USP Revision and Implementation Plan for the Elemental Impurities General Chapters <232> *Elemental Impurities—Limits*, <233> *Elemental Impurities—Procedures*, and <2232> Elemental Impurities in Dietary Supplements

Revised March 27, 2015

Background

General Chapters <232> and <233> were first published in the *Second Supplement to USP 35–NF 30* and became official on February 1, 2013. The intent was to apply the limits in <232> to all official drug products for which a monograph is provided in *USP–NF* through a new General Notices section 5.60.30. As detailed below, both <232> and <233> have since undergone various revisions, and *General Notices* section 5.60.30 was published in the *Second Supplement to USP 37–NF 32* with an official date of December 1, 2015. The revision of the official date for <232>, <233>, and *General Notices* 5.60.30 to January 1, 2018, including the initiation of the application of <232> through *General Notices*, and a delay in the omission of Heavy Metals <231> to also coincide with January 1, 2018 is the subject of this revised Implementation Plan.

General Chapters <232> *Elemental Impurities—Limits*, <233> *Elemental Impurities—Procedures*

On September 23, 2013, the Elemental Impurities Expert Panel met to review the Step 2 limits of the ICH Q3D Elemental Impurities Working Group, which were released in June 2013. At its meeting the Expert Panel recommended revisions to General Chapter <232> *Elemental Impurities—Limits* to partially align with the ICH Q3D limits. In addition, the Expert Panel recommended other minor editorial changes to both General Chapter <232> and General Chapter <233> *Elemental Impurities—Procedures*. On October 16-17, 2013 the General Chapters—Chemical Analysis Expert Committee met and endorsed the recommendations of the Expert Panel. The revisions were posted to USP's web site to provide an extended opportunity for public comment on the proposed changes in advance of its publication in *Pharmacopeial Forum* 40(2). The resulting version will become official on December 1, 2015.

General Chapter <2232> *Elemental Contaminants in Dietary Supplements*

General Chapter <2232> was published February 1, 2013 in the *First Supplement to USP 36–NF 31* and became official on August 1, 2013.

General Notices section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements

In December 2013, the Council of Experts approved *General Notices* section 5.60.30 *Elemental Impurities in USP Drug Products and Dietary Supplements*, which includes specific timing for the applicability of General Chapters <232> *Elemental Impurities–Limits* and <2232> *Elemental Contaminants in Dietary Supplements* to drug products and dietary supplements recognized in the *USP–NF*. The Council of Experts approved a revision to this section, which was published in a Revision Bulletin on March 27, 2015, specifying the new January 1, 2018 date of applicability for these General Chapters.

Revision Timeline

- **December 27, 2013:** USP posted the final version of General Notices section 5.60.30, which includes the previous date of applicability of <232> and <2232>. USP also pre-published the proposed revisions to <232> and <233> on the USP Elemental Impurities Key Issues web page

- **March 1, 2014:** USP published the proposed revisions to <232> and <233> in *PF* 40(2) [Mar.–Apr. 2014] for public comment through May 31, 2014. Comments were accepted only on the proposed revisions to the general chapters.

- **May 2014:** The General Chapters—Chemical Analysis Expert Committee balloted on the removal of General Chapter <231> *Heavy Metals*. Note that the removal of <231> was previously proposed in *PF* 39(1) [Jan.–Feb. 2013] and specified an official date that aligned with the then-intended applicability of General Chapters <232> and <2232>, which was specified in *General Notices* section 5.60.30 as December 1, 2015.

- **June 2014:**
  - The Expert Panel considered comments received on the proposed revisions.
  - The revised *General Notices* appeared in the *Second Supplement to USP 37–NF 32* with an official date of December 1, 2015.
  - A Notice of Intent to Revise regarding the omission of General Chapter <231> and its references was posted on the USP website.

- **October 2014:** The Expert Panel met to review the draft ICH Q3D Step 4 document and made recommendations regarding final revisions to revised General Chapters <232> and <233>. The Expert Panel also reviewed correspondence from industry stakeholders related to implementation of the elemental impurities standards.

- **November 2014:**
  - General Chapter <231> was published in *USP 38–NF 33* as an omission with an official date of December 1, 2015. Numerous references to <231> in individual *USP 38–NF 33* monographs were marked for deletion with official dates of December 1, 2015, which aligned with the intended applicability of <232> and <233> via *General Notices* 5.60.30.
  - The Commentary for General Chapter <231> was posted on the USP web site.
  - General Chapters—Chemical Analysis Expert Committee met to review Elemental Impurities Expert Panel recommendations and consider final revisions to revised General Chapters <232> and <233>.

- **December 2014:** Following review of stakeholder input and the anticipated approval of the ICH Q3D *Guideline for Elemental Impurities*, USP's Council of Experts Executive Committee endorsed a revision of *General Notices* 5.60.30 that would more closely align the timing of applicability of <232> with the ICH Q3D implementation timing for existing products and, in the interim, enable the use of either the current <231> approach or the new approach specified in <232>.

- **January 2015:** USP posts two Notices of Intent to Revise (*General Notices* 5.60.30, and General Chapter <231> and its references). These revisions would align the timing of applicability of <232> and <2232> with the ICH Q3D implementation timing for existing products and, in the interim, enable the use of either the current <231> approach or the new approach specified in <232>/<2232> by delaying the omission of <231>.

- **February-March 2015:** The Expert Committee ballots on the revised General Chapters <232> and <233>. The Council of Experts ballots on revisions to General Notices.

- **March 2015:**
  - USP publishes the following Revision Bulletins consistent with the *USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF*. It is anticipated that these Revision Bulletins will be published on USP's web site on March 27, 2015 and become official on April 1, 2015. These revisions subsequently will be incorporated into *USP 39–NF 34*, which publishes on November 1, 2015:
    1. Revision of General Notices 5.60.30. to postpone the implementation dates of <232> and <2232> to January 1, 2018.
    2. Revision of General Chapter <231> to postpone the date of its omission to align with the full implementation of <232>/<2232>.
    3. Revision of the monographs and general chapters that include references to General Chapter <231> to postpone the omission of these references to align with the full implementation of <232>/<2232>. The affected monographs will be posted in a list rather than as individual Revision Bulletins.
  - USP posts approved revisions of General Chapters <232> and <233> in advance of their publication in *Second Supplement to USP 38–NF 33*

- **June 2015:**
  - The approved revisions to General Chapters <232> and <233> are published in the *Second Supplement to USP 38–NF 33*, which becomes official December 1, 2015.
  - The Commentary for General Chapters <232> and <233> is posted on the USP website.

- **November 1, 2015:** *USP 39–NF 34* is published, incorporating the Revision Bulletins for *General Notices* 5.60.30, <231>, and the monograph and general chapter references to <231>.

- **December 1, 2015:**
  - The *Second Supplement to USP 38–NF 33* becomes official, including the revisions to General Chapters <232> and <233>.

- **January 1, 2018:** *General Notices* section 5.60.30 applies <232> to official drug product monographs and <2232> to official dietary supplement dosage form monographs. The omission of General Chapter <231> and its references in monographs become official.

Updates

June 1, 2015: USP posts Notice of Intent to Revise for multiple monographs and general chapters that were revised in the Second Supplement to USP 38–NF 33 to reinstate the references to General Chapter <231> Heavy Metals and specify that General Chapter <231> will remain in effect until January 1, 2018.

March 27, 2015: USP announces a revision to General Notices section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements, establishing January 1, 2018 as the new date of applicability of General Chapters <232> Elemental Impurities—Limits and <2232> Elemental Contaminants in Dietary Supplements. USP also announces a revision to General Chapter <231> Heavy Metals and its references to delay their omission until January 1, 2018. Through these revisions, USP specifies that users could either continue to utilize the current <231> approach or implement the new <232>/<2232> approaches until January 1, 2018, at which time General Chapters <232> and <2232> will be made applicable to drug product and dietary supplement monographs as described in General Notices 5.60.30 and will be required unless specified otherwise in a monograph.

In addition, USP is posting the revised versions of General Chapters <232> and <233> Elemental Impurities—Procedures that will appear in Second Supplement to USP 38-NF 33 and become official on December 1, 2015. This version of General Chapter <232> contains limits that align with the ICH Q3D Step 4 document and will be implemented as described above.

Related Events

Workshop on Metals in Pharmaceuticals and Dietary Supplements (April 28–29, 2009)

Note: The content of these presentations reflects the ideas and suggestions of the participants at the workshop. These deliberations are advisory and are not binding in any way to the Council of Experts, its Expert Committees and Advisory Panels, or USP staff.

- General Presentation
- Final Summary Session

USP Heavy Metals Testing Methodologies Workshop (April 26–27, 2008)

- Summary of USP Heavy Metals Testing Methodologies Workshop held August 26–27, 2008

Background Documents

- The Digest of Comments Received on the Stimuli Article "General Chapter on Inorganic Impurities: Heavy Metals" Published in Pharmacopeial Forum 34(5)
- The USP Advisory Panel on Metal Impurities "Draft Metals and Limits Table"

Reference Standards

Following further consideration of the new Elemental Impurities General Chapters, USP does not intend to develop associated official USP Reference Standards at this time. For information on USP's currently available reference standards, Download the latest USP Reference Standards Catalog

USP Compendial Updates

Stay informed about any Revision Bulletin to General Chapter <231> Heavy Metals through USP's free Compendial Updates email service.

Past Updates

Click on the below dates to review past updates

- January 14, 2015

  USP is announcing plans to establish January 1, 2018 as the new date of applicability of General Chapters <232> Elemental Impurities—Limits and <2232> Elemental Contaminants in Dietary Supplements. This new date is intended to align the implementation of General Chapter <232> more closely with that of the ICH Q3D Guideline for Elemental Impurities. USP has posted a Notice of Intent to Revise General Notices Section 5.60.30, which will establish this new date. USP has posted a separate Notice of Intent to Revise General Chapter <231> Heavy Metals and its references in monographs to delay their omission. Through these changes it is USP's intention that users could either continue to utilize the current <231> approach or implement the new <232>/<2232> approaches until January 1, 2018, at which time General Chapters <232> and <2232> will be made applicable to drug product and dietary supplement monographs as described in General Notices 5.60.30.

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- October 24, 2014

  The USP Elemental Impurities Expert Panel met on October 14-15, 2014 and approved a recommendation to the General Chapters—Chemical Analysis Expert Committee that General Chapter <232> Elemental Impurities—Limits be revised to align with the ICH Q3D Step 4 document to the extent possible. Separately, USP is considering potential adjustments to the elemental impurities implementation timeline as specified in General Notices 5.60.30 based on developments related to the anticipated ICH Q3D Step 4 document, and is engaging in ongoing dialogue with representatives of industry and the Food and Drug Administration on this topic.

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- October 10, 2014

USP updates Revision Plan to change anticipated publication date for revised General Chapters <232> and <233> from the First Supplement to USP 38–NF 33 to the Second Supplement to USP 38–NF 33, which publishes June 2015 and becomes official December 1, 2015.

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- July 25, 2014

USP posts a Notice of Intent to Revise regarding monographs and General Chapters affected by the omission of General Chapter <231> Heavy Metals, and an updated Revision Plan under General Chapters and Related Information above.

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- April 25, 2014

Following further consideration of the new Elemental Impurities General Chapters, USP has determined that it does not intend to develop associated official USP Reference Standards at this time.

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- December 27, 2013

USP announces the approval of General Notices section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements with an official date of **December 1, 2015**. This General Notices section will make applicable General Chapters <232> Elemental Impurities—Limits and <2232> Elemental Contaminants in Dietary Supplements as of that date, which reflects a delayed official date approved by the Council of Experts Executive Committee to allow industry more time to implement the standard and is based in part on consultations with the Elemental Impurities Advisory Group. Additional information can be found in the newly revised Revision Plan and on the General Notices page. The implementation of General Chapters <232> and <2232> also will include removal of all references to General Chapter <231> Heavy Metals from monographs and general chapters in the USP—NF. The omission of <231> is scheduled to align with the date of applicability of <232> and <2232>, which will be in Supplement 2 to USP 38—NF 33 with an official date of December 1, 2015.

In addition, USP is posting proposed revisions to General Chapters <232> and <2232> Elemental Impurities—Procedures, which will be published for public comment in Pharmacopeial Forum 40(2) with a comment deadline of May 31, 2014. The 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. In some cases, USP's proposed limits diverge from the Q3D Step 2 limits, and USP has notified ICH of these divergences via a comment letter on the Q3D Step 2 document. In addition to the changes to the limits, other editorial changes are proposed.

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- October 25, 2013

Proposed revision plan (now obsolete)

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- August 30, 2013

  Elemental Impurities Implementation Advisory Group—Meeting #2 Summary

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- June 28, 2013

  USP Elemental Impurities Implementation Advisory Group— Meeting #1 Summary Posted

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- June 7, 2013

  USP forms and appoints members to the Elemental Impurities Implementation Advisory Group. Dr. Roger Williams, EVP–CEO and Chair, Council of Experts, has appointed nine individuals to the Elemental Impurities Implementation Advisory Group. The Advisory Group was formed in accordance with the Bylaws of the USP Convention, which state, "The EVP–CEO may appoint advisory bodies to advance the work of the Council of Experts and the Convention and provide advice to staff on policy matters."

  The Elemental Impurities Implementation Advisory Group members include:

  1. Jon Clark, FDA
  2. David Gaugh, GPhA
  3. John Kauffman, FDA and ICH Q3D Rapporteur (current)
  4. David Klug, IPEC–Americas
  5. John Leighton, FDA
  6. Robert Osterberg, USP Toxicology Expert Committee
  7. John Punzi, CHPA
  8. Mark Schweitzer, ICH Q3D Rapporteur (through Step 2)
  9. Phyllis Walsh, NJPQCA

  The Advisory Group will consider implementation recommendations to USP as it relates to the General Notices provision, with the expectation that it will conclude its work expeditiously so that a new implementation date can be established. The Elemental Impurities Expert Panel, reporting to the Chemical Analysis Expert Committee, will address needed adjustments to general chapter <232> and <233>.

  Working groups of the Implementation Advisory Group already have been formed to address the following areas of focus:

  - Implementation requirements related to <232> and <233>
  - The omission of <231>
  - Special impact on manufacturers

  USP will keep stakeholders informed through web postings on the Elemental Impurities Key Issues page, including summaries of the Advisory Group's deliberations.

  For further information about the Advisory Group or the General Notices, contact Angela G. Long (agl@usp.org or 301-816-8382). For questions about the General Chapters, contact Kahkashan Zaidi (kxz@usp.org or 301-816-8269).

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- May 29, 2013

USP posts FAQs on the Implementation of USP General Chapters <232> Elemental Impurities—Limits and <232> Elemental Impurities—Procedures following the decision to defer the proposed General Notices Section 5.60.30 Elemental Impurities.

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- May 24, 2013

USP announces deferral of proposed 5.60.30 Elemental Impurities in General Notices. This proposed revision suggested a May 14, 2014 date linking General Chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures to drug product monographs in the United States Pharmacopeia (USP). As such, section 5.60.30 will not be included in the General Notices that will be published in USP 37–NF 32, and therefore there is no requirement for any drug product in the USP–NF to comply with <232> and <233> at this time. USP also announces plans to form an Advisory Group on the Implementation of General Chapters <232> and <233>.

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- January 28, 2013

Revision Bulletin re-establishing the official dates for general chapters <232> and <233> to **February 1, 2013**, following adjudication by the Council of Experts Executive Committee of the combined appeals filed by three appellants.

It is important to note that although general chapters <232> and <233> will become official on February 1, 2013, there will be no requirement for an article covered by an applicable USP–NF monograph to comply with their provisions on this date. USP's position is that until a general chapter is referenced in a monograph or in General Notices, it is not applicable to any article named in USP–NF. Typically, a standard becomes official six months after publication in a book or supplement, and implementation is required as of that official date. In this case, however, the official date is separate from the implementation date, as implementation cannot occur until the general chapters are referenced in a monograph or in General Notices.

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- November 15, 2012

November 15, 2012/Updated November 21, 2012: Notice of Postponement (Accelerated Revision History)

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- April 27, 2012

The USP Expert Panel on Elemental Impurities has revised General Chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures to address the comments received, and has forwarded the revised General Chapters to the General Chapters—Chemical Analysis Expert Committee for approval. The Expert Committee approved these General Chapters for publication in Second Supplement to USP 35–NF 30 (official Dec 1, 2012). USP intends to implement these General Chapters through a proposed provision in the General Notices

that would make the chapters applicable to all articles in the compendia, as was done with General Chapter <467> Residual Solvents in Section 5.60.20 of the General Notices. This provision will be proposed in PF 39(1) [Jan–Feb 2013] for public comment. If, after review of the comments received, the Council of Experts Executive Committee (which is responsible for the General Notices) approves this General Notices provision, it will be published in USP 37–NF 32 with an official date of May 1, 2014. If this occurs, conformance with these chapters will be required as of May 1, 2014, when the General Notices provision becomes official.

Further, the implementation approach for general chapters <232> and <233> will include removal of all references to USP General Chapter <231> Heavy Metals from monographs in the compendia. This also is being proposed in PF 39(1) for public comment, and if after review of the comments received, and the Executive Committee of the Council of Experts approves this revision, it will be published in USP 37–NF 32 with an official date of May 1, 2014, simultaneously with the proposed implementation of general chapters <232> and <233> through the new General Notices provision.

USP indicated previously that it would be moving these general chapters forward to official status after the Expert Panel and Expert Committee considered the final set of public comments and after the ICH Q3D Expert Working Group developed an initial set of elements and limits for consideration. With the exception of mercury, the limits in the revised General Chapter <232> are consistent with those in the ICH-Q3D, pre-stage 2 draft. At a future date, the Expert Panel intends to revisit General Chapter <232> relative to the Step 4 outcome of ICH Q3D deliberations. At that time the Expert Panel may add additional elements and limits to General Chapter <232> based on ICH Q3D or may develop an informational chapter to incorporate elements of low toxicity. The revised General Chapter <2232> Elemental Contaminants in Dietary Supplements has appeared in PF 38(3) for comment, and an update related to this general chapter will be posted separately on the Elemental Impurities Hot Topics page on the USP Web site.

Revisions, Commentary, and Notice:

- Notice of Postponement
- Intent to Revise Notice
- Final approved General Chapter <232> Elemental Impurities–Limits as it will appear in the Second Supplement to USP 35–NF 30
- Commentary for General Chapter <232> Elemental Impurities–Limits
- Final approved General Chapter <233> Elemental Impurities–Procedures as it will appear in the Second Supplement to USP 35–NF 30
- Commentary for General Chapter <233> Elemental Impurities–Procedures
- Notice of Intent to Revise describing the proposed new General Notices provision

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- May 26, 2011

The USP Expert Panel on Elemental Impurities has revised the general chapters concerning elemental impurity limits and procedures (<232> and <233>) and the revised proposals appeared in Pharmacopeial Forum (PF) 37(3) (May-June 2011). The Expert Panel is proposing changes in both chapters to address the comments received. These chapters are presented in the PF for an additional comment period to assure that the chapter requirements are clear to all users and to obtain any final input.

The Expert Panel intends to incorporate the elements and limits described by the International Congress on Harmonization (ICH) Q3D, employing both general chapter <232> and an informational chapter as appropriate, as these become available. However, the Expert Panel does not intend to tie the implementation of general chapter <232> to the ICH implementation time frame. Instead, the Expert Panel intends to move forward with general

chapter <232> using limits consistent with the latest available ICH Q3D recommendations and revisit general chapter <232> relative to the final outcome of ICH Q3D deliberations at a future date. The Expert Panel will recommend an appropriate official date for <232> and <233>, balancing input from FDA, industry and other stakeholders to assure timely, yet orderly, implementation of this standard. Recommendations of the Expert Panel will be presented to the Chemical Analysis Expert Committee, and be voted on by the Expert Committee in its August ballot.

Revised general chapters proposed in PF 37(3):

- <232> Elemental Impurities–Limits
- <233> Elemental Impurities–Procedures

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- October 6, 2010

The proposed new general chapters concerning elemental impurity limits and procedures (<232> and <233>), initially published in Pharmacopeial Forum (PF) 36(1), have received a number of comments that have been individually reviewed and considered by the USP Expert Panel on Elemental Impurities. Based on these comments, the Expert Panel is recommending revisions to the chapters including numerous changes in wording intended to improve the clarity of the presentation. While these changes do not change the scientific content of the chapters, the presentation has changed sufficiently that the Expert Panel is recommending presenting the chapters for an additional comment period in PF to assure that the chapter requirements are clear to all users and obtain any final input.

In the spirit of transparency, the Expert Panel is presenting its revised general chapters on the USP website with the expectation that the Expert Committee will consider them for presentation in a future PF. These general chapters are only the preliminary recommendations from the Expert Panel to the Chemical Analysis Expert Committee and do not represent a proposed standard. In addition, the Expert Panel intends to incorporate the elements and limits described by the International Congress on Harmonization (ICH) Q3D, therefore the Expert Panel will await the outcome of the November meeting before making its final recommendation on general chapter <232> to the Chemical Analysis Expert Committee. Finally, because the scientific content of the standard is not significantly different than the initial presentation, the Expert Panel recommends no change to the proposed implementation date of September 2013.

The revised chapters presented herein are:

- <232> Elemental Impurities—Limits
- <233> Elemental Impurities—Procedures

The Chemical Analysis Expert Committee is currently reviewing these recommendations and will review and consider any further recommendations from the Expert Panel regarding <232> prior to republication of the chapters in PF.

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- July 20, 2010

USP proposed three new General Chapters on Elemental Impurities Limits, Methods, and Dietary Supplements Metals Limits in the January–February issue of Pharmacopeial Forum [PF 36(1)].

Other related information also appeared in PF 36(1), including a draft General Notices statement about the applicability of the standard to all monographs and two Stimuli articles outlining the rationale for the revisions and the comments received from an original Stimuli article and Workshop.

- <232> Elemental Impurities—Limits
- <233> Elemental Impurities—Procedures
- <2232> Elemental Contaminants in Dietary Supplements
- Stimuli article Elemental Impurities—Information
- Stimuli article Elemental Impurities—Comments and Responses

These revisions focus on two areas of work:

- Updating the methodology used to test for elemental impurities in drugs and dietary supplements to include procedures that rely on modern analytical technology; and
- Setting limits for acceptable levels of metal impurities (including, but not limited to, lead, mercury, arsenic, and cadmium) in drugs and dietary supplements.

The USP Metal Impurities Expert Panel, which will report to the USP Chemical Analyses Expert Committee in the new USP cycle, worked with USP staff and stakeholders to assess methodologies and limits that provide greater patient/consumer protection and can reasonably be deployed across industry laboratories. The limits for exposure are toxicologically based and developed by an expert consensus process to provide quality standards that reflect consensus views about potential health/toxicity concerns.

These new approaches are intended to replace the existing methods in General Chapter <231> Heavy Metals. Deadline to submit comments to USP ended on April 15, 2010. The USP Metal Impurities Expert Panel is currently reviewing comments and will propose a revision to these chapters in the next available PF. Although the official comment period has ended interested parties are encouraged to submit data at any time to Kahkashan Zaidi, Ph.D., Senior Scientific Liaison, General Chapters, Division of Standards Development (kxz@usp.org).