



**General Chapter on Inorganic Impurities: Heavy Metals**  
USP Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals and  
USP Staff\*

*The following Stimuli article is provided to interested parties in advance of publishing in the September-October Pharmacopeial Forum 34(5). You may send comments on this article to Kahkashan Zaidi, PhD, Senior Scientist, Documentary Standards Division, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8269; e-mail [kxz@usp.org](mailto:kxz@usp.org). The deadline for comments is **December 15, 2008**.*

**ABSTRACT** In the ICH Q3A *Impurities in Drug Substances* guidance, impurities are classified as organic, inorganic, and residual solvents. Within the inorganic impurities classification, the metals listed in *Table 1* are important to control in food, dietary supplements, and drug articles. Many toxic metal impurities found in pharmaceutical articles have been controlled for years by application of the Heavy Metals test described in *USP–NF General Chapter Heavy Metals <231>*. However, the procedures and the methods contained in <231> lack the sensitivity, specificity, and recovery to monitor properly the levels of these metals. A number of additional chapters for the control of specific metals and other inorganic impurities are contained in *USP–NF*. This *Stimuli* article proposes a new *USP General Chapter* for the control of inorganic impurities in drug and dietary supplement articles intended for use in humans. For the purposes of this article, *inorganic impurity, metal, and element* all refer to those elements listed in *Table 1*. The proposed new *General Chapter* recommends procedures that rely on modern analytical technology and includes limits that are based on toxicity and exposure levels for the selected metals. The new *General Chapter* also introduces a performance-based approach for the selection of the appropriate technology. This chapter is proposed to replace <231> and may impact other *General Chapters* that control metals.

### INTRODUCTION

Among the category of inorganic impurities, metal impurities have long been monitored in food and drug articles intended for consumption by humans and other animals. For purposes of this *General Chapter*, drug articles include: drug substances and products (including natural-source and rDNA biologics) and excipients. Dietary supplements and their ingredients are also included, but other foods and food ingredients will not be addressed. Some metals may pose no significant health hazard at sufficiently low exposure levels, when present as certain complexes, at certain oxidation states, or in organic combinations. This chapter should be considered a screening method to identify the presence of potentially hazardous elements. Where *speciation* of an element is important, further testing is necessary. In these cases, the monograph will include specific instructions for appropriate identification and control. The topic of *speciation* will not be covered further in this article.

Some inorganic impurities are toxic at low levels, and these impurities should be monitored to ensure safety. Sources of inorganic impurities include those that are deliberately added to the process (e.g., catalysts), those that are carried through a process that is conducted according to good manufacturing practices (e.g., undetected contaminants from starting materials or reagents), those coming from the process (e.g., leaching from pipes and other equipment), and those that occur naturally (e.g., from naturally derived plant or mineral sources). Regardless of source, the

control of these impurities may be certified by a vendor, but purchasers also must corroborate the absence of impurities before using these materials in a manufactured article.

The General Chapters Expert Committee of the USP Council of Experts formed an Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals to assist the Expert Committee in revision of General Chapter *Heavy Metals* <231>. As drafted by this Ad Hoc Advisory Panel and revised by the Expert Committee, the proposed revision specifies that the level of each inorganic impurity should not exceed the limit defined in *Table 1* or otherwise specified in the individual monograph. This level is determined by concomitant comparison with a monitor solution and *USP Reference Standard* solution(s).

The selection of an instrumental technique and a procedure for the evaluation of the inorganic impurities specified in *Table 1* requires the evaluation of a large number of variables including, among others, sensitivity, precision, accuracy, compatibility, time, and cost. The method selected may include plasma spectrochemistry, atomic absorption spectroscopy, or any other method that displays requisite accuracy (trueness and uncertainty) and established sensitivity and specificity. Meeting this requirement must be demonstrated experimentally using the *USP Reference Standard(s)*. Any procedure that provides measurement values within  $\pm 20\%$  of the certified concentration for each element in the appropriate *USP Reference Standard(s)* is considered to be an acceptable procedure to demonstrate compliance. A guide for the selection of a procedure is presented in *Figure 1*. When a manufacturer does not have a preferred procedure, or when the preferred procedure does not meet criteria for performance described above, proceed as directed in the remainder of this General Chapter.

**Procedure**—Determine the levels of individual inorganic impurities by the test, unless the individual monograph specifies otherwise.

**Reagents**—All reagents used for the preparation of sample and standard solutions should be free of inorganic impurities in accordance with *Plasma Spectrochemistry* <730>. Commercial, National Institute of Standards and Technology–traceable elemental stock standards, either single element or multi-element, containing Al, Sb, As, Be, B, Cd, Cr, Co, Cu, In, Ir, Fe, Pb, Li, Mg, Mn, Hg, Mo, Ni, Os, Pd, Pt, Rh, Rb, Ru, Se, Sr, Tl, Sn, W, or Zn at a recommended concentration of 100  $\mu\text{g/mL}$  or greater also are used as reagents.

**Performance-based USP Reference Standards**—

*USP Inorganic Impurities Class 1 Reference Standard* for test articles soluble in aqueous solutions.

*USP Inorganic Impurities Class 2 Reference Standard* for test articles soluble in organic solvents.

*USP Inorganic Impurities Class 3 Reference Standard* for closed-vessel microwave digestions.

**Equipment**—One of the following plasma spectrometers is required for an analyst to perform this multi-element analysis:

1. Inductively coupled plasma–atomic (optical) emission spectrometer.
2. Inductively coupled plasma–mass spectrometer.

In addition, a closed-vessel microwave digestion system may be required for the preparation of test materials (see *Figure 1*).

## METHOD

### *Sample Preparation*

Determine the means of sample preparation using the flow chart in *Figure 1*. The sample preparation scheme should provide sufficient sample loading to allow quantification of each element at the specified limit stated in the corresponding monograph or as stated in *Table 1*. For closed-vessel microwave digestions follow the manufacturer's recommended procedures to ensure safe usage. Use utmost caution if concentrated hydrofluoric acid (HF) is used for the preparation of test articles, and review or establish local procedures for safe handling, safe disposal, and HF-tolerant instrumental configurations. [NOTE: The specific details of the Sample preparation have not been included in this *Stimuli* article but have been developed by the Ad Hoc Advisory Panel. The decision to exclude the specific method details from the *Stimuli* article is based on the desire of the Ad Hoc Advisory Panel to receive feedback on the concepts proposed herein rather than on the specific method. Based on the feedback received, these details may be included in future chapter development.]

### **System Suitability Criteria—**

#### *Method reporting limit*

The method reporting limit (MRL) is defined as the lowest element concentration of a solution prepared in the working calibration standard matrix that can be experimentally determined to within  $\pm 30\%$  of the prepared concentration. The sensitivity criterion for the method is that the MRL is  $0.5 \times$  the *USP* limit for each applicable element.

#### *Recovery*

The suitability of the sample preparation scheme must be demonstrated by preparation and analysis of a suitable *USP Reference Standard* and by spike recovery measurements of the specific test article according to <730>. The spiked test article solution will be referred to as a *Monitor solution*. The experimental concentration results shall be  $\pm 20\%$  of the certified concentration for each required element in the analysis. The spike recovery results for the *Monitor solution* must be  $\pm 20\%$  of the spike concentration for each element. Analysis of a suitable *USP Reference Standard* shall be included with the analyses of test articles and must be within  $\pm 20\%$  of the certified concentration for each required element for the results to be considered acceptable.

#### *Calibration*

Prepare calibration standards in the same solution as used for preparation of the test articles. Analysts are encouraged to use internal standards according to <730> for preparation of test article and calibration standard solutions. Prepare 4 working standards plus a blank at element concentrations encompassing the required *USP* limits for the test article, the *USP Reference Standard*, and the *Monitor solution*. Standard curve acceptance criteria must be met according to <730>. If the concentration of an element in the test article solution is determined to be greater than 110% of the highest calibration standard concentration, the test article solution should be appropriately diluted within the range of the standard curve and then reanalyzed.

#### *Drift*

To monitor instrument drift, analyze a working standard solution at an intermediate concentration of each element immediately following standardization, following the final test solution, and during the analysis at a frequency of one working standard solution analysis per not more than 10 sample analyses during the analytical run. The check standard results should agree to within  $\pm 30\%$  of the prepared concentration for each element. Reanalyze element results for

test article solutions that are not bracketed with results within the tolerance for the check standard.

**Analysis** [NOTE: The specific details of the methods have not been included in this *Stimuli* article but have been developed by the Ad Hoc Advisory Panel. The decision to exclude the specific method details from the *Stimuli* article is based on the desire of the Ad Hoc Advisory Panel to receive feedback on the concepts proposed herein rather than on the specific method. Based on the feedback received, these details may be included in future chapter development.]

#### **Calculations and Reporting—**

Upon completion of the analysis, calculate the final concentration of a given element in the test article in  $\mu\text{g/g}$  from the solution element concentration in  $\mu\text{g/mL}$  as follows:

$$C = [(A \times V_1)/W] \times (V_2/V_3)$$

where:

$C$  = concentration of analyte in  $\mu\text{g/g}$ ,

$A$  = instrument reading in  $\mu\text{g/mL}$ ,

$V_1$  = volume of initial test article preparation,

$W$  = weight of test article preparation in g,

$V_2$  = total volume of any dilution performed in mL, and

$V_3$  = aliquot of initial test article preparation used in any dilution performed in mL.

Similarly, calculate the final concentration of a given element in the test article in  $\mu\text{g/g}$  from the solution element concentration in  $\text{ng/mL}$  as follows:

$$C = [(A \times V_1)/W] \times (1 \mu\text{g}/1000 \text{ ng})(V_2/V_3)$$

where:

$C$  = concentration of analyte in  $\mu\text{g/g}$ ,

$A$  = instrument reading in  $\text{ng/mL}$ ,

$V_1$  = volume of initial test article preparation,

$W$  = weight of test article preparation in g,

$V_2$  = total volume of any dilution performed in mL, and

$V_3$  = aliquot of initial test article preparation used in any dilution performed in mL.

Calculate the results for each analyte, and compare the values obtained for the test article to those provided in *Table 1*. The results should not exceed the values in the table.

### **CONCLUSION**

The USP Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals invites comments on the recommendations regarding the use of appropriate analytical instrumentation with limits that are based on toxicity and exposure levels for the metals and the new approach for the determination of an appropriate analytical procedure by the application of *USP Reference Standards* described in this *Stimuli* article. Please send detailed comments to: Kahkashan Zaidi, PhD, Senior Scientist, Documentary Standards Division, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8269; e-mail [kxz@usp.org](mailto:kxz@usp.org).

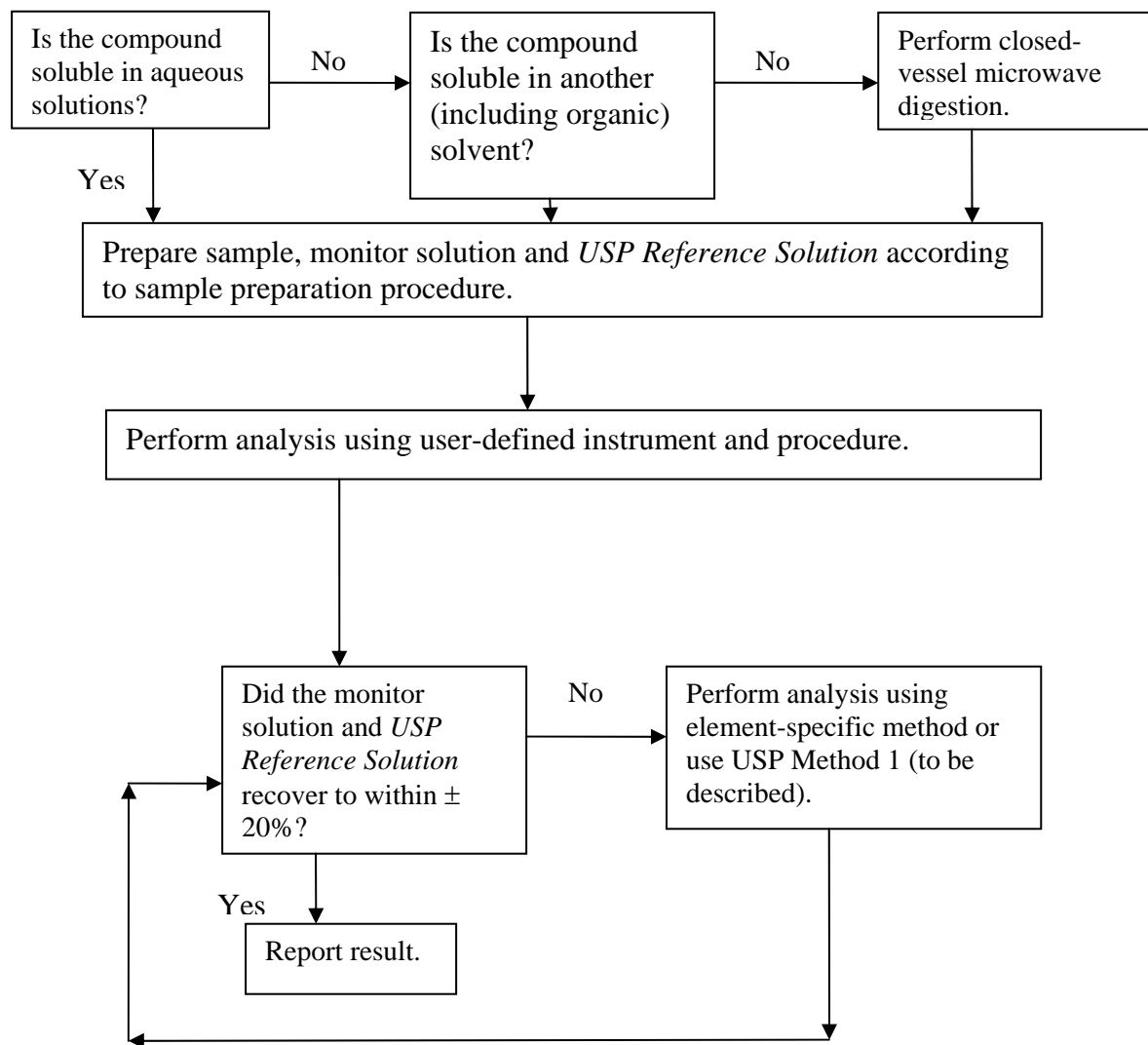


Figure 1. Inorganic impurity decision tree.

**Table 1.** Element limits for oral and parenteral materials. [NOTE: The contents of this table represent a first approximation by members of the Ad Hoc Advisory Panel and are under active discussion internationally.]<sup>a</sup>

Element	Oral Permitted Daily Exposure for Dosage Forms, µg/day	USP Oral Limit, µg/g	USP Parenteral Limit, µg/g
Aluminum (Al)	50,000	5000	500
Antimony (Sb)	20	2	0.2
Arsenic (As)	15	1.5	0.15
Beryllium (Be)	100	10	1
Boron (B)	10,000	1000	100
Cadmium (Cd)	25	2.5	0.25
Chromium (Cr)	150	15	1.5
Cobalt (Co)	1000	100	10
Copper (Cu)	500	50	5
Indium (In)	100	10	1
Iridium (Ir)	100	10	1
Iron (Fe)	15,000	1500	150
Lead (Pb)	10 <sup>b</sup>	1	0.1
Lithium (Li)	600	60	6
Magnesium (Mg)	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>
Manganese (Mn)	7000	700	70
Mercury (Hg)	15	1.5	0.15
Molybdenum (Mo)	250	25	2.5
Nickel (Ni)	1000	100	10
Osmium (Os)	100	10	1
Palladium (Pd)	100	10	1
Platinum (Pt)	100	10	1
Rhodium (Rh)	100	10	1
Rubidium (Rb)	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>
Ruthenium (Ru)	100	10	1
Selenium (Se)	250	25	2.5
Strontium (Sr)	30,000	3000	300
Thallium (Tl)	4	0.4	0.04
Tin (Sn)	30,000	3000	300
Tungsten (W)	375	37.5	3.8
Zinc (Zn)	15,000	1500	150

<sup>a</sup> Some of the limits in this table were calculated using the criteria given in the EMEA *Guideline on the Specification Limits for Residues of Metal Catalysts*, available at: <http://www.emea.europa.eu/pdfs/human/swp/444600.pdf>, accessed 25 March 2008.

<sup>b</sup> Limit for lead calculated from the FDA limit for bottled drinking water: 5 µg/L assuming consumption of 2 L/day.

<sup>c</sup> Under deliberation.