Recommendations to the General Chapters Expert Committee
by the Metal Impurities Advisory Panel
for Metal Impurities Standards
April 30, 2009
Revised June 4, 2009

1. **The Metal Impurities Advisory Panel and USP Staff will undertake the following activities to fully elaborate the Metal Impurities Standard.** Except as otherwise indicated, the Advisory Panel will target the presentation of these elements in the **January-February *Pharmacopeial Forum (PF)* 36(1):**

   a. General Chapter <232> - Elements and Limits
   - Arsenic, Cadmium, Lead, Mercury (the "Big Four")
   - EMEA Metal Catalysts, including their scope as outlined in the EMEA Guideline (12 Catalysts; EMEA list with EMEA limits, less iron and zinc).
   - Include metals and limits for pharmaceuticals only (see Recommendation #2 below for dietary supplements).
   - Establish multiple options for limit calculation following the residual solvent model.
   - This General Chapter will be presented to the PDG for harmonization.

   b. General Chapter <233> - Methods
   - Provide a performance-based framework, with defined acceptance criteria and validation requirements.
   - Provide two default (not referee) procedures (ICP-OES and ICP-MS) if the user has no other procedure.

   c. General Chapter <1232> - Rationale for Metal impurity limits in <232>:
   - Present a detailed rationale for toxicity limits proposed in <232>. Provide level of detail similar to what is provided in the EMEA Guideline.
   - Consider adding a table with additional elements and limits, with accompanying rationale, as guidance for cases where multi-element methods show elements not included in <232>.

   d. A *Stimuli* article explaining these approaches and addressing public input
   - Responses to comments received on *PF* 34(5) *Stimuli* article and at Workshop.

   e. A General Notices Statement
   - USP is working on a set of revisions to General Notices that are expected to be published in *PF* 36(1) for comment. Included in the revisions will be a statement regarding the applicability of the metal impurities standard to all monographs and recognition of a separate metal impurity and limits chapter for dietary supplements.

2. **A General Chapter on metal impurities and limits for dietary supplements (>2000) similar to the General Chapter <232> Elements and Limits with some modification appropriate for botanical products as determined by the Dietary Supplements General Chapters Expert Committee.**

3. **Reference Materials**
   - USP will allow use of NIST-traceable standards for individual elements as calibration standards. USP will explore providing USP Reference Standard mixtures (e.g., a ratio mixture of the "big four" elements), to help users implement the standard.

4. **Key Assumptions for Establishing the Metal impurity Toxicity Limits:**
   - 10g dose for drug products and dietary supplements (aligned with EMEA and Residual Solvents)
   - 50kg person (aligned with EMEA)
   - Permissible Daily Exposures (PDE) will need to be monitored on a regular basis and updated as needed
   - USP accepts the EMEA levels, and communicates potential issues to EMEA
   - Limits will be expressed as concentration (ppm) and PDE

5. **Issues to be Resolved via New or Revised Individual Monographs as Relevant to the Article**
   - Speciation
   - Limits for routes of administration other than parenteral and oral
   - Cases in which articles are found (or need) to have inherently high metal impurity levels