

## Elemental Impurities—Comments and Responses

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**ABSTRACT** In *Pharmacopeial Forum* (PF) 34(5) (September–October 2008) the Metal Impurities Advisory Panel of the USP General Chapters Expert Committee presented a *Stimuli to the Revision Process* article that proposed a new General Chapter to replace General Chapter *Heavy Metals* <231>. The new Chapter presented a table of elements that could be limited and new approaches to evaluate those elements. Subsequently USPC initiated and participated in an Institute of Medicine workshop and hosted a separate Heavy Metals Testing Methodologies workshop. These public presentations and discussion forums yielded a large number of specific comments and suggestions from the pharmaceutical and excipient industries as well as the toxicological and regulatory fields. The comments can be broadly categorized into ten topics. This article presents a summary of these topics and the advisory panel's responses and approaches to incorporate the suggestions.

### ELEMENTAL IMPURITIES RECOMMENDATIONS

Before presenting the comment topics and responses, we present the Advisory Panel's recommendations. These recommendations include the development of four new general chapters, two additional *Stimuli* articles, and an implementation strategy that involves a *General Notices* revision and a number of monograph revisions.

#### General Chapters

The General Chapter additions include: General Chapter *Elemental Impurities—Limits* <232>, General Chapter *Elemental Impurities—Procedures* <233>, General Chapter *Elemental Contaminants in Dietary Supplements* <232>, and General Information Chapter *Elemental Impurities—Other Elements* <1232> (the name of <1232> is subject to change). The first three chapters are included in this PF, and the General Information Chapter will be developed over the course of the next few years.

**General Chapter *Elemental Impurities—Limits* <232>:** The limits presented in this Chapter are based on in-depth review of the toxicological literature and discussions involving several experts in metals toxicology. These limits are based on documented toxicity and regulatory recommendations and focus on the four most toxic and well-understood metals (Pb, Hg, As, and Cd). 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 EMEA—with the exception of iron and zinc, which were not included due to their low toxicity. This Chapter also describes three separate options for determination of compliance to the limits. These options are similar to those presented in General Chapter *Residual Solvents* <467>.

#### General Chapter *Elemental Impurities—Procedures* <233>:

The panel has determined that the procedures described in General Chapter *Heavy Metals* <231> are inadequate to provide the basis for control of the elements in <232> at their proposed limits. Instead, this chapter details two procedures and provides criteria for the approval of alternative procedures for the measurement of elemental impurities. The referee procedures, ICP-OES and ICP-MS with closed-vessel microwave digestion, are described. The choice of procedure, including the sample preparation and instrument parameters, are the responsibility of the user. The performance criteria necessary to demonstrate that an alternative procedure is equivalent to the referee procedures for quantitative determinations are described.

#### General Chapter *Elemental Contaminants in Dietary Supplements* <232>:

The limits presented in this Chapter are based on in-depth review of the toxicological literature of specific interest and impact to Dietary Supplements. These limits are based on documented toxicity and regulatory recommendations, and focus on the four most toxic and well-understood metals (Pb, Hg, As, and Cd). This Chapter also describes three separate options for determination of compliance to the limits. These oral limits and their described options for compliance are similar to those presented in General Chapter <232>. Finally, this Chapter presents several procedures for speciation of specific elements of particular concern for dietary supplements.

#### General Notices

A revision is proposed to the *General Notices* to indicate that General Chapters <232> and <233> will apply to all oral and parenteral articles in *USP–NF*. This revision is similar in content to that describing the residual solvents requirements.

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<sup>b</sup> For a list of the members of the Advisory Panel please see the Appendix.

**Stimuli Articles**

The Advisory Panel also recommended the development of two *Stimuli* articles. The first (this article) discusses the comments and responses of the panel, and the second, also in this volume of *PF*, presents the toxicological rationale for the limits presented in <232>.

**Implementation (General Notices and Monographs):**

The Advisory Panel recommends a staged approach to the implementation of the new General Chapters.

**Stage 1:** After the initial presentation of the standards in this *PF*, the Panel recommends consideration by the expert committee of a standard implementation period for the General Chapters.

**Stage 2:** The Advisory Panel recommends the adoption of the *General Notices* revision, also in *PF*, with an extended implementation date. They recommend that the committee consider an official date that coincides with the official date of the EMEA Metal Catalyst guideline (Sept. 2013).

**Stage 3:** The Advisory Panel recommends that all of the references to General Chapter <231> *Heavy Metals* be removed from *USP–NF* monographs in a manner to coincide with the official date approved for the *General Notices* revision.

**COMMENTS AND RESPONSES**

After reviewing all of the comments received to date, the authors have identified ten topics that encompass those comments. These topics include:

- Topic 1: Instrumental Details
- Topic 2: Implementation
- Topic 3: Specific Metals and Limits
- Topic 4: Using Residual Solvent Concepts
- Topic 5: Scope (Dosage Forms, Foods, Dietary Supplements)
- Topic 6: Reference Standards
- Topic 7: Imminent Threat <231>
- Topic 8: Harmonization (EDQM, EMEA, MHLW)
- Topic 9: GMPs and USP
- Topic 10: Other Comments.

In many cases, comments received from several sources are similar in nature. Therefore, individual comments are not specifically identified in this section. In addition to the comments received in response to the *Stimuli* article, the comments received at the two workshops will also be addressed in this section.

**Topic 1: Instrumental Details**

**Comment Summary 1.1:** The instruments necessary to meet the limits described can be complicated, expensive, and application dependant. Some preparations may also be dangerous. Defining a single procedure, including reagents, will not work for all applications.

**Number of Commenters:** 22

**Response:** General Chapter <233> specifically indicates that any procedure that is capable of meeting the critical validation parameters can be used. The choice of procedure, including sample preparation, instrument type and configuration, and reagents used are at the discretion of the user. The standard assumes that the user has evaluated the risk–benefit ratios of the available options and has selected the most appropriate procedure for the user's application. The referee procedures have been validated using a number of samples and the risk–benefit ratios have been evaluated. Because these procedures will be used for substances and products that have not been evaluated by the advisory panel, verification is indicated and steps that may pose health hazards have been noted. The use of multiple procedures is within the scope of a user's application of the standard.

**Comment Summary 1.2:** The instrumental requirements should be linked to the critical validation requirements and should be clearly defined.

**Number of Commenters:** 6

**Response:** The critical validation criteria necessary to define an acceptable procedure are included in General Chapter <233> and are based on the requirements for validation of a limit test and quantitative impurity procedure as described in General Chapter *Validation of Compendial Procedures* (1225).

**Comment Summary 1.3:** Several of the terms used in the proposal are confusing or are not well defined in the text. There are also specific contradictions in the text regarding precision.

**Number of Commenters:** 5

**Response:** The Advisory Panel has incorporated all of these comments in the draft Chapters. The confusing terminology has been removed, or terms have been better defined. The contradictions in the text have been resolved, and the presentation has been refined to aid in understanding.

**Comment Summary 1.4:** Clarification of the expectations for validation, ongoing verification, check standards, and spike and recovery details are requested.

**Number of Commenters:** 3

**Response:** General Chapter <233> has added clarifications that incorporate each of these suggested improvements.

**Topic 2: Implementation**

**Comment Summary 2.1:** A change that affects many monographs—as this change will—should have an extended implementation date.

**Number of Commenters:** 2

**Response:** The details of the proposed implementation approach are provided above. The Advisory Panel has recommended an extended implementation period.

**Comment Summary 2.2:** The development of this standard should be as transparent as possible, and updates should be posted on the USP Web site.

**Number of Commenters:** 5

**Response:** USP has added the progress of the development of this standard on the USP Web site in the Hot Topics section. The standard has been discussed at several open forums, and the development has been as open as possible.

**Comment Summary 2.3:** The new standard should be a screening procedure that should not quantify individual elemental impurities.

**Number of Commenters:** 2

**Response:** Although this standard may be used as a screen for impurities, it is designed to encompass the quantification of these impurities. Because of the wide range of elements and acceptance criteria, the use of a true screening procedure is not practical.

**Comment Summary 2.4:** The new standard should focus on the big four with the addition of other elemental impurities at a later date. The new standard should be limited to those metals that are expected to be present or that were added as part of the process.

**Number of Commenters:** 3

**Response:** The proposed chapters will focus on the big four and the metal catalysts defined in the EMEA guidance, except for zinc and iron. General Chapter <232> clearly differentiates between the big four and the other elemental impurities in such a way that both can exist in a single Chapter.

**Comment Summary 2.5:** Clarification of the expectations for calculations and units for calculations are requested.

**Number of Commenters:** 3

**Response:** General Chapter <232> has incorporated clarifications to each of these suggested improvements.

### Topic 3: Specific Metals and Limits

**Comment Summary 3.1:** The limits should be based on toxicology and should include only those elements that have a likelihood of being present. The rationale for the limits should be developed transparently and presented as a basis for the standard.

**Number of Commenters:** 12

**Response:** The limits have been developed by a team of toxicologists from industry, academia, ATSDR, BfArM, and FDA. The rationale for the limits for the big four is included in a separate *Stimuli to the Revision Process* article elsewhere in this number of *PF*.

### Topic 4: Using Residual Solvent Concepts

**Comment Summary 4.1:** A risk-based strategy like the one presented in General Chapter <467> is recommended. The Chapter should be referenced in the *General Notices* and should not be added to the monographs.

**Number of Commenters:** 3

**Response:** General Chapter <232> applies a risk-based approach like that of EMEA for Class 2 elements. The control of Class 1 impurities is required, but the extent of testing and the timing of that testing are the responsibility of the manufacturer. Although the Chapter does not require testing, it does require compliance for Class 1 impurities, regardless of source.

**Comment Summary 4.2:** Multiple options for the calculation of amount of impurity present like that in General Chapter <467> *Residual Solvents* should be used.

**Number of Commenters:** 5

**Response:** Three options for the calculation of measured impurities and assessment of their compliance to the limits for a drug product are included in General Chapter <232>.

### Topic 5: Scope (Dosage Forms, Foods, Dietary Supplements)

**Comment Summary 5.1:** To which articles do these standards apply? How about ophthalmics, food, preclinical supplies?

**Number of Commenters:** 6

**Response:** General Chapter <232> applies to drug substances and products including natural-source and rDNA biologics, ophthalmics, parenteral nutrients, and excipients. It does not apply to food or dietary supplements. General Chapter <2232> covers dietary supplements and dietary ingredients. Preclinical supplies are not covered by a *USP* monograph and are not within the scope of this standard.

**Comment Summary 5.2:** This standard should replace all of the other procedures for inorganic impurities in *USP–NF*, such as *Residue on Ignition*, *Lead*, *Aluminum*, *Sodium*, *Calcium*, and others.

**Number of Commenters:** 2

**Response:** Although the Advisory Panel considered the change, they determined that it was not within the scope of this revision or Advisory Panel to make a recommendation. USP will consider this proposal further.

### Topic 6: Reference Standards (RS)

**Comment Summary 6.1:** Commenters presented strong arguments both for and against the development of USP RS materials.

**Number of Commenters:** 7

**Response:** USP plans to develop standard mixtures that can be used in validation studies and for system suitability testing. USP currently has no plans to develop individual elemental impurity standards, but if a need is identified USP will consider developing such standards. When a USP standard is not available, a suitable NIST or NIST-traceable standard is recommended.

### Topic 7: Imminent Threat (231)

**Comment Summary 7.1:** There is no need to improve this standard. It has worked for a long time, there is significant uncontrolled environmental exposure, and the toxicity of these materials has not changed in the past 100 years.

**Number of Commenters:** 5

**Response:** The Advisory Panel disagrees with these comments. The current procedures in General Chapter (231) no longer represent the state of the industry, and the limits in the individual monographs are inconsistent with the recommendations of US and international regulatory authorities. The current lack of protection from environmental exposure increases the need to control those toxicants that are added with the intent of treating a medical condition or supplementing the diet. Although the toxicity of the elements has not changed in the past 100 years, our understanding of the detrimental effects of some of these impurities has increased manyfold.

**Comment Summary 7.2:** General Chapter (231) *Procedures I and III* are still usable procedures. Allow their use as a screening test.

**Number of Commenters:** 2

**Response:** Although the advisory panel considered these procedures of little value or to be an ineffective approach to the evaluation of the Class 1 impurities, provisions to allow their use have been included in General Chapter (233). Where one of the procedures has been successfully validated as described in the Chapter, then the procedure may be used for that application.

### Topic 8: Harmonization (EDQM, EMEA, MHLW)

**Comment Summary 8.1:** The limits and procedures should be harmonized with EMEA, EP, BP, and JP.

**Number of Commenters:** 5

**Response:** General Chapter (232) incorporates the limits described in the EMEA guidance as Class 2 impurities. A representative of BfArM has participated on the Advisory Panel to ensure that the standards are kept in harmony, and representatives from both EP and JP attended the USP workshop on this topic. USP is discussing these chapters with EP and JP as part of the PDG harmonization effort. The development of two chapters to replace (231) was executed on the advice of EP to allow an easier route to accomplish a harmonized standard.

### Topic 9: GMPs and USP

**Comment Summary 9.1:** The control of these elemental impurities is maintained by cGMP compliance, so testing is unnecessary.

**Number of Commenters:** 4

**Response:** The limits presented in General Chapters (232) and (2322) are the maximum amount of elemental impurities that may be present in a product or ingredient (depending upon application). The periodicity for testing, the extent of testing, and the elements included in the testing are established at the discretion of the drug product or dietary supplement manufacturer. All products are expected to comply with the standard.

### Topic 10: Other Comments

**Comment Summary 10.1:** We support the improvements proposed by USP.

**Number of Commenters:** 2

**Response:** The Panel appreciates the support of the commenters. Thank you.

**Comment Summary 10.2:** Several specific wording changes should be incorporated.

**Number of Commenters:** 5

**Response:** The changes have been incorporated.

**Comment Summary 10.3:** USP and FDA should work closely on this topic.

**Number of Commenters:** 2

**Response:** FDA toxicologists and reviewers are members of the Advisory Panel. USP staff have discussed the revisions with FDA, and copies of the proposed text have been provided to FDA before publication in *PF*.

**APPENDIX**

Members of the Advisory Panel are:

N Lewen (Chair); TL Shelbourn (Vice Chair); C Barton,  
PhD; CM Callis; SJ Dentali, PhD; AM Fan, PhD; R Frotschl,  
PhD; A Kazeminy, PhD; R Ko, PharmD, PhD; GC Turk,

PhD; R Wiens; Government Liaisons: R Blosser; M De,  
PhD; BA Fowler, PhD; JF Kauffman, PhD; and JC Merrill,  
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