removal. However, the limits provided in Table 2 are consistent with the Component Option limits.

**Comment Summary #34:** The commenter requested allowing the flexibility to use any of the three options: 1) drug product, 2) summation, or 3) individual component options, to demonstrate compliance for all routes of administration to align with the precedent set in General Chapter <467> Residual Solvents and reflect the current EMEA guidance.

**Response:** Comment not incorporated—see comment #33 above.

**Comment Summary #35:** The commenter requested to better align the “Acceptance Criteria” in this chapter with the intention of the text and ICH Q6A terminology.

**Response:** Comment not incorporated. Acceptance Criteria are not provided in General Chapter <232>. Instead, PDE that are used to calculate the acceptance criteria are presented.

**Comment Summary #35:** The commenter requested reevaluating the flow of the information and use illustrative means to guide the user through the requirements, such as flow diagrams and decision trees.

**Response:** Comment not incorporated. The broad scope of this chapter makes the inclusion of a comprehensive decision tree very difficult. It is anticipated that subsequent documents will be developed either by USP or external parties. These documents will provide step-by-step instructions for users that need guidance.

**Comment Summary #36:** The use of Exposure Factor listed in table 1 and Daily Dose PDE from table 2 will not yield the same limits as listed in EMEA Guideline.

**Response:** Comment incorporated. Exposure factors were removed from General Chapter <232>. See also the response to Comment #1.

**Comment Summary #37:** The commenter requested replacing the word “validate” with “ensure” in the following sentence (summation Option): “...Before products can be evaluated using this option, the manufacturer must validate that additional elemental impurities cannot be inadvertently added through the manufacturing process.”

**Response:** Comment incorporated.

**Comment Summary #38:** The commenter requested the following revision in the section on “Analytical Testing”: “If, by validated processes and supply chain control, manufacturers can demonstrate ensure the absence of impurities, then further testing is not needed.” This is to allow flexibility for the manufacturers and the agency to determine the optimal way to ensure compliance and not limit the choices to validation and supply chain controls.

**Response:** Comment not incorporated. USP does not specify when or how often to test. However, when tested, the article must pass. The ability to ensure compliance through control strategies and the extent of testing should be discussed with the appropriate regulatory body.