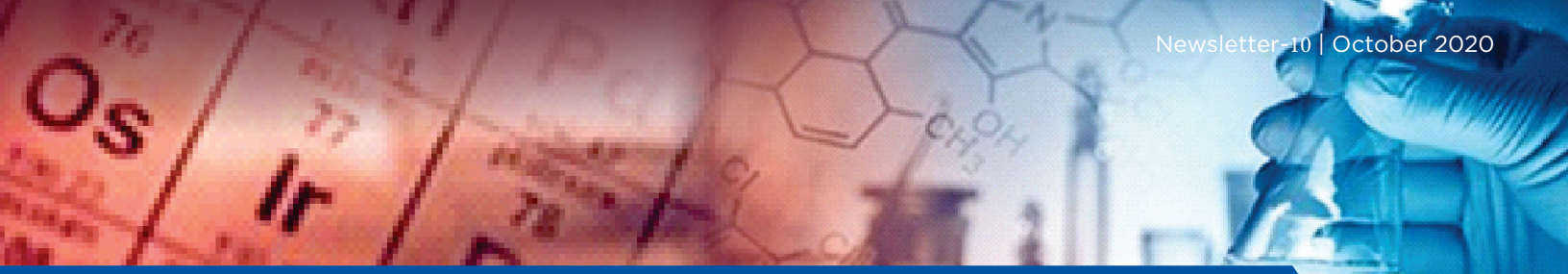


Elemental Impurities

Introduction

Impurity: As per the USP general chapter<1086> Impurities are critical quality attributes of drug substances and drug products because they have the potential to affect safety and efficacy of the product, They are classified as Organic(process or storage related), Inorganic(that results from the manufacturing process) and residual solvents(Organic liquids).

Elemental impurities includes catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, or added intentionally, or e introduced inadvertently (e.g., by interactions with processing equipment and the container closure system)

Elemental impurities in drug product may arise from several sources. Since elemental impurities do not provide therapeutic benefit to the patient, their levels should be controlled within the acceptable limits in the drug product.

ICH Q3D replaces the test of heavy metals published in monographs (EP, USP, and JP)

USP general chapter <232> and <233>& EP 5.20 introduced on elemental impurities . It is based on the instrumental techniques like ICP-OES (Inductively coupled plasma Optical emission Spectrometry), ICP-MS (Inductively coupled plasma Mass Spectrometry) instrumental technique.

General Principle

IDENTIFY

Identify known & potential sources of elemental impurities that may find their way into the drug product

ANALYZE

Determine the probability of observance of particular elemental impurities in the drug product.

EVALUATE

Compare the observed or predicted levels of elemental impurities with the established permitted daily exposure (PDE).

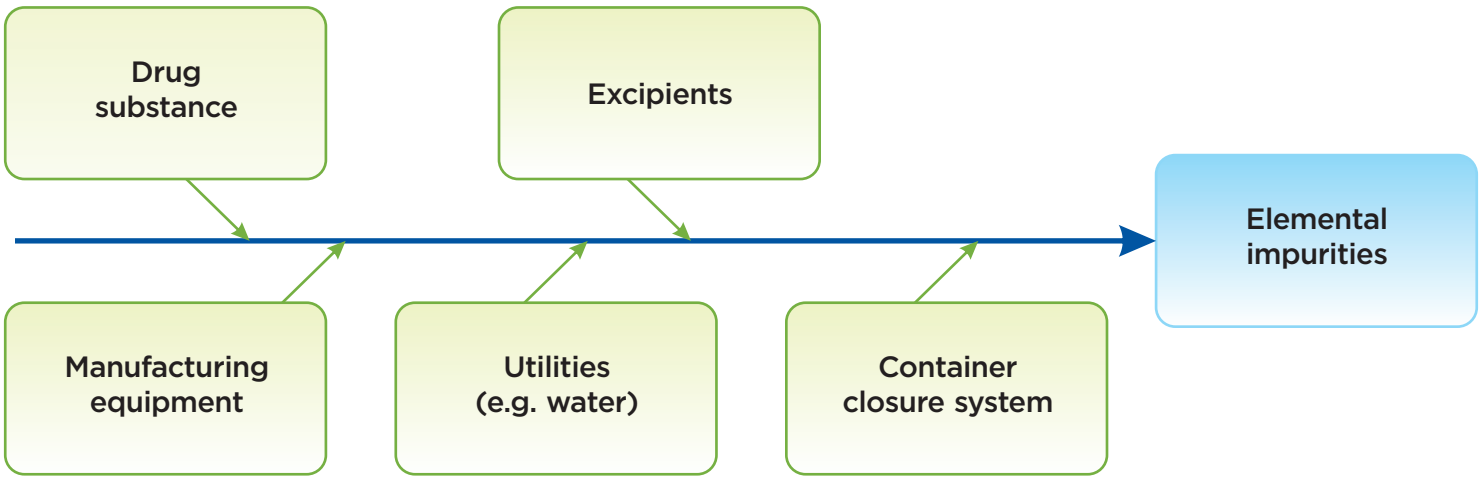
CONTROL

Document and implement a control strategy to limit elemental impurity in drug product.

Potential Sources of Elemental Impurities

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

Residual elemental impurities resulting from elemental intentionally added to reactions or processes leading up to the preparation of the drug substance, reagents, starting materials, or excipients (e.g. metal catalysts)



Element Classification

Class 1: The elements AS, Cd, Hg & Pb are human toxicants that have limited or no use in manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g. mined excipients), because of their unique nature, these four elements require evaluation during the risk assessment, across all potentials sources of elemental impurities & routes of administration.

Class 2: Elements in this class are generally considered as route-dependent human toxicants. Class 2 elements are further divided in subclasses 2A and 2B based on their relative likely-hood of occurrence in the drug product.

Class 2A: Elements have relatively high probability of occurrence in the drug product and thus required risk assessment across all potential sources of elemental impurities and route of administration.

The Class 2A elements are : Co, Ni, and V.

Class 2B: Elements have reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials. As a result, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other component of drug product.

The elemental impurities in Class 2B include: Ag, Au, Ir, Pd, Pt, Rh, Ru, and Se.

Class 3: The elements in this class have relatively low toxicities by the oral route of administration (high PDEs, generally >500 Qg/day) but may require consideration in the risk assessment for inhalation and parenteral routes.

The elements in Class 3 includes: Ba, Cr, Cu, Li, Mo, Sb, and Sn.

Other elements: Some elemental impurities for which PDEs have not been established due to their low inherent toxicity and or differences in regional regulations are not addressed in guideline ICH Q3D. Some of the elements considered include: Al, B, Ca, Fe, K, Mg, Mn, Na, W, and Zn.

Elemental impurties for drug products

Element	Daily Oral PDE µg/day	Daily Parental PDE µg/day	Daily Inhalation PDE µg/day	Listing Document
Cadmium	5	2	2	USP <232>, ICH Q3D
Lead	5	5	5	USP <232>, ICH Q3D
Inorganic Arsenic	15	15	2	USP <232>, ICH Q3D
Inorganic Mercury	30	3	1	USP <232>, ICH Q3D
Cobalt	50	5	3	ICH Q3D
Vanadium	100	10	1	ICH Q3D
Nickel	200	20	5	USP <232>, ICH Q3D
Thallium	8	8	8	ICH Q3D
Gold	100	100	1	ICH Q3D
Iridium	100	10	1	USP <232>, ICH Q3D
Osmium	100	10	1	USP <232>, ICH Q3D
Palladium	100	10	1	USP <232>, ICH Q3D
Rhodium	100	10	1	USP <232>, ICH Q3D
Ruthenium	100	10	1	USP <232>, ICH Q3D
Selenium	150	80	130	ICH Q3D
Silver	150	10	7	ICH Q3D
Platinum	100	10	1	USP <232>, ICH Q3D
Lithium	550	250	25	ICH Q3D
Anitmony	1200	90	20	ICH Q3D
Barium	1400	700	300	ICH Q3D
Tin	6000	600	60	ICH Q3D
Chromium	11000	1100	3	USP <232>, ICH Q3D
Molybdenum	3000	1500	10	USP <232>, ICH Q3D
Copper	3000	300	30	USP <232>, ICH Q3D

ICH Q3D: Limits for elemental impurities

Table A.2.1: Permitted Daily Exposures for Elemental Impurtities[1]

Element	Class[2]	Oral PDE µg/day	Parental PDE µg/day	Inhalation PDE µg/day
Cd	1	5	2	2
Pb	1	5	5	5
Ag	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

Opt 1: Assume 10g/day dose. If all components meet PDE concentration, they may be used in any proportion.

Opt 2a: Use the actual dose to calculate PDE concentration. if all components meet the PDE, they may be used in any proportion.

Opt 2b: Use the amounts of each component present and data on metals present to set limits for individual components.

Opt 3: Drug product analysis with limits based on daily dose.

Control of Elemental Impurities

1. Identification of the steps in the manufacturing process that result in the reduction of elemental impurities through specific or nonspecific purification steps.
2. Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity in drug product.
3. Establishment of material (e.g. synthetic intermediates and raw materials) or excipient specifications to limit the level of elemental impurity contribution from those sources.
4. Establishment of specification limits for the drug substance.
5. Establishment of specification limits for the drug product.
6. Reliance on the compliance with compendial standards for materials used in drug product processes.
7. Selection of appropriate container closure systems.

JRF has experience and expertise to undertake the tests for elemental impurities, as per the guidelines SANCO, U.S. EPA OCSPP, ABNT NBR, ICH etc.

At JRF, we have a legacy of **more than 25 years in carrying out GLP studies** and complying with the regulatory requirements for various countries and guidelines SANCO, EPA, ICH etc. Our state-of-art laboratories are equipped in handling difficult matrices and achieving lower detection limits. We are also experienced to carry our various physchem studies, 5-Batch analysis, residue testing, bioanalytical, environment fate and metabolism studies and ecotoxicity studies.

References

1. Guideline of ICH Q3D for Elemental Impurities.
2. USP General Chapters <232> & EP 5.20 Elemental Impurities.
3. Monographs of EP, USP, and JP for Elemental Impurities.

About the Author:

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She has expertise in conducting GLP studies like method development, method validation, characterisation as per regulatory guideline for various sectors including agrochemical, pharmaceuticals, and specialty chemicals. She is a pioneer with excellent analytical performance and proven success in directing, leading and managing projects from concept to completion. She is actively involved in research activities. She has an experience of more than 4 years, including academic research, R&D, biological extraction, analytical instrumentation, and CRO industry.

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