STANDARD OPERATING PROCEDURE	
Department: Quality Control	**SOP No.:**
Title: Elemental Impurities Analysis	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down a procedure for Elemental Impurity Analysis in Finished good products.

2.0 SCOPE:

This SOP is applicable of procedure for Elemental Impurity Analysis in Finished good products in quality control department.

3.0 RESPONSIBILITY:

Executive quality control / Asst. Manager.

4.0 ACCOUNTABILITY:

Manager Quality Control / Manager Quality Assurance

5.0 DEFINITION:

NA

6.0 PROCEDURE:

6.1 Elemental Impurity Analysis shall be performed by approved outside contact testing Laboratory **.**

6.2 Elemental Impurity Analysis shall be performed based on the requirement raised by the Clients/regulatory authority/based on product submission requirement etc.

6.3 Elemental Impurity Analysis report shall be reviewed and signed followed stamping on it.

6.4 **Elemental Impurity Analysis Requirements:**

6.4.1 Regulatory authorities are responsible for ensuring that pharmaceutical products are both effective and safe. Potentially toxic and harmful contaminants—including elemental impurities—must be identified, and limits defined for the maximum levels that a patient should be exposed to.

New procedures for the analysis of elemental (inorganic) impurities in pharmaceutical products and ingredients were finalized. Existing wet chemical and colorimetric tests, such as European Pharmacopoeia Heavy Metals chapter 2.4.8 and United States Pharmacopeia Convention (USP)

General Chapter <231>, have been replaced with instrumental methods.

These methods provide specific, quantitative determination of individual elemental impurities in drug products.

The latest ICH Q3D and USP<232> chapters include catalyst elements, and other inorganic contaminants

That may enter a drug product. Such contaminants can come from raw materials exposure limits are defined according to each impurity's toxicity and route of administration, rather than, the manufacturing process, the environment, packaging, and container closure systems (CCS)

6.4.2 **Elemental Impurity Limits (Drug Products):**

The permitted daily exposure (PDE) limits for elemental impurities in drugs intended for oral, parenteral, and inhalational routes of administration, as per the ICH and USP chapters, are shown in Table 1.

The potential toxicity of an elemental impurity is different depending on the route of administration. Elemental impurities must be considered in a product risk assessment, appropriate for the intended

route of administration of the final drug product. The likelihood of the element being naturally present (e.g. elements associated with a mineral-based raw material) or intentionally or unintentionally added (e.g. as a catalyst in chemical reactions, or via contamination from process equipment) must also be considered. The most toxic and ubiquitous Class 1 elements (Cd, Pb, As, and Hg) must be considered in the risk assessment for all drug products. Other elements, such as the Class 3 impurities, may need to be considered only if the drug is intended for parenteral or inhalational administration. The three classes are defined based on the toxicity of the elements and the likelihood of them occurring in drug products intended for each route of administration. If a risk assessment is performed, it must follow the guidelines defined in USP<232>, summarized in Table 1.

STANDARD OPERATING PROCEDURE

Department: Quality Control	**SOP No.:**
Title: Elemental Impurities Analysis	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

Table 1. The permitted daily exposure (PDE) limits for elemental impurities in drug products, according to their route of administration. Elements shaded in the table should be considered in product risk assessment. All elements listed should be included in risk assessment if naturally present or if intentionally or unintentionally added

ICH/USP Class	Element	Oral PDE (µg/day)	Parenteral PDE(µg/day)	Inhalational PDE(µg/day)
Class 1	Cd – Cadmium	5	2	3
	Pb - Lead	5	5	5
	As - Arsenic inorganic)	15	15	2
	Hg - Mercury (inorganic)	30	3	1
Class 2A	Co – Cobalt	50	5	3
	V - Vanadium	100	10	1
	Nickel	200	20	5
Class 2B	Tl - Thallium	8	8	8
	Au – Gold	100	100	1
	Pd – Palladium	100	10	1
	Ir – Iridium	100	10	1
	Os – Osmium	100	10	1
	Rh – Rhodium	100	10	1
	Ru – Ruthenium	100	10	1
	Se – Selenium	150	80	130
	Ag - Silver	150	10	7
	Pt - Platinum	100	10	1
Class 3	Li – Lithium	550	250	25
	Sb – Antimony	1200	90	20
	Ba - Barium	1400	700	300
	Mo – Molybdenum	3000	1500	10
	Cu – Copper	3000	300	30
	Sn – Tin	6000	600	60
	Cr – Chromium	11000	1100	3

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
Cd – Cadmium	1	Yes	Yes	Yes	Yes
Pb - Lead	1	Yes	Yes	Yes	Yes
As - Arsenic (inorganic)	1	Yes	Yes	Yes	Yes
Hg - Mercury (inorganic)	1	Yes	Yes	Yes	Yes
Co – Cobalt	2A	Yes	Yes	Yes	Yes
V - Vanadium	2A	Yes	Yes	Yes	Yes
Nickel	2A	Yes	Yes	Yes	Yes
Tl - Thallium	2B	Yes	No	No	No
Au – Gold	2B	Yes	No	No	No
Pd – Palladium	2B	Yes	No	No	No
Ir – Iridium	2B	Yes	No	No	No
Os – Osmium	2B	Yes	No	No	No
Rh – Rhodium	2B	Yes	No	No	No
Ru – Ruthenium	2B	Yes	No	No	No
Se – Selenium	2B	Yes	No	No	No
Ag - Silver	2B	Yes	No	No	No
Pt - Platinum	2B	Yes	No	No	No
Li – Lithium	3	Yes	No	Yes	Yes
Sb – Antimony	3	Yes	No	Yes	Yes
Sb – Antimony	3	Yes	No	No	Yes
Mo – Molybdenum	3	Yes	No	No	Yes
Cu – Copper	3	Yes	No	Yes	Yes
Sn – Tin	3	Yes	No	No	Yes
Cr – Chromium	3	Yes	No	No	Yes

Options for Demonstrating Compliance:

Drug Product Analysis Option

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

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

The measured amount of each impurity is NMT the daily dose PDE, unless otherwise stated in the individual monograph.

Summation Option

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

$$\text{Daily dose PDE} \geq [\Sigma M1(CM \times WM)] \times DD$$

M	= each ingredient used to manufacture a dosage unit
CM	= element concentration in component (drug substance or excipient) (µg/g)
WM	= weight of component in a dosage unit (g/dosage unit)
DD	= number of units in the maximum daily dose (unit/day)

The result of the summation of each impurity is NMT 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.

6.4.3 **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 summary should consider the significance of the observed or predicted level of the elemental impurity relative 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 the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.

STANDARD OPERATING PROCEDURE	
Department: Quality Control	**SOP No.:**
Title: Elemental Impurities Analysis	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

6.4.4 **Elemental Impurity Limits (Drug Products):** 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 excipient in order to meet the criteria mentioned herewith. Drug product manufacturers can use elemental impurity test data on components from tests performed by the drug substances 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 the compliance 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. 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 the **Table 3** are example concentrations limit for components (drug substance and excipient) of drug products dosed at a maximum daily dose of 10 g/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

ICH/USP Class	Element	Oral Concentration (µg/day)	Parenteral Concentration (µg/day)	Inhalational Concentration (µg/day)
Class 1	Cd – Cadmium	0.5	0.2	0.3
	Pb - Lead	0.5	0.5	0.5
	As - Arsenic inorganic)	1.5	1.5	0.2
	Hg - Mercury (inorganic)	3	0.3	0.1
Class 2A	Co – Cobalt	5	0.5	0.3
	V - Vanadium	10	1	0.1
	Nickel	20	2	0.5
Class 2B	Tl - Thallium	0.8	0.8	0.8
	Au – Gold	10	10	0.1
	Pd – Palladium	10	1	0.1
	Ir – Iridium	10	1	0.1
	Os – Osmium	10	1	0.1
	Rh – Rhodium	10	1	0.1
	Ru – Ruthenium	10	1	0.1
	Se – Selenium	15	8	13
	Ag - Silver	15	1	0.7
	Pt - Platinum	10	1	0.1
Class 3	Li – Lithium	55	25	2.5
	Sb – Antimony	120	9	2
	Ba - Barium	140	70	30
	Mo – Molybdenum	300	150	1
	Cu – Copper	300	30	3
	Sn – Tin	600	60	6
	Cr – Chromium	1100	110	0.3

STANDARD OPERATING PROCEDURE	
Department: Quality Control	**SOP No.:**
Title: Elemental Impurities Analysis	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

7.0 ABBREVIATION:

Pvt.	:	Private
Ltd	:	Limited
ICH	:	International Conference for Harmonization
USP	:	United States Pharmacopoeia Convention
DD	:	Daily Dose
CM	:	element concentration in component
WM	:	weight of component in a dosage unit
M	:	Each ingredient used to manufacture a dosage unit
PDE	:	Permitted Daily Exposure
µg	:	Micro gram
NMT	:	Not More than
%	:	Percent
≥	:	More than equal to
CCS	:	Container closure systems
QA	:	Quality Assurance
QC	:	Quality Control

8.0. ANNEXURES:

NA

9.0 DISTRIBUTION:

- Master Copy — Quality Assurance Department (QA)
- Controlled Copy — Quality Control Department (QC)

STANDARD OPERATING PROCEDURE	
Department: Quality Control	**SOP No.:**
Title: Elemental Impurities Analysis	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

10.0 REFERENCES:

- USP-43 General Chapter <232> (Elemental Impurities – Limits)
- ICH Q3D (Elemental Impurities)

11.0 REVISION HISTORY:

Revision No.	Change Control No.	Details of Changes	Reason of Changes	Effective Date	Done By