⟨233⟩ ELEMENTAL IMPURITIES—PROCEDURES

Change to read:

INTRODUCTION

This chapter describes two analytical procedures (*Procedures 1* and *2*) for the evaluation of the levels of the elemental impurities. The chapter also describes criteria for acceptable alternative procedures.■2S (USP38) By means of ■validation■2S (USP38) studies, analysts will confirm that the analytical procedures described herein ■■2S (USP38) are suitable for use on specified material.

■Use of Alternative Procedures

The chapter also describes criteria for acceptable alternative procedures. Alternative procedures that meet the validation requirements herein may be used in accordance with *General Notices and Requirements 6.30, Alternative and Harmonized Methods and Procedures*. Information on the *Requirements for Alternate Procedure Validation* is provided later in this chapter.■2S (USP38)

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 *USP–NF* and in the literature.

Change to read:

COMPENDIAL PROCEDURES 1 AND 2

■System standardization and suitability evaluation using applicable reference materials should be performed on the day of analysis.■2S (USP38)

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 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 ■validated■2S (USP38) preparation procedures. In cases where spiking of a material under test is necessary to provide an acceptable signal intensity, the blank should be spiked with the same *Target elements*, and where possible, using the same spiking solution. 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. ■Total metal extraction is the preferred sample preparation approach to obtain an *indirect solution*.■2S (USP38) Digest the sample using ■the■2S (USP38) *Closed vessel digestion* procedure ■provided below or one■2S (USP38) similar to ■it.■2S (USP38) 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 used 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 min 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.]

■Alternatively, leachate extraction may be appropriate with justification following scientifically validated metal disposition studies, which may include animal studies, speciation, or other means of studying disposition of the specific metal in the drug product.■2S (USP38)

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–■OES■2S (USP38)

Standardization solution 1: ■1.5■2S (USP38)*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 ■1.5■2S (USP38)*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 analysis of the *Sample solution*.

Suitability criteria: NMT 20% for each *Target element*. [NOTE—If samples are high in mineral content, rinse system well ■■2S (USP38) 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. [NOTE—Appropriate measures must be taken to correct for matrix-induced interferences (e.g., wavelength overlaps).]

Procedure 2: ICP–MS

Standardization solution 1: ■1.5■2S (USP38)*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 ■1.5■2S (USP38)*J*.

Blank: *Matched matrix*

Elemental spectrometric system

(See *Plasma Spectrochemistry* ⟨730⟩.)

Mode: ICP. [NOTE—An instrument with a cooled spray chamber is recommended. (A collision cell or reaction cell may also be beneficial.)]

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 analysis of the *Sample solution*.

Suitability criteria: *Drift* NMT 20% for each *Target element*. [NOTE—If samples are high in mineral content, rinse system well ■■2S (USP38) 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).]

Change to read:

▪REQUIREMENTS FOR■2S (USP38) ALTERNATE PROCEDURE VALIDATION

▪If the specified compendial procedures do not meet the needs of a specific application, an alternative procedure may be developed (see *General Notices and Requirements 6.30, Alternative and Harmonized Methods and Procedures*). Alternative procedures must be validated and shown to be acceptable, in accordance with the validation requirements for alternative procedures as described below.■2S (USP38) The level of validation necessary to ensure that an alternative procedure is acceptable depends on whether a limit test or a quantitative determination is ▪specified in the monograph.■2S (USP38) The requirements for the validation of an elemental impurities procedure for ▪each■2S (USP38) type of determination are described below. ▪Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use.■2S (USP38)

Change to read:

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. ▪■2S (USP38)

The suitability of the method must be determined by conducting studies with the material or mixture under test supplemented with known concentrations of each *Target element* of interest at the appropriate acceptance limit concentration. The material or mixture under test 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 concentration*
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*.
Unspiked sample 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 *Spiked sample solution 1*. [NOTE—The signal from each *Spiked sample solution* is NLT the *Unspiked sample solution* determination.]
Instrumental procedures: The average value of the three replicate measurements of *Spiked sample solution 1* is within ±15% 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 *Unspiked sample solution*.]

Precision for Instrumental Methods (Repeatability)

[NOTE—Non-instrumental precision is demonstrated by meeting the *Detectability* requirement above.]
Sample solutions: Six independent samples of the material under test, spiked with appropriate reference materials for the *Target elements* at the *Target concentration*
Acceptance criteria
Relative standard deviation: NMT 20% for each *Target element*

Specificity

The procedure must be able to unequivocally assess (see *Validation of Compendial Procedures* ⟨1225⟩) each *Target element* in the presence of components that may be expected to be present, including other *Target elements*, and matrix components.

Change to read:

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

materials. 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 (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% ■($N = 6$)■2S (USP38) for each *Target element*

■INTERMEDIATE PRECISION (■2S (USP38)RUGGEDNESS■)■2S (USP38)

Perform the *Repeatability* analysis ■again either on a different day, with a different instrumentation, with a different analyst, or a combination thereof. Combine the results of this analysis with the *Repeatability* analysis so the total number of analyses is 12.■2S (USP38)
Acceptance criteria
Relative standard deviation: NMT 25% ■($N = 12$)■2S (USP38) for each *Target element*

Specificity

The procedure must be able to unequivocally assess (see ⟨1225⟩) 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.

Change to read:

APPENDIX

Concentrated acid: Concentrated ultra-pure nitric, sulfuric, hydrochloric, or hydrofluoric acids or *Aqua regia*
Aqua regia: *Aqua regia* is a mixture of concentrated hydrochloric and nitric acids, typically at ratios of 3:1 or 4:1, respectively.
Matched matrix: Solutions having the same solvent composition as the *Sample solution*. In the case of an 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. Include arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) in the target element evaluation when testing is done to demonstrate compliance. *Target elements* should also include any elements that may be added through material processing or storage. ■2S (USP38)
Target limit or Target concentration: The 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—When applying this chapter to *Elemental Impurities—Limits* ⟨232⟩ and *Elemental Contaminants in Dietary Supplements* ⟨2232⟩, *Target limits* can be approximated by dividing the *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⟩.]
J: The concentration (w/w) of the element(s) of interest at the *Target limit*, appropriately diluted to the working range of the instrument. For example, if the target elements are lead and arsenic for an analysis of an oral solid drug product with a daily dose of 10 g/day using inductively coupled plasma–mass spectrometry (ICP–MS), the target limit for these elements would be 0.5 μg/g and ■1.5■2S (USP38) μg/g (see *Table 2* in ⟨232⟩). However, in this case, the linear dynamic range of the ICP–MS is known to extend from 0.01 ng/mL to 0.1 μg/mL for these elements. Therefore, a dilution factor of at least ■1:100■2S (USP38) is

required to ensure that the analysis occurs in the linear dynamic range of the instrument. *J* would thus equal ■5 ng■2S *(USP38)* and ■15 ng■2S *(USP38)*/mL for lead and arsenic, respectively, when the dilution factor is added.

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