Council of Experts Executive Committee
Special Meeting #2 on Elemental Impurities Appeals Requests
Monday, January 7, 2012
10:00 a.m.–1:00 p.m. (Eastern Time)
Via WebEx

Minutes–Redacted

Attendees

USP Council of Experts Executive Committee Members

1. Roger L. Williams, M.D., Chair, Council of Experts
2. James E. Akers, Ph.D., Chair, General Chapters–Microbiology
3. Gregory E. Amidon, Ph.D., Chair, General Chapters–Physical Analysis
4. Lawrence H. Block, Ph.D., Chair, Monographs–Excipients
5. Matthew W. Borer, Ph.D., Chair, Reference Standards
6. Michael A. Cutrera, M.Sc., Chair, Monographs–Small Molecules 4
7. Gigi S. Davidson, R.Ph., DICVP, Chair, Compounding
8. Mary Foster, Ph.D., Chair, General Chapters–Packaging, Storage, and Distribution
9. Jean F. Huxsoll, Ph.D., Chair, Monographs–Biologics and Biotechnology 2
10. Michael G. Mulkerrin, Ph.D., Chair, Monographs–Biologics and Biotechnology 1
11. Bernard Olsen, Ph.D., Chair, Monographs–Small Molecules 3
12. Robert E. Osterberg, Ph.D., Chair, Toxicology
13. Ernest Parente, Ph.D., Chair, Monographs–Small Molecules 2
14. Thomas P. Reinders, Pharm.D., Chair, Nomenclature, Safety, and Labeling
15. Maria Ines Santoro, Ph.D., Chair, Medicines Compendium–Latin America
16. Robert Singer, M.S., Chair, Statistics
17. Glenn A. Van Buskirk, Ph.D., Chair, Monographs–Small Molecules 1
18. Wesley E. Workman, Ph.D., Chair, General Chapters–Biological Analysis
19. Timothy J. Wozniak, Ph.D., Chair, General Chapters–Chemical Analysis

Unable to Attend

James E. De Muth, Ph.D., Chair, General Chapters–Dosage Forms
Andrew G. Ebert, Ph.D., Chair, Food Ingredients
Antony Raj Gomas, Ph.D., Chair, Medicines Compendium–South Asia
Dennis K.J. Gorecki, Ph.D., Chair, Monographs–Dietary Supplements
Dhananjay B. Patankar, Ph.D., Chair, Medicines Compendium–Biologics
Jiasheng Tu, Ph.D., Chair, Medicines Compendium–East Asia

Invited Guests

Jon Clark, M.S., Associate Director for Policy, FDA
John Kauffman, Ph.D., Research Chemist, FDA
Nancy Lewen, Chair, Elemental Impurities Expert Panel
Paul Seo, Ph.D., Director, Compendial Operations, FDA
Tim Shelbourn, M.S., MBA, Vice Chair, Elemental Impurities Expert Panel

USP Staff

Susan S. de Mars, J.D., Executive Vice President and Chief Legal Officer

V. Srini Srinivasan, Ph.D., Executive Vice President, Global Science and Standards Division
Todd Cecil, Ph.D., Vice President, Chemical Medicines, Medicines Compendium
Anthony J. DeStefano, Ph.D., Senior Vice President, General Chapters and Healthcare Quality Standards
Shawn Dressman, Ph.D., Vice President, Chemical Medicines, *USP-NF*
Ben Firschein, Director, Government Affairs
Angela G. Long, M.S., Senior Vice President, Global Alliances and Organizational Affairs
Tina S. Morris, Ph.D., Vice President, Biologics & Biotechnology, *USP-NF*
Laura Provan, Director, Public Relations
Karen Russo, Ph.D., Vice President, Portfolio and Project Management
Mario Sindaco, M.S., MBA, Director, Compendial Affairs
Marie Temple, Executive Secretariat Liaison
Matthew Van Hook, Vice President and Assistant General Counsel
Kahkashan Zaidi, Ph.D., Senior Scientific Liaison

1. Opening and Procedural Matters

a. Roll Call, Quorum

Ms. Long welcomed attendees. Mr. Sindaco called roll and determined that 19 of the 25 members of the Council of Experts Executive Committee (CoE EC) were present.

b. Call Meeting to Order, Purpose of Meeting

Dr. Roger Williams, Chair of the CoE EC, called the meeting to order at 10:10 a.m. and welcomed the attendees to the second CoE EC Special Meeting on Elemental Impurities Appeals Requests. Attendees included members of the CoE EC as well as invited guests. The meeting pertained to three separate appeals of USP General Chapters <232> *Elemental Impurities–Limits* and <233> *Elemental Impurities–Methods.* Background material available to members was provided separately via electronic transmission.

c. Review of Special Meeting #1 Decisions and Approval of Minutes

Dr. Williams explained that, at its November 9, 2012 meeting, the CoE EC decided to:

- Allow the appeals related to General Chapters <232> and <233> to proceed,
- Deny the appeal related to the implementation of the General Chapters through a proposed *General Notices* provision,
- Consider the appeals as a single group,
- Postpone the official dates of the General Chapters pending the appeal, and
- First consider the appeal through a documentation review and then decide if an oral hearing is needed to obtain further information for a final determination and adjudication.

Ms. Long explained that General Chapters <232> and <233> were published in *USP 35–NF 30, Second Supplement,* with a December 1, 2012 official date. This official date was postponed pending the adjudication of the appeal by the CoE EC.

Dr. Williams asked CoE EC members to approve the previous meeting minutes. He noted that minor typographical errors will be corrected. CoE EC members did not provide any additional edits.

Vote: By voice vote, the CoE EC unanimously approved the previous meeting minutes with no abstentions.

Action Item 1: Correct typographical errors and finalize the previous meeting's minutes. (USP Executive Secretariat Staff)

d. Review Appeals Process and Objectives of Meeting #2

Ms. Long reviewed the *Management of USP Appeal Requests and Appeals* (November 5, 2012) provided in the briefing materials. She noted the following meeting objectives:

- Begin the adjudication process
- Review the standards-setting record and appeals documentation
- Determine the need for an oral hearing

e. Declaration of Potential Conflicts of Interest

Ms. de Mars clarified that CoE EC members should declare conflicts before discussion begins. If a member is uncertain whether a particular interest presents an actual conflict, the member should disclose said interest for consideration. Conflicted members may be asked to abstain from voting (see item 4), but may participate in discussion.

Mr. Sindaco again called roll and asked CoE EC members to declare any conflicts. The following members declared potential conflicts for consideration:

- Dr. [redacted]
- Dr. [redacted]
- Dr. [redacted]
- Dr. [redacted]

Ms. Long added that Dr. Wozniak in accordance with USP requirements will abstain from all voting because he chairs the General Chapters–Chemical Analysis Expert Committee (CA EC) that made the formal decisions on these standards.

f. Rules and Procedures and Issues to be Considered

Ms. de Mars explained that the CoE EC would consider the following issues at this meeting:

Issue 1: Whether the CA EC and the Elemental Impurities Expert Panel (EI EP) appropriately followed USP processes and adequately considered appellants' prior comments on the general chapters before determining the final standards.

Issue 2: Whether the appellants have submitted any new scientific data or evidence in their appeals that was not previously available to the CA EC/EI EP that may have altered the determinations reached by the CA EC/EI EP.

Issue 3: Whether, even if there is no cause to reconsider the general chapters under Issues 1 or 2 above, the official dates of the chapters should continue to be postponed so that these dates can be aligned with the implementation of the chapters.

Ms de Mars noted the proposed May 2014 implementation date was not an issue for this meeting. The CoE EC will discuss the implementation date after comments have been received on the proposed implementation through the *General Notices* provision published in *PF* 39(1).

2. Scientific Review of General Chapters <232> and <233>

a. Standard-setting Record

Dr. Zaidi, Scientific Liaison for elemental impurities general chapters, explained that although General Chapter <231> *Heavy Metals* has been in the *USP-NF* since 1905, few changes were made to the chapter prior to 1975. She summarized the history of USP elemental impurities standards from 1975 to the present (see briefing materials), including the following highlights:

- 1975: In a *PF* Stimuli article, the Heavy Metals Task Force identified issues and recommended that Method I be replaced by the three-tube monitor procedure, and that all future monographs specify Method II for heavy metals determinations.
- 1991–1993: Stimuli articles and revisions addressed the Magnesium Stearate monograph, including the deletion of the colorimetric Lead test and the addition of atomic absorption tests for Cadmium, Lead, and Nickel. The current Magnesium Stearate monograph contains harmonized methods to detect Cadmium, Lead, and Nickel.
- 1995: A significant Stimuli article by Katherine Blake compared heavy metals testing methodologies of the *USP-NF*, *European Pharmacopoeia (Ph.Eur.)* and *Japanese Pharmacopoeia*. Another Stimuli article presented the results of a USP survey to obtain maximum daily intake data for 28 frequently used excipients.
- 1998: USP revised Method II and added a statement that the procedure does not recover Mercury.
- 2000–2005: The Pharmaceutical Analysis 6 Expert Committee (PA6 EC) initiated USP laboratory work to determine an alternative sampling method. The PA6 EC then formed a working group to address issues more closely and prepare other methodology.
- 2003–2004: Three Stimuli articles proposed consideration of inductively coupled plasma (ICP) methods for heavy metals testing
- 2003–2005: Five revisions were completed.
- 2006: USP reverted to an older method because of issues with the revised methods.
- 2005–2010: The Heavy Metals Advisory Panel was formed and included European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) representatives. Panel members initiated work in their own laboratories and published a Stimuli article covering 32 elements with ICP as the method of choice.
- 2008 and 2009: In response to stakeholder requests, USP held two elemental impurities workshops.
- 2010: The CA EC proposed three new chapters in *PF*: General Chapters <232>, <233>, and <2232> *Elemental Contaminants in Dietary Supplements*. Comments on these proposals did not include any new information.
- 2011: The CA EC published General Chapters <232> and <233> in *USP 35–NF 30* with a December 1, 2012 official date.

Dr. Zaidi also noted that ICH formed an Expert Working Group (EWG) to consider elemental impurity elements and limits in 2009, after the USP Stimuli article and proposed chapters had been published. USP is an EWG observer. The final USP chapters published in 2011 include the ICH Q3D impurities limits, except mercury (the CA EC did not agree with the ICH limit). The EI EP will consider limits proposed in the ICH Q3D pre-Step 2 draft at its January 28–29, 2013 meeting.

b. Expert Panel Perspective

Ms. Lewen, Chair of the EI EP, provided the following comments.

- The Expert Panel includes expert toxicologists from all over the world; elemental impurities limits were based on their input.
- When the first Advisory Panel was convened in 2005, a USP Project Team with industry experts was also working on elemental impurities. The Project Team was dissolved because its approach matched the Expert Panel's approach.
- Over the last ten years, USP sought feedback at numerous external meetings, including plasma spectrochemistry conferences; the Spectroscopy Society of Pittsburgh and the Society for Analytical Chemists of Pittsburgh (Pittcon) Conference and Expo; and American Association of Pharmaceutical Sciences meetings.
- At the 2009 USP Metals in Pharmaceuticals and Dietary Supplements Workshop, EI EP members attended as observers and listened to attendee feedback. After the workshop, EI EP members met to consider the comments.

Ms. Lewen emphasized that the Expert Panel carefully considered all comments.

Dr. Williams thanked Ms. Lewen and the Expert Panel for their work.

c. Expert Committee Perspective

Dr. Wozniak described the challenge faced by the EI EP in writing a legal standard, not a guideline. Many appellant and public comments focused on issues such as acute vs. chronic and oral vs. parenteral, topics that were appropriate for a guideline but not feasible for a legal standard. Commenters also expressed concern that the standard would be applied to cosmetics and personal care products, even though the standard is not applicable to those products.

Discussion

An FDA representative noted that the ICH Q4B document is not ready for Step 2 public comment, but rather is a pre-Step 2 draft. Dr. Williams noted that, although the limits could be reconsidered to align with ICH revisions, an ICH Step 2 document is not available for formal consideration.

3. Appellant Concerns

a. Overview

Dr. Zaidi explained the following:

- The General Chapter <232> requirements only apply to drug products. Excipients and active pharmaceutical ingredients do not need to meet the limits, but impurity levels in products containing these ingredients should be determined.

- In General Chapter <232>, limits for 11 of the 15 elements listed are from the 2008 EMEA guidance. Limits for the "big four," (i.e., Lead, Cadmium, Mercury, and Arsenic) are aligned with the previous ICH Q3D draft. The EI EP will consider revised ICH Q3D limits at its January 2013 meeting.
- In General Chapter <233>, two procedures are based on ICP techniques. The validation and verification section of this chapter provides specific guidance relevant to the *USP-NF* or alternative procedures.

Dr. Zaidi emphasized that, although comments were received on both chapters over the past four years, none of the comments were new. The Expert Panel had considered all of the comments in the past.

b. Appellant Comments and Expert Panel Consideration

Dr. Zaidi presented a table containing the appellants' comments and concerns, dates that the comments were received, dates that the comments were reviewed by the Expert Panel, and the outcome of the Expert Panel's assessments. She noted that several comments received from industry and IPEC were very similar. The comments could be grouped into three categories:

1. Bioavailability and bioaccessibility
2. Dosing strength: chronic and short term use of product
3. Implementation timeline

Dr. Zaidi reviewed each set of comments and provided the following additional details:

- USP began stakeholder outreach before the chapters became official. Industry trade representatives were present at all of the USP workshops and stakeholder forums. These representatives had the opportunity to reach out to their members. USP also made many public presentations to inform stakeholders and obtain their feedback.
- USP has not received any bioavailability and bioaccessibility data for specific products. Such data could be accommodated through *USP-NF* monographs.

Final *Commentary* containing USP's official responses to the comments was sent to CoE EC members prior to the meeting.

Attendees provided the following comments:

- General Chapter <232> largely concurs with the EMA guideline. Appellants have not expressed concerns with complying with the EMA limits.
- Some appellant objections might be resolved by revising General Chapter <232> to focus only on oral and parenteral products.
- EMA and ICH activities help justify the revisions, suggesting that a mandate for the new standards exists.

c. Rationale for Official Dates and Implementation Dates

Dr. DeStefano explained the following:

- The December 1, 2012 official date follows USP's established processes and accommodates manufacturers that want to start using newer technologies.
- General Chapters <232> and <233> are not currently mentioned in any monographs or the *General Notices* and therefore do not create mandatory requirements.

- Manufacturers or other bodies may adopt General Chapters <232> or <233> at any time according to the early adoption provisions of *General Notices* Section 3.10. *Applicability of Standards:*

  Early adoption of revised standards is allowed. Where revised standards for an existing article have been published as final approved "official text" (as approved in section 2.10) but are not yet official (six months after publication, unless otherwise specified; see "official date," section 2.20) compliance with the revised standard shall not preclude a finding or indication of conformance with USP official standards, unless USP specifies otherwise by prohibiting early adoption in a particular standard.
- The official date for the EMA limits is September 2013.

4. Executive Committee Discussion and Decisions

Ms. de Mars reviewed conflict of interest provisions pertaining to Expert Committees (ECs) and Expert Panels in the Rules and Procedures of the 2010–2015 Council of Experts (included in the briefing materials). She explained that for the purposes of these deliberations, CoE EC members employed by companies affected by the standard do not need to recuse themselves, but may if they choose. If a member has had any personal active involvement in the appellant's activity related to the appeal or if the member's company has been directly involved in the appellant's activity directly related to the appeal, however, the member may participate in discussion but must recuse himself or herself from the vote.

Dr. Williams asked for forthright dialog and encouraged members to express opinions as they deem appropriate. He emphasized that the deliberations and all attendee comments are confidential pending USP's decision to speak publicly in the matter.

The CoE EC then considered each issue and the related options.

Issue 1: Adherence to the Standards-setting Process

Dr. Williams asked the CoE EC to consider whether the CA EC and EI EP appropriately followed USP processes and adequately considered appellants' prior comments on the general chapters before determining the final standards.

Vote 1: By unanimous consent, the CoE EC decided that comments were adequately considered.

Vote 2: By unanimous consent, the CoE EC decided that processes were appropriately followed.

The CoE EC then considered Option 1, which stated:

Option 1: Rule in favor of appellants based on a finding that USP processes were not appropriately followed and appellants' comments were not adequately considered by the CA EC/EI EP and continue the postponement of the official dates of General Chapters <232> and <233> to allow further consideration of appellants' substantive objections to the standard. Remand the general chapters to the CA EC/EI EP to reconsider appellants' comments.

Consensus Decision: By deciding that comments were adequately considered and processes were appropriately followed, the CoE EC rejected Option 1.

Issue 2: Availability of New Data or Evidence
Dr. Williams asked CoE EC members to consider whether the appellants have submitted any new scientific data or evidence in their appeals that was not previously available to the CA EC/EI EP that may have altered the determinations reached by the CA EC/EI EP.

Vote 3: By unanimous consent, the CoE EC decided that no new scientific evidence or data was submitted that was not previously available to the Expert Panel.

The CoE EC then considered Option 2, which stated:

Option 2: Rule in favor of appellants based on a finding that appellants have provided new scientific data and evidence not previously available and continue the postponement the official dates of General Chapters <232> and <233> to allow consideration of this new data and evidence. Remand the general chapters to the CA EC/EI EP to consider this new data and evidence.

Consensus Decision: By deciding that no new scientific evidence or data was submitted, the CoE EC rejected Option 2.

Issue 3: Official Dates
Dr. Williams asked the CoE EC to consider whether, even if there is no cause to reconsider the general chapters under Issue 1 or Issue 2 above, the official dates of the chapters should continue to be postponed so that these dates can be aligned with the implementation of the chapters.

Dr. Williams explained the following:

- The December 1, 2012 official date was postponed pending adjudication of the appeals.
- The *General Notices* revision that was recently published in *PF* for public comment would make the General Chapters applicable to all monographs when it becomes official on May 1, 2014. Approval of this revision will be based on the CoE's review of comments received and final CoE ballot, which will occur after the comment period closes on March 31, 2013.
- The focus of this discussion is whether the December 1, 2012 official date should continue to be postponed.

Ms. de Mars clarified the following:

- Since the chapters have already been published in *USP-NF*, the *General Notices* early adoption provision applies despite the postponement (see item 3c). Early adoption is already possible and is not germane to this discussion. Continued postponement would not prevent a manufacturer from using the unofficial chapters.
- An unusual aspect of this revision is that the chapters will not be required until they are referred to in the *General Notices* or monographs.

CoE EC members provided the following comments:

- Manufacturers may refer to the General Chapters in their private standards and implement them now for new products. Staff clarified that implementation for older products would not occur until the chapters are referenced in the *General Notices* or specific monographs.

- The postponement could be continued until after ICH meets in June 2013. An FDA representative emphasized that the draft ICH document is not yet at Step 2. Staff added that the final Step 4 ICH document is not expected until 2014.
- ICH's actions are not pertinent to USP's actions. The new chapters are needed now because current elemental impurities standards cannot differentiate between safe and unsafe products. USP has been working on this issue for many years, and ICH began considering these issues fairly recently. Further delay could put patients at risk.

The CoE EC then considered Options 3 and 4, which stated:

Option 3: Rule in favor of appellants based on a finding that while the CA EC/EI EP appropriately followed its processes and adequately considered appellants' comments and no new data or evidence has been submitted that justifies further consideration by the CA EC/EI EP, the official dates of the general chapters nevertheless should continue to be postponed to align with their implementation date. Once the *General Notices* provision implementing the general chapters has completed the notice and comment process, and the CoE EC (as the Committee responsible for *General Notices*) has made a determination as to this provision and implementation of the general chapters, the official dates of the general chapters can be established to accord with the official date of the *General Notices* provision.

Option 4: Rule against the appellants, finding that the CA EC/EI EP appropriately followed their processes and adequately considered appellants' comments and there is no new data or evidence available that justifies further consideration by the CA EC/EI EP. Establish an official date for the general chapters, ending their postponement.

USP staff clarified the following:

- A vote for Option 3 would be a partial ruling in favor of the appellant and continue the official date postponement.
- USP standards do not usually have different official and implementation dates. In most cases, these dates are the same, and implementation can be delayed by delaying the official date. General Chapter <467> Residual Solvents is a rare example of a chapter with different official and implementation dates, and that was because that chapter also was implemented through a separate *General Notices* provision.
- Manufacturers needed time to develop analytical procedures for their articles to conform to the new, more rigorous standards. The original targeted implementation date of September 2013 had aligned with the publication of the EMA limits. The date was changed to May 2014 to align with USP's publication of *USP 37–NF 31*.

CoE EC members provided the following comments:

- If the official date postponement is continued, then it may make it more likely that the implementation date also would be delayed. Reinstituting an official date would lend weight to the May 2014 implementation date.
- USP should not wait for the *ICH Q3D* limits to be finalized.
- If the official date was revised to match the implementation date, industry may want more time to implement the standard.

- Continued postponement would create uncertainty and confusion in the marketplace. Manufacturers would not know when the standard would become official.
- Removing the postponement and denying the appeal could result in more stakeholder feedback.
- USP should clearly communicate the meaning of official and implementation dates.

Vote 4: By voice vote with 18 members voting, a majority of the CoE EC did not approve Option 3, with two members voting to approve. Drs. [redacted] abstained for the reasons described above.

Vote 5: By voice vote, the CoE EC unanimously adopted Option 4. Drs. [redacted] abstained for the reasons described above.

Official Date: Ms. de Mars noted that the new official date should allow enough time to communicate the appeal results. Staff confirmed that a February 1, 2013 official date would allow enough time for this communication. CoE EC members agreed that the official date should allow as much time as possible before the proposed May 2014 implementation date.

Vote 6: By voice vote, the CoE EC unanimously adopted February 1, 2013 as the new General Chapters <232> and <233> official date. Drs. [redacted] abstained for the reasons described above.

Action Item 2: Prepare communications regarding the appeal results and the new February 1, 2013 official date for General Chapters <232> and <233>. (USP Executive Secretariat, General Chapters, and Legal staff)

5. **Final discussion**
   Ms. de Mars emphasized that it was critical for all attendees to maintain the confidentiality of the discussion and decisions until further notice.

Dr. Williams thanked the CoE EC for a deliberative discussion and vote. The meeting adjourned at 12:55 p.m. by consensus

Summary of Decisions

The CoE EC:

1. Decided that previous comments were adequately considered and USP processes were appropriately followed, and rejected Option 1.
2. Decided that no new scientific evidence or data was submitted that was not previously available to the Expert Panel, and rejected Option 2.
3. Approved Option 4, determining to end the postponement of the General Chapters.
4. Established official date of February 1, 2013 for General Chapters <232> and <233>.

Summary of Action Items

1. Correct typographical errors and finalize the previous meeting's minutes. (USP Executive Secretariat Staff)
2. Prepare communications regarding the appeal results and the new February 1, 2013 official date for General Chapters <232> and <233>. (USP Executive Secretariat, General Chapters, and Legal staff)