Change as follows:

2.66 Elemental Impurities

(2.66 元素不純物)

I. Control of Elemental Impurities in Drug Products

1. Introduction

Elemental impurities in drug products may arise from several sources; they may be residues intentionally added such as catalysts in the synthetic process of drug substances, drug substances being components of the drug product, impurities from natural products contained in additives, etc., and contaminants from manufacturing equipment and container/closure systems. The amounts of these impurities in drug products should be controlled within acceptable limits, except when they are stipulated in monographs.

The permitted daily exposures (PDEs) of elemental impurities are established to protect the health of all patients based on the evaluation of the toxic data of elemental impurities, and more strict limits are not needed if elemental impurities in drug products do not exceed the PDEs. In some cases, lower level of elemental impurities may be warranted when it is known that elemental impurities have been shown to have an impact on the quality attributes of the drug product (e.g., element catalyzed degradation of drug substances).

Elemental impurities in drug products are assessed and controlled based on a risk management approach.

2. Scope

The acceptable limit of elemental impurities apply to drug products, and also apply to drug products containing purified proteins and peptides (including proteins and peptides produced from genetic recombinant or non-recombinant origins), their derivatives, and drug products which they are components (e.g., conjugates) are within the scope of this guideline, as are drug products containing synthetic peptides, polynucleotides, and oligosaccharides.

It does not apply to crude drugs, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellar blood components, blood derivatives including plasma and plasma preparations, dialysate solutions not intended for systematic circulation, and drug products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering). Also, it does not apply to elements that are intentionally included in the drug product for therapeutic benefit.

3. The PDEs for Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration, and Element Classification

The PDEs of elemental impurities established for preparations for oral, parenteral and inhalation routes of administration are shown in Table 1. If the PDEs for the other administration route are necessary, generally consider the oral PDE as a starting point in the establishment, and assess if the elemental impurity is expected to have local effects when administered by the intended route of administration.

Parenteral drug products with maximum daily volumes up to 2 L may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes or general clinical practice may exceed 2 L (e.g., saline, dextrose, total parenteral nutrition, solutions for irrigation), a 2-L volume is used to calculate permissible concentrations from PDEs.

Table 2.66-1 PDEs for Elemental Impurities

Element	Class	Oral PDE (μg/day)	Parenteral PDE (μg/day)	Inhalation PDE (μg/day)
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
TI	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

As shown in Table 2.66-1, elemental impurities are divided into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is judged from several factors, such as probability of use in pharmaceutical processes, impurities in materials used in pharmaceutical processes, the observed natural abundance and environmental distribution of the element.

Class 1: The elements, As, Cd, Hg, and Pb, are classified as this category and are human toxicant elements. As these elements are limited in the manufacture of pharmaceuticals, they are rarely used. Their presence in drug products usually comes from used materials such as mined excipients. These four elements require evaluation during the risk assessment,

across all sources and routes of administration having possibility of contamination. Testing should only be applied when the risk assessment identifies it necessary to ensure that the PDE will be met, however it is not necessary for all components to determine for Class 1 elemental impurities.

Class 2: Elemental impurities classified as Class 2 have lower toxicity than the elements in Class 1, and are route-dependent human toxicants. These elements are further divided in 2A and 2B based on their relative likelihood of occurrence in the drug products. The class 2A elements are Co, Ni and V, which are known to exist naturally. These elements have relatively high probability of occurrence in drug products, and thus require evaluation during the risk assessment, across all sources and routes of administration having possibility of contamination. Because the Class 2B elements have the low probability of their existence in natural, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product. The elemental impurities in Class 2B include Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Class 3: The elements in this class have relatively low toxicities by the oral route of administration, and their oral PDEs are more than 500 μg/day. For oral routes of administration, unless these elements are intentionally added, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental impurities should be evaluated even in the case where they are not intentionally added, unless the route specific PDE is above 500 μg/day. The elements in this class include Ba, Cr, Cu, Li, Mo, Sb and Sn.

4. Risk Assessment and Control of Elemental Impurities

The technique of quality risk management should be considered in controls for elemental impurities in drug products, and the risk assessment should be based on scientific knowledge and principles. The risk assessment would be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs. Useful information for this risk assessment includes measured data of drug products and components, measured data and the risk assessment result supplied by drug substance and/or excipient manufacturers, and/or data available in published literature, but is not limited to them.

The risk assessment should be performed depending on the level of risk, and do not always require a formal risk management process. The use of informal risk management processes may also be considered acceptable.

4.1. General Principles

The risk assessment process consists of the following three steps.

1) Identify known and potential sources of elemental impurities that may find their way into the drug product.

2) Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.

3) Summarize the risk assessment, and identify if controls built into the process are sufficient. Identify additional controls to be considered to limit elemental impurities in the drug product.

In many cases, the steps are considered simultaneously. The risk assessment may be iterated to develop a final approach to ensure the elemental impurities do not exceed the PDE certainly.

4.2. Sources of Elemental Impurities

In considering the production of a drug product, there are broad categories of potential sources of elemental impurities.

・Residual impurities resulting from elements intentionally added (e.g., metal catalysts) in the formation of the drug substance, excipients or other components. The risk assessment of the drug substance should be studied about the potential for inclusion of elemental impurities in the drug product.

・Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product.

・Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.

・Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

During the risk assessment, the potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the drug product.

4.3. Identification of Potential Elemental Impurities

Potential elemental impurities derived from intentionally added catalysts and inorganic reagents: If any element is intentionally added, it should be considered in the risk assessment.

Potential elemental impurities that may be present in drug substances and excipients: While not intentionally added, some elemental impurities may be present in some drug substances and excipients. The possibility for inclusion of these elements in the drug product should be reflected in the risk assessment.

Potential elemental impurities derived from manufacturing equipment: The contribution of elemental impurities from this source may be limited and the subset of elemental impurities that should be considered in the risk assessment

will depend on the manufacturing equipment used in the production of the drug product. The specific elemental impurities of concern should be assessed based on the knowledge of the composition of the components of the manufacturing equipment that come in contact with components of the drug product. The risk assessment of this source of elemental impurities is one that can potentially be utilized for many drug products using similar process trains or processes.

In general, the processes used to prepare a given drug substance are considerably more aggressive than processes used in preparing the drug product when assessed relative to the potential to leach or remove elemental impurities from manufacturing equipment. Contributions of elemental impurities from drug product processing equipment would be expected to be lower than contributions observed for the drug substance. However, when this is not the case based on process knowledge or understanding, the potential for incorporation of elemental impurities from the drug product manufacturing equipment in the risk assessment (e.g., hot melt extrusion) should be considered.

Elemental impurities leached from container closure systems: The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf-life of the drug product. Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed.

Factors that should be considered (for liquid and semi-solid dosage forms) are shown as follows, but are not limited.

・Hydrophilicity/hydrophobicity, Ionic content, pH, Temperature (cold chain vs room temperature and processing conditions), Contact surface area, Container/material composition, Terminal sterilization, Packaging process, Material sterilization, Duration of storage

Table 2.66-2 provides recommendations for inclusion of elemental impurities in the risk assessment. This can be applied to all sources of elemental impurities in the drug product.

Table 2.66-2 Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	○	○	○	○
Pb	1	○	○	○	○
As	1	○	○	○	○
Hg	1	○	○	○	○
Co	2A	○	○	○	○
V	2A	○	○	○	○
Ni	2A	○	○	○	○
Tl	2B	○	×	×	×
Au	2B	○	×	×	×
Pd	2B	○	×	×	×
Ir	2B	○	×	×	×
Os	2B	○	×	×	×
Rh	2B	○	×	×	×
Ru	2B	○	×	×	×
Se	2B	○	×	×	×
Ag	2B	○	×	×	×
Pt	2B	○	×	×	×
Li	3	○	×	○	○
Sb	3	○	×	○	○
Ba	3	○	×	×	○
Mo	3	○	×	×	○
Cu	3	○	×	○	○
Sn	3	○	×	×	○
Cr	3	○	×	×	○

○: necessary ×: unnecessary

4.4. Evaluation

As the potential elemental impurity identification process is concluded, there are following two possible outcomes.

1) The risk assessment process does not identify any potential elemental impurities.

2) The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities.

During the risk assessment, a number of factors that can influence the level of the potential elemental impurity in the drug product should be considered.

4.5. Summary of Risk Assessment Process

The risk assessment is summarized by reviewing relevant product or component specific data combined with information and knowledge gained across products or processes to identify the significant probable elemental impurities that may be observed in the drug product.

The significance of the observed or predicted level of the elemental impurity should be considered in relation to the PDE of the elemental impurity. As a measure of the significance of the observed elemental impurity level, a control threshold is defined as a level that is 30% of the established PDE in the drug product. The control threshold may be used to determine if additional controls may be required.

If the total elemental impurity level from all sources in the drug product is expected to be consistently less than

30% of the PDE, then additional controls are not required, provided adequate controls on elemental impurities are demonstrated by the appropriate assessment of the data.

If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product.

The variability of the level of an elemental impurity should be factored into the application of the control threshold to drug products. Sources of variability may include the following.

- Variability of the analytical method
- Variability of the elemental impurity level in the specific sources
- Variability of the elemental impurity level in the drug product

For some components that have inherent variability (e.g., mined excipients), additional data may be needed to apply the control threshold.

5. Converting between PDEs and Concentration Limits

The PDEs reported in μg per day (μg/day) give the maximum permitted quantity of each element that may be contained in the maximum daily intake of a drug product. Because the PDE reflects total exposure from the drug product, it is useful to convert the PDE into concentrations as a tool in evaluating elemental impurities in drug products or their components. Any of the following options may be selectable as long as the resulting permitted concentrations assure that the drug product does not exceed the PDEs. In the choice of a specific option the daily dose of the drug product needs to be determined or assumed.

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily doses of not more than 10 g: This option is not intended to imply that all elements are present at the same concentration, but rather provides a simplified approach to the calculations. The option assumes the daily dose of the drug product is 10 g or less, and that elemental impurities identified in the risk assessment (the target elements) are present in all components of the drug product. Using Equation (1) below and a daily dose of 10 g of drug product, this option calculates a common permissible target elemental concentration for each component in the drug product.

$$\text{Concentration } (\mu\text{g/g}) = \frac{PDE\ (\mu\text{g/day})}{\text{daily dose of drug product (g/day)}} \qquad (1)$$

This approach, for each target element, allows determination of a fixed common maximum concentration in μg per g in each component. The permitted concentrations are provided in Table 2.66-3.

Table 2.66-3 Permitted Concentrations of Elemental Impurities for Option 1

Element	Class	Oral Concentration (μg/g)	Parenteral Concentration (μg/g)	Inhalation Concentration (μg/g)
Cd	1	0.5	0.2	0.3
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
TI	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

If all the components in a drug product do not exceed the Option 1 permitted concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product. If the permitted concentrations in Table 2.66-3 are not applied, Options 2a, 2b, or 3 should be followed.

Option 2a: Common permitted concentration limits of elements across drug product components for a drug product with a specified daily dose: This option is similar to Option 1, except that the drug daily dose is not assumed to be 10 g. The common permitted concentration of each element is determined using Equation (1) and the actual maximum daily dose. This approach, for each target element, allows determination of a fixed common maximum concentration in μg per g in each component based on the actual daily dose provided. If all components in a drug product do not exceed the Option 2a permitted concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product.

Option 2b: Permitted concentration limits of elements in individual components of a drug product with a specified daily dose: Permitted concentrations based on the distribution of elements in the components (e.g., higher concentrations in components with the presence of an element in

question) may be set. For each element identified as potentially present in the components of the drug product, the maximum expected mass of the elemental impurity in the final drug product can be calculated by multiplying the mass of each component material times the permitted concentration pre-established in each material and summing over all components in the drug product, as described in Equation (2). The total mass of the elemental impurity in the drug product should comply with the PDEs unless justified according to other relevant sections of this general information. If the risk assessment has determined that a specific element is not a potential impurity in a specific component, there is no need to establish a quantitative result for that element in that component. This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product. Equation (2) may be used to demonstrate that component-specific limits for each element in each component of a drug product assure that the PDE will be met.

$$PDE\ (\mu g/day) \geqq \sum_{k=1}^{N} C_k \cdot M_k \qquad (2)$$

k = an index for each of N components in the drug product

C_k = permitted concentration of the elemental impurity in component k (μg/g)

M_k = mass of component k in the maximum daily dose of the drug product (g)

Option 3: Finished Product Analysis: The concentration of each element may be measured in the final drug product. Equation (1) may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity.

6. Speciation and Other Considerations

Speciation is defined as the distribution of elements among chemical species based on the difference of molecular structure including ionic element, molecules, or complexes, reflecting isotopic composition, electronic or oxidation state. When the toxicities of different species of the same element are known to be different, the PDE has been established using the toxicity information on the species expected to be in the drug product.

When elemental impurity measurements are used in the risk assessment, total elemental impurity levels in drug products may be used to assess compliance with the PDEs. The identification of speciation is not particularly expected, however such information could be used to justify lower or higher levels when the identified species is more or less toxic, respectively, than the species used for the calculation of the PDEs.

When total elemental impurity levels in components are used in the risk assessment, providing information on release of an elemental impurity from the component in which it is found is not expected. However, such information could be used to justify levels higher than those based on the total elemental impurity content of the drug product.

7. Analytical Procedures

The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the risk assessment. Ⅱ. Elemental Impurities-Procedures or suitable alternative procedures for determining levels of elemental impurities should be used.

8. Lifecycle Management

If changes to the drug product or components have the potential to change the elemental impurity content of the drug product, the risk assessment, including established controls for elemental impurities, should be re-evaluated. Such changes could include changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems or facilities.

Ⅱ. Elemental Impurities－Procedures

Procedures of Elemental Impurities are methods to control elemental impurities contained in drug products and their components, etc. 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. As elemental impurities may be ubiquitous they have the potential to be present in trace amounts therefore special precautions may be necessary to avoid sample contamination. (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. 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 samples measurable without addition of solvent.

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: Generally, an indirect solution is obtained 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 results in a clear solution. 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 for each analytical sequence.

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 *Matrix matched solution*

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

Sample stock solution: Proceed as directed in 1. *Sample Preparation* above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer, if necessary.

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: *Matrix matched solution*

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 *Matrix matched solution* 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% deviation 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 using a wavelength necessary for the detection of the *Target element(s)* according to manufacture's recommended procedure. 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 *Matrix matched solution*

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

Sample stock solution: Proceed as directed in 1. *Sample Preparation* above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer, if necessary.

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: *Matrix matched solution*

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 *Matrix matched solution* 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% deviation 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 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 method and 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)* at 1.0*J* in a *Matrix matched solution*.

Spiked sample solution 1: Prepare a solution of the sample under test, spiked with appropriate reference materials for the *Target element(s)* 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 for the *Target element(s)* at 80% of the *Target concentration*, 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 0.5 to 1.5 of *J*, using appropriate reference materials, in a *Matrix matched solution* and blank.

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*. The concentrations of the added reference materials after the preparation of the samples range from 0.5 to 1.5 of *J*, and should contain at least three different concentrations.

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*. Or at least 9 determinations (e.g., 3 replicates of 3 concentrations) covering the specified range.

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% (n = 12) 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 less than or equal to 50% of J.

4. Glossary

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

(ii) Matrix matched solution: Solutions having the same solvent composition as the *Sample solution*. In the case of an aqueous solution, *Matrix matched solution* would indicate that the same acids, acid concentrations and mercury stabilizer are used in both preparations.

(iii) Target elements: Elements whose levels in the drug product must be controlled within acceptable limits.

(iv) 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 *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*.

(v) *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.

(vi) 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.

(vii) **Cross validate:** Verification whether or not the same result can be obtained from the corresponding analyses for the same sample.