



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.