2.66 Elemental Impurities－Procedures

(2.66 元素不純物試験法)

1. Introduction

This chapter describes two analytical procedures (Procedures 1 and 2) and validation criteria for the evaluation of the levels of elemental impurities. The chapter permits the use of any procedure that meets the validation criteria specified in this chapter. As the chemical composition of the considered substances and the specification limits for the element(s) of interest vary considerably, it is difficult to describe all suitable sample preparation and measurement methods. By means of validation studies, analysts will confirm that the analytical procedure is suitable for use on specified material. It is not necessary to cross validate against either procedure 1 or 2 provided that requirements for procedure validation are met. (Note: Methods such as atomic absorption spectrometry other than methods described in this chapter, if validated, can also be used without cross validation against analytical procedure 1 or 2.)

1.1. 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 appropriately validated sample preparation procedure, including but not limited to procedures described below. 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. The material or mixture under test must be spiked before any sample preparation steps are performed. Standard solutions may contain multiple *Target elements*. (Note: If intended for a quantitative test, appropriate material handling procedures should be followed e.g. volatile liquids should be pipetted, viscous liquids should be weighed.)

Neat: Used for liquids or analytical 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 when 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*. Digest the sample using the *Closed vessel digestion* procedure provided below or one similar to it.

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 material under test 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.)

Clear solutions are expected in the validation. In those cases where a clear solution cannot be obtained, appropriate studies should ensure that the recovery is suitable for the intended use.

Reagents: All reagents used for the preparation of sample and standard solutions should be sufficiently pure for the intended purpose.

2. Analytical Procedures 1 and 2

System standardization and suitability evaluation using applicable reference materials should be performed on the day of analysis.

2.1. 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 procedure validation requirements below.

2.2. Procedure 1: ICP–OES

Standard solution 1: 1.5*J* of the *Target element(s)* in a *Matched matrix*

Standard solution 2: 0.5*J* of the *Target element(s)* in a *Matched matrix*

Sample stock solution: Proceed as directed in 1.1. *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 element(s)* within the calibrated range.

Blank: *Matched matrix*

Elemental spectrometric system

Mode: ICP

Detector: Optical detection system

Rinse: Diluent used

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

System suitability Sample: Standard solution of the Target element(s) in a Matched matrix at a concentration within the calibrated range

Suitability requirements

Short term Instrumental Stability: Compare results obtained from *System suitability sample* 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 the system well in order to minimize carryover and check it by measuring a blank solution before introducing the *System Suitability Sample*.)

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).]

2.3. Procedure 2: ICP—MS

Standard solution 1: 1.5*J* of the *Target element(s)* in a *Matched matrix*

Standard solution 2: 0.5*J* of the *Target element(s)* in a *Matched matrix*

Sample stock solution: Proceed as directed in 1.1 *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 element(s)* within the calibrated range.

Blank: *Matched matrix*

Elemental spectrometric system

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

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

System suitability Sample: *Standard solution of the Target element(s) in a Matched matrix at a concentration within the calibrated range*

Suitability requirements

Short term Instrumental Stability: Compare results obtained from *system suitability sample* before and after the analysis of the *Sample solution*.

Suitability criteria: NMT 20% drift between both samples for each *Target element*. [Note: If samples are high in mineral content, rinse the system well in order to minimize carryover and check it by measuring a blank solution before introducing the *System suitability sample*.)

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).]

3. Requirements for Procedure Validation

All procedures must be validated and shown to be acceptable, in accordance with the validation requirements described below. The level of validation necessary to ensure that a procedure is acceptable depends on whether a limit test or a quantitative determination is used. Any procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use. If appropriate, the validation criteria may be changed according to the purpose of evaluating the levels of the content of elemental impurities. They may differ from the requirements to meet the system suitability criteria described in Inductively Coupled Plasma-Atomic Emission Spectrometry and Inductively Coupled Plasma-Mass Spectrometry <*2.63*>.

3.1. Procedures for Limits Tests

The following section defines the validation parameters for the acceptability of limit tests. Meeting these requirements must be demonstrated experimentally using an appropriate system suitability test and reference materials.

The suitability of the method must be determined by conducting studies with the material or mixture under test spiked with known concentrations of each *Target element* of interest at the appropriate *Target concentration*.

3.1.1. Detectability

Standard solution: A preparation of reference materials for the *Target element(s)* 100% of J in a *Matched matrix*.

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 spiked *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*.)

3.1.2. 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.

3.1.3. Precision, only for Instrumental Methods (Repeatability)

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*

3.2. Procedures for Quantitative Tests

The following section defines the validation parameters for the acceptability of procedures for quantitative tests. Meeting these requirements must be demonstrated experimentally, using an appropriate system suitability test and reference materials.

3.2.1. Accuracy

Standard solutions: Prepare solutions containing the *Target element(s)* at three concentrations ranging from 50% to 150% of *J*, using appropriate reference materials, in a *Matched matrix*.

Test samples: Prepare samples of the material under test spiked with appropriate reference materials for the *Target element(s)* before any sample preparation steps (digestion or solubilization) at 3 concentrations ranging from 50% to 150% of the *Target concentration*.

Acceptance criteria

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

3.2.2. 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 *Target concentration*.

Acceptance criteria

Relative standard deviation: NMT 20% (N = 6) for each *Target element*

Intermediate precision (ruggedness)

Perform the *Repeatability* analysis again at least once 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 samples is at least 12.

Acceptance criteria

Relative standard deviation: NMT 25% for each *Target element*

3.2.3. 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.

3.2.4. Range and Linearity

Demonstrated by meeting the *Accuracy* requirement.

3.2.5. Limit of Quantification

LOQ of 50% of J is confirmed when the accuracy acceptance criteria for the corresponding spiked solution is met.

Acceptance criterion: the LOQ is smaller or equal to 50% of J.

4. Glossary

Concentrated acid: Concentrated ultra-pure nitric, sulfuric, hydrochloric, or hydrofluoric acids or any other acid or mixture of acids that is demonstrated suitable.

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 whose levels in the drug product must be controlled within acceptable limits.

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. *Target limits* in the final

drug product can be approximated by dividing the *permitted daily exposures (PDEs)* by the maximum daily dose. When evaluating the significance of elemental impurity levels, it is possible to set the *Target limits* to the values obtained by dividing 30% of *PDEs* by the maximum daily dose. Furthermore, when the permitted concentration limit of each element in the individual components of the drug product is set, it can be set as the *Target concentration*.

J: The concentration (w/v) of the *Target element(s)* at the *Target limit*, appropriately diluted to the working range of the instrument. If a dilution is not necessary, *J* is equal to the *Target concentration*. 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 μg/g. However, in both cases, 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 is required to ensure that the analysis occurs in the linear dynamic range of the instrument. *J* would thus equal 5 ng/mL and 15 ng/mL for lead and arsenic, respectively.

Appropriate reference materials: In principle, 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.