BRIEFING

〈 **233** 〉 **Elemental Impurities—Procedures,** page 201 of *PF* 36(1) [Jan.–Feb. 2010]. This revision to the general test chapter, *Elemental Impurities—Procedures* 〈 233 〉 is based on comments received during the public comment period. The Expert Committee on elemental impurities has reviewed these comments and is proposing this revision to provide additional clarity and flexibility. Although these proposed changes do not materially impact the scientific content of the chapter, they are being published in *PF* to assure that the chapter requirements are clear to all users and also to seek any final input. This chapter is expected to be included on the official ballot along with general chapter *Elemental Impurities—Limits* 〈 232 〉 for approval by the Expert Committee.

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Comment deadline: July 31, 2011

Add the following:

〈 ■233 〉 ELEMENTAL IMPURITIES—PROCEDURES

~~INTRODUCTION~~

~~This chapter describes analytical procedures for the evaluation of elemental impurities in *USP* for drug substances and drug products (including natural-source and rDNA biologics); in *NF* for excipients; and in the *USP Dietary Supplements Compendium* for dietary supplements and dietary ingredients (all drug articles). Two referee procedures are described. Criteria for the approval of alternative procedures are also described. An alternative procedure will require complete validation for each element of interest. In addition, a system suitability evaluation using a USP Reference Standard or its equivalent should be demonstrated on the day of analysis. Alternative procedures that meet the validation requirements described herein are considered to be equivalent to Procedures 1 and 2. A decision-tree that can be used to guide a user to an appropriate alternative procedure is presented in *Figure 1*. The test requirement is specified in *General Notices* or the individual monograph.~~

~~Speciation~~

~~When elements are present in certain complexes, oxidation states, or organic combinations, they may show more significant toxicity than in other forms and may require further testing and control. The determination of the oxidation state or organic complex or combination is termed *speciation*. Analytical procedures for speciation are not included in this chapter.~~

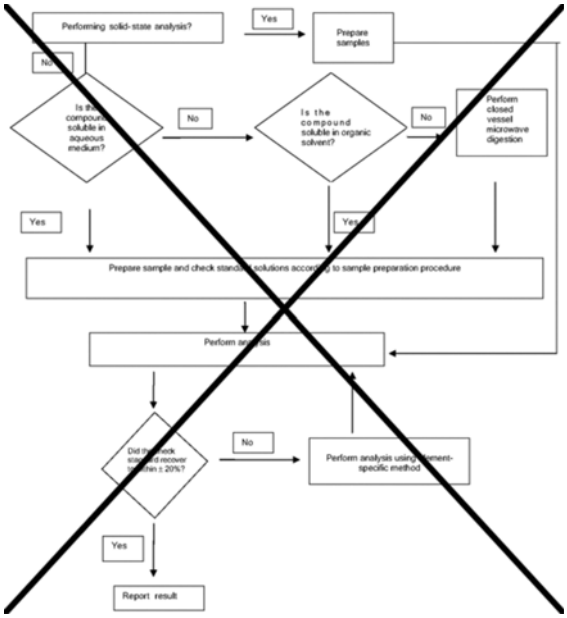

Figure 1. Elemental impurities decision tree.

ALTERNATIVE PROCEDURE VALIDATION REQUIREMENTS

The level of validation necessary to ensure that a procedure is appropriate for its intended purpose—that is, that it is acceptable—will differ, depending on whether a limit test or a quantitative determination is necessary. The requirements for validation of an elemental impurities procedure for either type of determination are described below.

VALIDATION OF LIMIT PROCEDURES

For elemental impurities, validation of a limit procedure should include accuracy, precision, and specificity. Following are acceptable validation parameters that allow a procedure to be deemed appropriate as a limit procedure:

Accuracy

Control Sample—A preparation of certified reference materials for the element of interest at the indicated level

Test Sample—A sample of material under test, spiked with certified reference materials for the element of interest at the indicated level, prepared in triplicate

Acceptance Criteria—Each *Test sample* provides a signal of intensity or value equivalent to or greater than that of the *Control sample*. [NOTE—The signal obtained must show a change from the value obtained compared to a blank determination.] The accuracy of the method must be determined by conducting studies with test materials supplemented with known concentrations of each element at the appropriate acceptance limit concentration. The test materials must be spiked before any sample preparation steps are taken. For example, if a test material is to be digested with a closed vessel microwave digestion apparatus, the material must be spiked before the digestion procedure.

Precision for Instrumental Methods (Repeatability)

[NOTE—Noninstrumental precision is demonstrated by meeting the *Accuracy* requirement above.]

Test Samples: Six independent samples of the material under test, spiked with certified reference materials for the element of interest at the indicated level

Acceptance Criteria: Relative standard deviation, NMT 20%

Specificity

Specificity (false-negative) for an element in the material under test will be deemed acceptable if acceptance criteria for accuracy and precision are obtained for that element in the presence of other elements that, at their indicated limits, may interfere with the evaluation.

Specificity (false-positive) must also show an absence of signal for an element in the presence of other elements that, at their indicated limits, may interfere with the evaluation.

VALIDATION OF QUANTITATIVE PROCEDURES

The following section defines the validation parameters for the acceptability of a quantitative procedure. Meeting these requirements must be demonstrated experimentally, using an appropriate system suitability procedure and reference material.

Accuracy

Control Sample 1:0.5*J*, of the certified reference materials for the element of interest, where *J* is the indicated limit

Control Sample 2:*J*, of the certified reference materials for the element of interest, where *J* is the indicated limit

Control Sample 3:1.5*J*, of the certified reference materials for the element of interest, where *J* is the indicated limit

Test Sample 1:Sample of material under test, spiked with certified reference materials for the element of interest at 0.5*J*, where *J* is the indicated limit [NOTE—Prepare in triplicate.]

Test Sample 2:Sample of material under test, spiked with certified reference materials for the element of interest at *J*, where *J* is the indicated limit [NOTE—Prepare in triplicate.]

Test Sample 3:Sample of material under test, spiked with certified reference materials for the element of interest at 1.5*J*, where *J* is the indicated limit [NOTE—Prepare in triplicate.]

Acceptance Criteria:Spike recovery: 80%–150% for the mean of three replicate preparations at each concentration. The test materials must be supplemented before any sample preparation steps. For example, if a test material is to be digested with a closed vessel microwave digestion apparatus, the material must be spiked at the beginning of the digestion procedure.

Precision

REPEATABILITY

Test Samples:Six independent samples of material under test, spiked with certified reference materials for the element of interest at the indicated level

Acceptance Criteria:Relative standard deviation, NMT 20%

INTERMEDIATE PRECISION

The effect of random events on the analytical precision of the method must be established. Acceptable experiments for establishing intermediate precision include performing the *Repeatability* analysis

1. On different days,
2. With different instrumentation, or

3. With different analysts.

Note that executing only one of the three experiments listed is required in order to demonstrate intermediate precision.

Acceptance Criteria:Relative standard deviation, NMT 25%

Specificity

Specificity (false-negative) for an element in the material under test will be deemed acceptable if acceptance criteria for accuracy and precision are obtained for that element in the presence of other elements that may interfere with the evaluation, at their indicated limits.
Specificity (false-positive) must also show an absence of signal for an element in the presence of other elements that, at their indicated limits, may interfere with the evaluation.

Limit of Quantitation (Sensitivity)—Demonstrated by meeting the *Accuracy* requirement.

REFEREE PROCEDURES 1 AND 2

Procedure and Detection Technique

Procedure 1 can be used for elemental impurities generally amenable to detection by inductively coupled plasma–atomic (optical) emission spectroscopy (ICP-OES). Procedure 2 can be used for elemental impurities generally amenable to detection by inductively coupled plasma–mass spectrometry (ICP-MS).

Verification

Before the initial use of a referee procedure, the analyst should ensure that the procedure is appropriate for the instrument and sample used. This is accomplished by procedure verification, as described in *Verification of Compendial Procedures* ⟨1226⟩.

Sample Preparation

Sample preparation is critical to the successful completion of the evaluation. Use the flow chart in *Figure 1* to determine the means of sample preparation. The sample preparation scheme should yield sufficient sample to allow quantification of each element at the specified limit stated in the corresponding monograph or chapter. [NOTE—All liquid samples should be weighed.]

Closed Vessel Microwave Digestion—This sample preparation procedure is designed for samples that must be digested. The procedure also applies to samples that are not soluble in nitric acid. [NOTE—Weights and volumes provided may be adjusted to meet the requirements of the microwave digestion apparatus used, if proportions remain constant.]

Sample Preparation—Dehydrate and predigest 0.5 g of sample in 5 mL of freshly prepared aqua regia.[1] Sulfuric acid may also be used as a last resort.[2] Allow the sample to sit loosely covered for 30 min in a fume hood. Add 10 mL more of aqua regia, and digest, using a closed vessel microwave technique. Microwave until digestion or extraction is complete. Repeat if necessary by adding 5 mL more of aqua regia. [NOTE—Where closed vessel microwave digestion is necessary, follow the manufacturer's recommended procedures to ensure safe usage.] [NOTE—In closed vessel microwave digestion, the use of concentrated hydrofluoric acid (HF) is not recommended. However, when its use is

necessary, practice the utmost caution in the preparation of test articles, and review or establish local procedures for safe handling, safe disposal, and HF-tolerant instrumental configurations.]

Reagents—All reagents used for the preparation of sample and standard solutions should be free of elemental impurities, in accordance with *Plasma Spectrochemistry* ‹730›. Reagents should be commercial elemental stock standards that are National Institute of Standards and Technology (NIST)–traceable, at a recommended concentration of 100 µg/mL or greater; or appropriate USP Reference Standards, as either single element or multielement.

Procedure 1: ICP-OES

Sample Solution:Proceed as directed in *Sample preparation* above. When closed vessel microwave digestion is used, proceed as directed above, allow the digestion vessel to cool (add an appropriate stabilizer, such as gold at about 0.1 ppm, for mercury measurement), and dilute with *Purified Water* to 50.0 mL.

Calibration Solution 1:2*J* of the element of interest in a matched matrix (acid concentrations similar to that of the *Sample solution*), where *J* is the limit for the specific elemental impurity. [NOTE—Multiple elements of interest may be included in this solution at the same concentration ratio. For mercury analysis, add an appropriate stabilizer, such as gold at about 0.1 ppm.]

Calibration Solution 2:0.1*J* of the element of interest in a matched matrix (acid concentrations similar to that of the *Sample solution*), where *J* is the limit for the specific elemental impurity. [NOTE—Multiple elements of interest may be included in this solution at the same concentration ratio. For mercury analysis, add an appropriate stabilizer, such as gold at about 0.1 ppm.]

Check Standard Solution:1 ppm of the element of interest in a matched matrix (acid concentrations similar to that of the *Sample solution*) [NOTE—Multiple elements of interest may be included in this solution at 1 ppm each. For mercury analysis, add an appropriate stabilizer, such as gold at about 0.1 ppm.]

Blank:Matched matrix (acid concentrations similar to that of the *Sample solution*)

Elemental Spectrometric System (see *Plasma Spectrochemistry* ‹730›)

Mode:ICP

Detector: Optical emission spectroscopy

Rinse:5% aqua regia

Calibration: Two-point, using *Calibration solution 1, Calibration solution 2,* and *Blank*

System Suitability

Sample:*Check Standard Solution*

Suitability requirements—

Drift: differs from actual concentration by NMT 20%. [NOTE—If samples are high in mineral content, to minimize sample carryover, rinse system well (60 sec) before introducing *Check Standard Solution*.]

Analysis:Analyze according to manufacturer's suggestions for program and wavelength. Calculate and report results on the basis of the original sample size.

Procedure 2: ICP-MS

Sample Solution:Proceed as directed in *Sample preparation* above, and add appropriate internal standards at appropriate concentrations.
When closed vessel microwave digestion is used, proceed as directed above, allow the digestion vessel to cool, add

appropriate internal standards at appropriate concentrations (gold should be one of the internal standards for mercury measurement), and dilute with *Purified water* to 50.0 mL.

Calibration Solution 1:2*J* of the element of interest in a matched matrix (acid concentrations similar to that of the *Sample solution*), where *J* is the limit for the specific elemental impurity. [NOTE—Multiple elements of interest may be included in this solution at the same concentration ratio. For mercury analysis, add an appropriate stabilizer, such as gold at about 0.1 ppm.]

Calibration Solution 2:0.1*J* of the element of interest in a matched matrix (acid concentrations similar to that of the *Sample solution*), where *J* is the limit for the specific elemental impurity. [NOTE—Multiple elements of interest may be included in this solution at the same concentration ratio. For mercury analysis, add an appropriate stabilizer, such as gold at about 0.1 ppm.]

Blank:Matched matrix (acid concentrations similar to that of the *Sample solution*)

Elemental Spectrometric System (see *Plasma Spectrochemistry* ‹730›)

Mode:ICP [NOTE—An instrument with a cooled spray chamber is recommended.]

Detector: Mass spectrometer

Rinse: 5% aqua regia

Calibration:*Calibration solution 1*, *Calibration solution 2*, and *Blank*

System Suitability

Sample:*Calibration solution 1*

Suitability requirements—

*Drift:*differs from actual concentration by NMT 20%. [NOTE—If samples are high in mineral content, rinse system well (60 sec) before introducing *Check Standard Solution* to minimize sample carryover.]

Analysis:Analyze per manufacturer's suggestions for program and m/z. Calculate and report results based on the original sample size. [NOTE—Arsenic is subject to interference from argon chloride. Appropriate measures, including a sample preparation without aqua regia, must be taken to correct for the interference, depending on instrumental capabilities.]

CALCULATIONS AND REPORTING

Upon completion of the analysis, calculate the final concentration of a given element in the test article (µg/g) from the solution element concentration (µg/mL) as follows:

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

where

- C = concentration of analyte (µg/g)
- A = instrument reading (µg/mL)
- V_1 = volume of initial test article preparation (mL)
- W = weight of test article preparation (g)
- V_2 = total volume of any dilution performed (mL)
- V_3 = aliquot of initial test article preparation used in any dilution performed (mL)

~~Similarly, calculate the final concentration of a given element in the test article (µg/g) from the solution element concentration (ng/mL) as follows:~~

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

~~C = concentration of analyte (µg/g)~~
~~A = instrument reading (ng/mL)~~
~~V_1 = volume of initial test article preparation (mL)~~
~~W = weight of test article preparation (g)~~
~~V_2 = total volume of any dilution performed (mL)~~
~~V_3 = aliquot of initial test article preparation used in any dilution performed (mL)~~

INTRODUCTION

This chapter describes two analytical procedures (*Procedures 1* and *2*) for the evaluation of the levels of the elemental impurities that are described in *Elemental Impurities—Limits* ⟨ 232 ⟩ and *Elemental Contaminants in Dietary Supplements* ⟨ 2232 ⟩. The chapter also describes criteria for acceptable alternative procedures. Alternative procedures that meet the validation requirements described herein may be considered equivalent to *Procedures 1* and *2* for the purposes of this test. In addition, system standardization and suitability evaluation using applicable reference materials should be performed on the day of analysis. The requirement for an elemental impurity test is specified in *General Notices and Requirements* or in the individual monograph. By means of verification studies, analysts will confirm that the analytical procedures described herein, as well as alternative analytical procedures, are suitable for use on specified material.

Speciation

The determination of the oxidation state, organic complex or combination is termed *speciation*. Analytical procedures for speciation are not included in this chapter but examples may be found elsewhere in the *USP–NF* and in the literature.

Definitions

Concentrated Acid: Concentrated ultra-pure nitric, sulfuric, hydrochloric, or hydrofluoric acids or Aqua Regia
Matched Matrix: Solutions having the same solvent composition as the *Sample solution.* In the case of aqueous solution, *matched matrix* would indicate that the same acids, acid concentrations, and mercury stabilizer are used in both preparations.
Target Elements: Elements with the potential of being present in the material under test. *Target Elements* must include lead, mercury, arsenic, and cadmium and should include any of those remaining elemental impurities presented in general chapter *Elemental Impurities—Limits* ⟨ 232 ⟩ that are used in production of the material under test or the components therein. *Target Elements* should also include any other elements that may be added through material processing or storage or any elements whose presence may interfere with the operation of the analytical procedures. [NOTE—Exclusion of elements from the list does not exempt the user from compliance with the requirements described in *Elemental Impurities—Limits* ⟨ 232 ⟩ or in this chapter.]
Target Limit or Target Concentration: The uppermost acceptance value for the elemental impurity being evaluated. Exceeding the target limit indicates that a material under test exceeds the acceptable value. The determination of

compliance is addressed in other chapters. [NOTE—*Target Limits* can be approximated by dividing the *Modified Daily Dose PDEs* by the maximum daily dose for the *Drug Product Analysis Option* in ⟨ 232 ⟩ or the *Daily Serving PDE* divided by the maximum daily serving size in ⟨ 2232 ⟩] (see *Elemental Impurities—Limits* ⟨ 232 ⟩ or *Elemental Contaminants in Dietary Supplements* ⟨ 2232 ⟩).

J: The concentration (w/w) of the element(s) of interest at the *Target Limit*, appropriately diluted to the working range of the instrument.

Appropriate Reference Materials: Where *Appropriate Reference Materials* are specified in the chapter, certified reference materials (CRM) from a national metrology institute (NMI, e.g., the National Institute of Standards and Technology in the United States) or reference materials that are traceable to the CRM of a NMI should be used.

COMPENDIAL PROCEDURES 1 AND 2

Procedure and Detection Technique

Procedure 1 can be used for elemental impurities generally amenable to detection by inductively coupled plasma–atomic (optical) emission spectroscopy (ICP–AES or ICP–OES). *Procedure 2* can be used for elemental impurities generally amenable to detection by inductively coupled plasma–mass spectrometry (ICP–MS). Before initial use, the analyst should verify that the procedure is appropriate for the instrument and sample used (procedural verification) by meeting the *Alternative Procedure Validation* requirements below.

Sample Preparation

Forms of sample preparation include *Neat*, *Direct Aqueous Solution*, *Direct Organic Solution*, and *Indirect Solution*. The selection of the appropriate sample preparation depends on the material under test and is the responsibility of the analyst. When a sample preparation is not indicated in the monograph, an analyst may use any of the following appropriately verified preparation procedures. Samples and blanks may be spiked with *Target Elements* where an analyte has limited solubility in the solvent system of choice. Standard solutions may contain multiple *Target Elements.* [NOTE—All liquid samples should be weighed.]

Neat: Used for liquids or alternative procedures that allow the examination of unsolvated samples.

Direct Aqueous Solution: Used when the sample is soluble in an aqueous solvent.

Direct Organic Solution: Used where the sample is soluble in an organic solvent.

Indirect Solution: Used when a material is not directly soluble in aqueous or organic solvents. Digest the sample using a closed-vessel digestion procedure, similar to the procedure provided below. The sample preparation scheme should yield sufficient sample to allow quantification of each element at the limit specified in the corresponding monograph or chapter.

Closed Vessel Digestion: This sample-preparation procedure is designed for samples that must be digested in a *Concentrated Acid* using a closed-vessel digestion apparatus. Closed-vessel digestion minimizes the loss of volatile impurities. The choice of a *Concentrated Acid* depends on the sample matrix. The use of any of the *Concentrated Acids* may be appropriate, but each introduces inherent safety risks. Therefore, appropriate safety precautions should be employed at all times. [NOTE—Weights and volumes provided may be adjusted to meet the requirements of the digestion apparatus used.]

An example procedure that has been shown to have broad applicability is the following:

Dehydrate and predigest 0.5 g of primary sample in 5 mL of freshly prepared *Concentrated Acid*. Allow to sit loosely covered for 30 minutes in a fume hood. Add an additional 10 mL of *Concentrated Acid*, and digest, using a closed vessel technique, until digestion or extraction is complete. Repeat if necessary by adding an additional 5 mL of

Concentrated Acid. [NOTE—Where closed vessel digestion is necessary, follow the manufacturer's recommended procedures to ensure safe use.]

Reagents: All reagents used for the preparation of sample and standard solutions should be free of elemental impurities, in accordance with *Plasma Spectrochemistry* ⟨ 730 ⟩ .

Procedure 1: ICP-AES

Standardization Solution 1: 2*J* of the *Target Element(s)* in a *Matched Matrix*

Standardization Solution 2: 0.5*J* of the *Target Element(s)* in a *Matched Matrix*

Sample Stock Solution: Proceed as directed in *Sample Preparation* above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer.

Sample Solution: Dilute the *Sample Stock Solution* with an appropriate solvent to obtain a final concentration of the *Target Elements* at NMT 2*J.*

Blank: *Matched Matrix*

Elemental Spectrometric System
(See *Plasma Spectrochemistry* ⟨ 730 ⟩ .)

Mode: ICP

Detector: Optical detection system

Rinse: Diluent used

Standardization: *Standardization Solution 1*, *Standardization Solution 2*, and *Blank*

System Suitability

Sample: *Standardization Solution 1*

Suitability requirements

Drift: Compare results obtained from *Standardization Solution 1* before and after the analyis of the *Sample Solutions*.

Suitability criteria: NMT 20% for each *Target Element*. [NOTE—If samples are high in mineral content, rinse system well (60 seconds) before introducing the *Sample* in order to minimize carryover.]

Analysis: Analyze according to the manufacturer's suggestions for program and wavelength. Calculate and report results on the basis of the original sample size.

Procedure 2: ICP-MS

Standardization Solution 1: 2*J* of the *Target Element(s)* in a *Matched Matrix*

Standardization Solution 2: 0.5*J* of the *Target Element(s)* in a *Matched Matrix*

Sample Stock Solution: Proceed as directed for *Sample Preparation* above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer.

Sample Solution: Dilute the *Sample Stock Solution* with an appropriate solvent to obtain a final concentration of the *Target Elements* at NMT 2*J.*

Blank: *Matched Matrix*

Elemental Spectrometric System

(See *Plasma Spectrochemistry* ⟨ 730 ⟩.)

Mode: ICP. [NOTE—An instrument with a cooled spray chamber is recommended.]

Detector: Mass spectrometer

Rinse: Diluent used

Standardization: *Standardization Solution 1*, *Standardization Solution 2*, and *Blank*

System Suitability

Sample: *Standardization Solution 1*

Suitability requirements

Drift: Compare results obtained from *Standardization Solution 1* before and after the analyis of the *Sample Solutions*.

Suitability criteria: NMT 20% for each *Target Element*. [NOTE—If samples are high in mineral content, rinse system well (60 seconds) before introducing the *Sample* in order to minimize carryover.]

Analysis: Analyze according to the manufacturer's suggestions for program and *m*/*z*. Calculate and report results based on the original sample size. [NOTE—Appropriate measures must be taken to correct for matrix-induced interferences (e.g., argon chloride interference with arsenic determinations.]

ALTERNATE PROCEDURE VALIDATION

If a specified compendial procedure does not meet the needs of a specific application, an alternative procedure may be used (see *General Notices* 6.30). Alternative procedures must be validated and must be acceptable and therefore equivalent to the compendial procedures for the purposes of the test. The principles of validation are provided in general chapter *Validation of Compendial Procedures* ⟨ 1225 ⟩. The level of validation necessary to ensure that an alternative procedure is acceptable depends on whether a limit test or a quantitative determination is necessary. The requirements for validation of an elemental impurities procedure for either type of determination are described below. Where this information differs from that presented in *Validation of Compendial Procedures* ⟨ 1225 ⟩, the parameters and acceptance criteria presented in this chapter take precedence. Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be equivalent to the compendial procedures for the purposes of this test.

LIMIT PROCEDURES

The following section defines the validation parameters for the acceptability of alternative limit procedures. Meeting these requirements must be demonstrated experimentally using an appropriate system suitability procedure and reference material. Meeting these requirements demonstrates that the procedure is equivalent to the compendial procedure as a limit procedure for the *Target Element*.
The suitability of the method must be determined by conducting studies with test materials supplemented with known concentrations of each *Target Element* of interest at the appropriate acceptance limit concentration. The test materials must be spiked before any sample preparation steps are performed.

Detectability

Standard Solution: A preparation of reference materials for the *Target Element(s)* at the *Target Concentrations*.

Spiked Sample Solution 1: Prepare a solution of sample under test, spiked with appropriate reference materials for the *Target Elements* at the *Target Concentration*, solubilized or digested as described in *Sample Preparation*.

Spiked Sample Solution 2: Prepare a solution of the sample under test, spiked with appropriate reference materials at 80% of the *Target Concentration* for the *Target Elements*, solubilized or digested as described in *Sample Preparation*.

Blank solution: A sample of material under test, solubilized or digested in the same manner as the *Sample Solutions*.

Acceptance Criteria

Non-Instrumental Procedures: *Spiked Sample Solution 1* provides a signal or intensity equivalent to or greater than that of the *Standard Solution. Spiked Sample Solution 2* must provide a signal or intensity less than that of the *Spiked Solution 1.* [NOTE—The signal from each *Spiked Sample* is NLT the blank determination.]

Instrumental Procedures: The average value of the replicate measurements of *Spiked Sample Solution 1* is equivalent to (±10%) or greater than that of the average value obtained for the replicate measurements of the *Standard Solution*. The average value of the replicate measurements of *Spiked Sample Solution 2* must provide a signal intensity or value less than that of the *Standard Solution*. [NOTE—Correct the values obtained for each of the spiked solutions using the *Blank Solution.*]

Precision for Instrumental Methods (Repeatability)

[NOTE—Non-instrumental precision is demonstrated by meeting the *Limit of Detection* requirement above.]

Sample Solutions: Six independent samples of the material under test, spiked with appropriate reference materials for the *Target Elements* at the indicated levels.

Acceptance Criteria

Relative standard deviation: NMT 20% for each *Target Element.*

Specificity

The procedure must be able to unequivocally assess each *Target Element* in the presence of components that may be expected to be present, including other *Target Elements*, and matrix components.

QUANTITATIVE PROCEDURES

The following section defines the validation parameters for the acceptability of alternative quantitative procedures. Meeting these requirements must be demonstrated experimentally, using an appropriate system suitability procedure and reference material. Meeting these requirements demonstrates that the procedure is equivalent to the compendial procedure for the purpose of quantifying the *Target Elements.*

Accuracy

Standard Solutions: Prepare solutions containing the *Target Elements* at concentrations ranging from 50% to 150% of *J,* using appropriate reference materials.

Test Samples: Prepare samples of the material under test spiked with appropriate reference materials before any sample preparation steps (digestion or solubilization) at concentrations ranging from 50% to 150% of *J* for each *Target Element*.

Acceptance Criteria

Spike recovery: 70%–150% for the mean of three replicate preparations at each concentration.

Precision

REPEATABILITY

Test Samples: Six independent samples of material under test [NOTE—Taken from the same lot] spiked with appropriate reference materials for the *Target Element(s)* at the indicated level.

Acceptance Criteria

Relative standard deviation: NMT 20% for each *Target Element.*

RUGGEDNESS

Perform the *Repeatability* analysis

1. on different days, or
2. with different instrumentation, or
3. with different analysts.

Executing only one of the three experiments listed is required to demonstrate ruggedness.

Acceptance Criteria

Relative standard deviation: NMT 20% for each *Target Element.*

Specificity

The procedure must be able to unequivocally assess each *Target Element* in the presence of components that may be expected to be present, including other *Target Elements*, and matrix components.

Limit of Quantitation, Range, and Linearity: Demonstrated by meeting the *Accuracy* requirement.

■1S (*USP35*)

[1] ~~Ultra pure nitric acid/hydrochloric acid (1:3) prepared as needed. (A 1%–5% solution of aqua regia is used as a rinsing solution between analyses and as calibration blanks.)~~

[2] ~~Sulfuric acid should be used only when absolutely needed, for the following reasons:~~

~~Upon addition of sulfuric acid, elements may be lost as a result of extreme exothermic reaction.~~

~~The viscosity of sulfuric acid is higher than that of other acids, which affects the overall flow of solution.~~

Auxiliary Information - Please check for your question in the FAQs before contacting USP.