5.10. Elemental Impurities

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This draft proposal contains general chapter text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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5.10. Elemental Impurities

The Procedure section of this General Chapter has been harmonized with corresponding texts of the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia.

Portions of the IP text that and are not part of the PDG harmonized text, are marked with symbols (♦♦).

This chapter specifies limits and procedures for the amounts of elemental impurities in drug products. Regardless of the approach used, compliance with the limits specified is required for all drug products unless otherwise specified in an individual monograph or specifically excluded in this chapter.

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard. Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment.

This chapter does not apply to herbal products, radiopharmaceuticals; vaccines; cell metabolites; DNA products; allergenic extracts; cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives; products based on genes (gene therapy); cells (cell therapy); tissue (tissue engineering); dialysate solutions not intended for systemic circulation; total parenteral nutrition (TPN).

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. However, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data, or if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using Table 2 in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment.

Speciation

The determination of the oxidation state, organic complex, or combination is termed “speciation”. Each of the elemental impurities has the potential to be present in differing oxidation or complexation states. However, arsenic and mercury are of particular concern because of the differing toxicities of their inorganic and complexed organic forms.

The arsenic limits are based on the inorganic (most toxic) form. Arsenic can be measured using a total-arsenic procedure under the assumption that all arsenic contained in the material under test is in the inorganic form. Where the limit is exceeded using a total-arsenic procedure, it may be possible to show, via a procedure that quantifies the different forms, that the inorganic form meets the specification.

The mercury limits are based upon the inorganic (2^+) oxidation state. The methyl mercury form (most toxic) is rarely an issue for pharmaceuticals. Thus, the limit was established assuming the most common (mercuric) inorganic form. Limits for articles that have the potential to contain methyl mercury (e.g., materials derived from fish) are to be provided in the monograph.

Routes of administration

The elements included in the tables below have been placed into three classes, based on their toxicity and likelihood of occurrence in the drug product. The classification scheme is intended to focus the risk assessment on those elements that are the most toxic but also have a reasonable probability of inclusion in the drug product, shown in Table 2.

The toxicity of an elemental impurity is related to its extent of exposure (bioavailability). The extent of exposure has been determined for each of the elemental impurities of interest for the following routes of administration: oral, parenteral, inhalational and cutaneous and transcutaneous. These limits are based on chronic exposure. For other routes of administration, consider the oral permitted daily exposures (PDEs) in Table 1 as a starting point in developing specific PDEs for other routes of administration, except where otherwise stated in the individual monograph. Some elemental impurities for which PDEs have not been established due to their low inherent toxicity, if these elemental impurities are present or included in the drug product, they are addressed by ICH Q3D guideline.

Drug Products

The limits described in the third through sixth columns of Table 1 are the base daily dose PDEs of the elemental impurities of interest for a drug product taken by a patient according to indicated routes of administration.

Parenteral products. Parenteral drug products with maximum daily volumes up to 2 liter may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 litre (e.g., saline, dextrose, and solutions for irrigation), a 2- litre volume may be used to calculate permissible concentrations from PDEs.

Permitted daily exposures. The information in Table 1 applies to oral, parenteral, inhalation, and cutaneous and transcutaneous drug products (referred to as cutaneous product) whether intended for local or systemic effects. This table does not apply to products intended for mucosal administration. Products not covered by Table 1 should be assessed following the principles described for other routes of administration. For cutaneous products, an additional limit is provided for elements that have been demonstrated to be sensitizers (i.e., cobalt and nickel). The cutaneous and transcutaneous concentration limit (CTCL) was added because sensitization interactions have a concentration effect (not simply related to the total amount of the sensitizing element). The current limits for the stated routes of exposure for each element are provided in Table 1.

Table 1 – Permitted Daily Exposures for Elemental Impurities

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)	Cutaneous Products	
					PDE (µg/day)	CTCL for Sensitizers (µg/g)
Cadmium	1	5	2	3	20	-
Lead	1	5	5	5	50	-
Arsenic	1	15	15	2	30	-
Mercury	1	30	3	1	30	-
Cobalt	2A	50	5	3	50	35*
Vanadium	2A	100	10	1	100	-
Nickel	2A	200	20	6	200	35*
Thallium	2B	8	8	8	8	-
Gold	2B	300	300	3	3000	-
Palladium	2B	100	10	1	100	-
Iridium	2B	100	10	1	100	-
Osmium	2B	100	10	1	100	-
Rhodium	2B	100	10	1	100	-

Ruthenium	2B	100	10	1	100	-
Selenium	2B	150	80	130	800	-
Silver	2B	150	15	7	150	-
Platinum	2B	100	10	1	100	-
Lithium	3	550	250	25	2500	-
Antimony	3	1200	90	20	900	-
Barium	3	1400	700	300	7000	-
Molybdenum	3	3000	1500	10	15000	-
Copper	3	3000	300	30	3000	-
Tin	3	6000	600	60	6000	-
Chromium	3	11000	1100	3	11000	-

*For elements with a cutaneous PDE and a CTCL, both limits need to be met. In case the results are conflicting, the lowest limit is applied. Using cobalt as an example, based on the PDE and a 1 g maximum daily dose of drug product, the calculated cutaneous concentration is 50 µg/g, which exceeds the CTCL of 35 µg/g. In this situation, the CTCL should be used.

Recommendations for Elements to be considered in the Risk Assessment

Table 2 identifies elemental impurities for inclusion in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 2 – Elements to be Considered in the Risk Assessment

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added*			
			Oral	Parenteral	Inhalation	Cutaneous
Cadmium	1	Yes	Yes	Yes	Yes	Yes
Lead	1	Yes	Yes	Yes	Yes	Yes
Arsenic	1	Yes	Yes	Yes	Yes	Yes
Mercury	1	Yes	Yes	Yes	Yes	Yes
Cobalt	2A	Yes	Yes	Yes	Yes	Yes
Vanadium	2A	Yes	Yes	Yes	Yes	Yes
Nickel	2A	Yes	Yes	Yes	Yes	Yes
Thallium	2B	Yes	No	No	No	No
Gold	2B	Yes	No	No	No	No
Palladium	2B	Yes	No	No	No	No
Iridium	2B	Yes	No	No	No	No
Osmium	2B	Yes	No	No	No	No
Rhodium	2B	Yes	No	No	No	No
Ruthenium	2B	Yes	No	No	No	No
Selenium	2B	Yes	No	No	No	No
Silver	2B	Yes	No	No	No	No
Platinum	2B	Yes	No	No	No	No
Lithium	3	Yes	No	Yes	Yes	No
Antimony	3	Yes	No	Yes	Yes	No

Barium	3	Yes	No	No	Yes	No
Molybdenum	3	Yes	No	No	Yes	No
Copper	3	Yes	No	Yes	Yes	No
Tin	3	Yes	No	No	Yes	No
Chromium	3	Yes	No	No	Yes	No

[*]**This also applies to materials for which the element is intrinsically associated with (e.g., as can be found in naturally occurring materials).**

Options for Demonstrating Compliance

A. Drug Product Analysis Option

The results obtained from the analysis of a typical dosage unit, scaled to a maximum daily dose, are compared to the Daily Dose PDE.

Daily Dose PDE ≥ measured value (µg per g) × maximum daily dose (g per day)

The measured amount of each impurity is not more than the Daily Dose PDE, unless otherwise stated in the individual monograph.

Based on this, calculation formula mentioned for limit is as follows.

$$\text{Measures value µg per g (ppm)(Specification Limit)} = \frac{\text{PDE } (\mu\text{g per day})}{\text{Maximum daily dose (g per day)}}$$

Example for Limit

Elements	Class	PDE (µg per day)	Daily dose (g per day)	Specification Limit
Cadmium	1	5	10	0.5

B. Summation Option

Separately, add the amounts of each elemental impurity (µg per g) present in each of the components of the drug product:

$$\text{Daily Dose PDE} \geq \left[\sum_{1}^{M} (C_M \times W_M\right] \times D_D$$

Where, M = each ingredient used to manufacture a dosage unit;
C_M = element concentration in component (drug substance or excipient) (µg per g);
W_M = weight of component in a dosage unit (g per dosage unit);
D_D = number of units in the maximum daily dose (unit per day).

The result of the summation of each impurity is not more than the Daily Dose PDE, unless otherwise stated in the individual monograph. Before products can be evaluated using this option, the manufacturer must ensure that additional elemental impurities cannot be inadvertently added through the manufacturing process or via the container–closure system over the shelf life of the product.

C. Individual Component Option

For drug products with a daily dose of not more than 10 g, if all drug substances and excipients in a formulation meet the concentration limits shown in Table 3, then these components may be used in any proportion. No further calculation is necessary. While elemental impurities derived from the manufacturing process or the container–closure system are not specifically provided for in the Individual Component Option, it is expected that the drug product manufacturer will ensure that these sources do not contribute significantly to the total content of elemental impurities.

Drug Substance and Excipients

The acceptable levels of elemental impurities depend on the material's ultimate use. Therefore, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance manufacturers or excipient manufacturers, who may provide test data, or, if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using Table 2 in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment.

The values provided in Table 3 are example concentration limits for components (drug substances and excipients) of drug products dosed at a maximum daily dose of 10 g per day. These values serve as default concentration limits to aid discussions between drug product manufacturers and the suppliers of the components of their drug products.

NOTE — Individual components may need to be limited at levels different from those in the table depending on monograph-specific mitigating factors.

Table 3 – Permitted Concentrations of Elemental Impurities for Individual Component Option (based on a maximum 10 g dose)

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)	Cutaneous Concentration (µg/g)	CTCL for Sensitizers (µg/g)
Cadmium	1	0.5	0.2	0.3	2	-
Lead	1	0.5	0.5	0.5	5	-
Arsenic	1	1.5	1.5	0.2	3	-
Mercury	1	3	0.3	0.1	3	-
Cobalt	2A	5	0.5	0.3	5*	35
Vanadium	2A	10	1	0.1	10	-
Nickel	2A	20	2	0.6	20*	35
Thallium	2B	0.8	0.8	0.8	0.8	-
Gold	2B	30	~~10~~ 30	~~0.1~~ 0.3	300	-
Palladium	2B	10	1	0.1	10	-
Iridium	2B	10	1	0.1	10	-
Osmium	2B	10	1	0.1	10	-
Rhodium	2B	10	1	0.1	10	-
Ruthenium	2B	10	1	0.1	10	-
Selenium	2B	15	8	13	80	-
Silver	2B	15	1.5	0.7	15	-
Platinum	2B	10	1	0.1	10	-
Lithium	3	55	25	2.5	250	-
Antimony	3	120	9	2	90	-
Barium	3	140	70	30	700	-
Molybdenum	3	300	150	1	1500	-
Copper	3	300	30	3	300	-
Tin	3	600	60	6	600	-
Chromium	3	1100	110	0.3	1100	-

*For elements with a cutaneous PDE and a CTCL, both limits need to be met. If the results are conflicting, the lowest limit is applied. Using cobalt as an example, based on a 10 g maximum daily dose of the drug product, the calculated cutaneous concentration is 5 µg/g; based on a 1 g maximum daily dose of drug product, the calculated cutaneous concentration is 50 µg/g, which exceeds the CTCL of 35 µg/g. In this situation, the CTCL should be used.

Analytical Testing

If, by process monitoring and supply chain control, manufacturers can demonstrate compliance, then further testing may not be needed. When testing is done to demonstrate compliance, following procedures may be used.

Procedures

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 cmposition of the considered substances and the specification limits for the element(s) of interest vary considerably, it is difficult to describe all suitable test solution 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 verify whether or not the same result can be obtained from the corresponding analyses for the same sample against either procedure 1 or 2.

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.)*♦

Test solution preparation

Forms of test solution preparation include *Neat*, *Direct aqueous solution*, *Direct organic solution*, and *Indirect solution*. The selection of the appropriate test preparation depends on the substance under examination and is the responsibility of the analyst. When a test preparation is not indicated in the monograph, an analyst may use any appropriately validated test preparation procedures, including but not limited to procedures described below. In cases where spiking of a substance under examination 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 test solution preparation steps are performed. Reference solutions 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 alternative procedures that allows the examination of unsolved 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. Generally, an indirect solution is obtained when a material is not directly soluble in aqueous or organic solvents. Total digestion is the preferred test solution preparation approach to obtain an *indirect solution*. Digest the sample using the *Closed vessel digestion* procedure provided below or one similar to it. ♦ (*Note- The test solution 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 test solution preparation procedure is designed for samples that must be digested in 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 0.5g of substance under examination 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 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 test and reference solutions should be sufficiently pure for the intended purpose.

Analytical Procedures 1 and 2

System standardization and suitability evaluation using applicable reference materials should be performed for each analytical sequence.

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 test used (procedural verification) by meeting the procedure validation requirements below.

Procedure 1. Inductively Coupled Plasma- Optical Emission Spectrometry (ICP-OES) (2.4.42).

Reference solution (a). 1.5 J of the *Target element(s)* in a matrix matched solution.

Reference solution (b). 0.5 J of the *Target element(s)* in a matrix matched solution.

Test solution (a). Proceed as directed in *test solution* preparation above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer.

Test solution (b). Dilute the *test solution (a)* 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.

Standardization. Reference solution (a), Reference solution (b), and blank.

System suitability

Sample. Reference 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 *Test solution (b)*.

Suitability criteria. Not more than 20 per cent deviation from the theoretical concentration of the system suitability sample.

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).

Procedure 2. Inductively Coupled Plasma- Mass Spectrometry (ICP-MS) (2.4.42).

Reference solution (a). 1.5 *J* of the *Target element(s)* in a matrix matched solution

Reference solution (b). 0.5 *J* of the *Target element(s)* in a matrix matched solution.

Test solution (a). Proceed as directed for *test solution* preparation above. Allow the sample to cool, if necessary. For mercury determination, add an appropriate stabilizer.

Test solution (b). Dilute the *test solution (a)* with an appropriate solvent to obtain a final concentration of the *Target elements* 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.

Standardization. Reference solution (a), Reference solution (b), and blank.

System suitability

Sample. Reference 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 *Test solution (b)*.

Suitability criteria. Not more than 20 per cent deviation from the theoretical concentration of the system suitability sample.

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).

Requirements for Procedure Validation

♦*NOTE — Some validation requirements provided below may differ from those provided in chapter 2.4.2 and 2.4.42.*♦

All procedures must be validated in accordance with the validation requirements described below. The level of validation necessary to ensure that an alternative procedure is acceptable depends on whether a limit test or a quantitative determination is used. Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use.

During procedure validation, the system suitability requirements as established for the procedure must be met.

Procedures for Limit Tests

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

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.

Detection Limit

The detection limit is shown to be sufficiently low by the analysis of samples with known concentrations of analyte at and below the target concentration.

For the purposes of this chapter, detection limit does not mean that the procedure must demonstrate lowest possible analytical result.

Reference solution. A preparation of reference materials for the *Target element(s)* at 1.0 J in a matrix matched solution.

Spiked test solution (a). 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 test solution (b). Prepare a solution of the sample under test, spiked with appropriate reference materials for the *Target element(s)* at 80 per cent of the target concentration, solubilized or digested as described in *sample preparation*.

Unspiked test solution. A sample of material under examination, solubilized or digested in the same manner as the spiked sample solutions.

Acceptance criteria

Non-instrumental procedures. Spiked test solution (a) provides a signal/ response, e.g., color, or intensity equivalent to or greater than that of the Reference solution. Spiked test solution (b) must provide a signal / response, e.g., color, or intensity less than that of spiked test solution (a) (*NOTE — The signal/response, e.g., color, or intensity from each spiked test solution is not less than the unspiked test solution determination).*

Instrumental procedures. The average value of the three replicate measurements of spiked test solution (a) is within ± 15 per cent of the average value obtained for the replicate measurements of the reference solution. The average value of the replicate measurements of spiked test solution (b) must provide a signal intensity or value less than that of the reference solution (*NOTE — Correct the values obtained for each of the spiked solutions using the unspiked test solution*).

Specificity

The procedure must be able to unequivocally assess (2.5.10 Validation of Analytical Procedures) each *Target element* in the presence of components that may be expected to be present, including other *Target elements*, and matrix components.

Precision, only for Instrumental Methods (Repeatability)

Test solutions. Six independent samples of the substance under examination, spiked with appropriate reference materials for the *Target elements* at the target concentration.

Acceptance criteria

The relative standard deviation is not more than 20 per cent for each *Target element*.

Procedure 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 tests and reference materials.

Accuracy

Reference solutions. Prepare solutions containing the *Target elements* at three concentrations ranging from 0.5 J to 1.5 J, using appropriate reference materials, in a Matrix matched solution.

Test solutions. 3 independent sample preparations of the substance under examination spiked with appropriate reference materials for the Target element(s) at the target concentration, J, before any sample preparation steps (digestion or solubilization). Spike concentrations should range from 0.5 J to 1.5 J and should include at least 3 individual concentrations.

Acceptance criteria

Spike recovery: 70 per cent –150 per cent for the mean of three independent sample preparations at each concentration

Precision

Repeatability

Test solutions. Six independent samples of substance under examination (taken from the same lot) spiked with appropriate reference materials for the *Target element(s)* at the 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 in both cases, not more than 20 per cent for each *Target* element.

Intermediate precision (ruggedness)

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.

Acceptance criteria

Relative standard deviation is not more than 25 per cent 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.

Range and Linearity

Demonstrated by meeting the Accuracy requirement.

Quantitation Limit

Use the results from the accuracy study.

QL of 0.5 J is confirmed when the accuracy acceptance criteria for 0.5 J spiked solution is met.

Acceptance criterion: the QL is less than or equal to 0.5 J.

Definition of Terms

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

Matrix matched solution: Solutions having the same solvent composition as the test 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.

Target elements: Elements which must be evaluated according to the requirements defined in other chapters.

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. [*Note- Target limits can be approximated by dividing the permitted daily exposures (PDEs) by the maximum daily dose of the drug product.]*

J: Final concentration of the Target element(s) in the standard and the sample solutions. It corresponds to 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 (Note: the density of the sample solution may have to be considered).

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.

Cross validation: Verification whether or not the same result can be obtained from the corresponding analyses for the same sample.