



A Review on Elemental Impurity Control under ICH Q3D

Kurni Lakshmi Deepthi¹, T. Gayathri Samhitha², Vasudha Vodnala,³

¹Associate Professor Dept. of Pharmaceutical chemistry, Malla Reddy college of Pharmacy, Maisammaguda, Dhulapally kompally, Secunderabad- 500100

²Dept. of Pharmaceutical Analysis, Malla Reddy college of Pharmacy, Maisammaguda, Dhulapally kompally, Secunderabad- 500100

³Assiatant Professor Dept. of Pharmaceutical chemistry, Malla Reddy college of Pharmacy, Maisammaguda, Dhulapally kompally, Secunderabad- 500100

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ABSTRACT:

The presence of elemental impurities (EIs) in pharmaceuticals arising from catalysts, environmental contaminants, or manufacturing equipment poses a significant risk to patient safety due to potential systemic toxicity and lack of therapeutic benefit. This review evaluates the implementation of the ICH Q3D guideline, which transitioned the industry from non-specific "heavy metals" tests to a rigorous, science-based toxicological framework. The article details the classification of 24 elements, the calculation of Permitted Daily Exposure (PDE) across different administration routes, and the requirement for multi-disciplinary risk assessments. It further examines the technical superiority of Inductively Coupled Plasma (ICP) technologies over legacy methods. ICH Q3D represents a pivotal shift in pharmaceutical quality assurance, emphasizing proactive risk management and high-sensitivity analytical validation to ensure global regulatory alignment and patient protection.

Key Words: Elemental impurities, ICH Q3D, PDE, risk assessment, ICP-MS, pharmaceutical quality, heavy metals

Introduction:

Elemental impurities are defined as traces of metals or metalloids that may be present in a drug product but provide no therapeutic benefit [1]. The shift from the legacy "heavy metals" concept to the modern ICH Q3D approach is fundamental; whereas the old methods relied on the non-specific precipitation of metal sulfides, the modern approach is based on individual element toxicity [1, 3]. These impurities originate from diverse sources, including intentionally added catalysts, environmental contaminants in raw materials, leaching from stainless steel manufacturing equipment, and migration from container-closure systems [2, 5]. Because many of these elements, such as Lead (Pb) and Cadmium (Cd), are known to bioaccumulate and cause chronic organ toxicity, the guideline mandates a move away from simple "pass/fail" limit tests toward a comprehensive risk-based assessment that evaluates the specific hazard to the patient [4, 7].

REGULATORY BACKGROUND

Evolution of Guidelines

For over a century, the pharmaceutical industry relied on USP <231>, a colorimetric sulfide precipitation test that was notoriously inaccurate, often yielding false negatives for elements like Mercury and Selenium [4, 11]. The recognition of these technical flaws led to the development of USP <232> (Limits) and USP <233>

Address for Correspondence: Kurni Lakshmi Deepthi, Department of Pharmaceutical Chemistry, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Hyderabad, 500100; **E-Mail:** deepthi.kurni@gmail.com

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(Procedures), which served as the regional precursors to the global harmonization efforts of the International Council for Harmonisation (ICH) [11, 14].

Overview of ICH Q3D

The ICH Q3D guideline provides a global policy for limiting EIs in drug products, aiming to protect patient health while providing a predictable regulatory environment for manufacturers [1, 3]. Its scope encompasses new finished drug products, though it generally excludes radiopharmaceuticals, vaccines, and certain herbal products unless there is a specific safety concern [3, 6].

CLASSIFICATION OF ELEMENTAL IMPURITIES

Class 1 Elements (As, Cd, Hg, Pb):

These are considered significant human toxicants. Due to their high toxicity across all routes of administration and their common occurrence as environmental contaminants, they must be included in every risk assessment conducted by a manufacturer [1, 5].

Class 2 Elements:

- **Class 2A (Co, Ni, V):** These have a high probability of occurrence in drug products and are considered significant toxicants [4].
- **Class 2B (Ag, Au, Ir, Pd, Pt, Rh, Ru, Se, Tl):** These have lower toxicity or a lower probability of being present; they are usually only included in the assessment if they were intentionally added during the synthesis of the drug substance [5, 15].

Class 3 Elements (Ba, Cr, Cu, Li, Mo, Sb, Sn)

These elements have relatively low toxicity when administered orally but can pose risks via parenteral or inhalation routes. They are generally only assessed if the route of administration warrants it or if they are expected to be present in concentrations exceeding the PDE [6, 8].

PERMITTED DAILY EXPOSURE (PDE)

The PDE is the maximum allowed daily intake of an elemental impurity, typically expressed in $\mu\text{g/day}$ [1].

Basis of PDE Calculation

PDE values are derived from the No-Observed-Adverse-Effect Level (NOAEL) or the Lowest-Observed-Adverse-Effect Level (LOAEL) found in toxicological studies [1, 7]. These values are adjusted using five safety factors to account for interspecies differences, study duration, and data reliability [7, 9]:

$$\text{PDE} = \frac{\text{NOAEL} \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

Route-Specific PDE

Limits are established for Oral, Parenteral, and Inhalation routes. Inhalation PDEs are the most stringent (lowest) because the lungs have a large surface area and lack the first-pass metabolism of the liver, making the body more vulnerable to absorbed metals [1, 6].

Table 1: Permitted Daily Exposure (PDE) for Elemental Impurities

Element	Symbol	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Arsenic	As	1	15	15	2
Cadmium	Cd	1	5	2	2
Mercury	Hg	1	30	3	1
Lead	Pb	1	5	5	5
Cobalt	Co	2A	50	5	3
Nickel	Ni	2A	220	22	6
Vanadium	V	2A	100	10	1
Silver	Ag	2B	150	15	7
Gold	Au	2B	130	130	1
Iridium	Ir	2B	100	10	1
Palladium	Pd	2B	100	10	1
Platinum	Pt	2B	100	10	1
Rhodium	Rh	2B	100	10	1
Ruthenium	Ru	2B	100	10	1
Selenium	Se	2B	150	80	130
Thallium	Tl	2B	8	8	8
Barium	Ba	3	13000	1300	300
Chromium	Cr	3	11000	1100	3
Copper	Cu	3	3000	300	30
Lithium	Li	3	550	250	25
Molybdenum	Mo	3	3000	1500	10
Antimony	Sb	3	1200	90	20
Tin	Sn	3	6000	600	60
Zinc	Zn	3	13000	1300	400

SOURCES OF ELEMENTAL IMPURITIES

Drug Substance Related

Many modern synthetic routes require metal catalysts (e.g., Palladium or Platinum). If purification processes are not optimized, these metals can remain as residues in the active pharmaceutical ingredient (API) [5, 15].

Excipients

Excipients derived from natural minerals, such as Talc, Bentonite, or Titanium Dioxide, are significant sources of Lead and Arsenic due to their geochemical origin [9, 14].

Manufacturing Equipment

High-energy processes like milling or the use of corrosive solvents can cause leaching from stainless steel vessels (releasing Cr, Ni, or Fe) or gaskets (releasing Zn) [8, 14].

Container Closure System

Leaching can occur from glass (Aluminum, Barium), plastic additives, or rubber stoppers, particularly in liquid formulations stored for long durations [14, 15].

RISK ASSESSMENT APPROACH

This is the "Identify, Evaluate, Control" cycle.

- **Identification:** Manufacturers must map the entire supply chain to find potential metal entries [7, 8].
- **Evaluation:** Observed levels are compared to the PDE. If levels are below the Control Threshold (30% of the PDE), routine testing may be avoided [8, 9].
- **Control:** If levels exceed 30%, a control strategy (e.g., intermediate testing or process changes) must be implemented [7, 15].

ANALYTICAL METHODS

ICP-MS

Inductively Coupled Plasma Mass Spectrometry is the gold standard, offering part-per-billion (ppb) sensitivity and the ability to detect multiple elements in a single run [10, 11].

ICP-OES

ICP Optical Emission Spectrometry is suitable for higher concentration limits and is often more cost-effective for Class 3 elements [12, 13].

AAS & Validation

While Atomic Absorption (AAS) is still used for single-element analysis, it is becoming rare [10]. All methods must meet USP <233> criteria for accuracy, precision (repeatability and ruggedness), and specificity [11, 13].

Elemental Impurities (ICH Q3D)

Class	1	2
PDE Parental	15 (µg/day)	2 (µg/day)
PDE Oral	15 (µg/day)	
	As	PDE Inhalation

1 15 As 15	1 3 Hg 30	1 5 Pb 5	1 2 Cd 5	2A 5 Co 50	2A 20 Ni 200	2A 10 V 100	2B 8 Ti 8
2B 100 Au 100	2B 10 Pd 100	2B 10 Ir 100	2B 10 Os 100	2B 10 Rh 100	2B 10 Ru 100	2B 80 Se 150	2B 10 Ag 150
2B 10 Pt 100	3 250 Li 550	3 90 Sb 1200	3 700 Ba 1400	3 1500 Mo 3000	3 300 Cu 3000	3 600 Sn 6000	3 1100 Cr 11000

Table 1: Permitted Daily Exposure (PDE) for Elemental Impurities [1, 2, 3]

8. IMPLEMENTATION & 9. CHALLENGES

Implementation requires extensive documentation and collaboration with suppliers [14]. Challenges include the cost of equipment, the variability of natural excipients, and the lack of data from non-pharmaceutical grade suppliers, which complicates the "component approach" to risk assessment [14, 15].

9. CASE STUDIES & FUTURE PERSPECTIVES

Literature highlights failures in removing Palladium catalysts in early-phase development and the emerging use of Green Chemistry to reduce heavy metal usage [15]. Future directions include automated risk-scoring software and more advanced detection techniques like Laser-Induced Breakdown Spectroscopy (LIBS) [10, 15].

10. Risk-Based Decision Tree for ICH Q3d Compliance

A practical implementation of ICH Q3D follows an iterative Identify–Evaluate–Control process. Potential sources are first identified, the expected or measured level of each impurity is then compared with the applicable PDE, and the outcome is documented with appropriate controls where necessary [16]. The control threshold is defined as 30% of the established PDE and may be used to determine whether additional controls are warranted, taking variability into account [16].

11. Potential Entry Points

The major entry points can be represented as: raw materials → API synthesis → purification → excipients and water → manufacturing equipment → formulation → container-closure system → finished drug product. The relative importance of each source depends on the manufacturing process and dosage form. For liquid and semi-solid products, packaging-related leaching may require particular attention because the formulation remains in contact with the container for an extended period [16].

12. Elemental Impurities Across The Pharmaceutical Manufacturing Lifecycle

Elemental impurities can enter a pharmaceutical product at several stages from raw-material procurement to final packaging. ICH Q3D identifies four broad source categories: intentionally added elements such as catalysts or inorganic reagents; impurities present in drug substances, excipients or water; contributions from manufacturing equipment; and leachables from container-closure systems [16]. A lifecycle-based assessment helps manufacturers identify where preventive controls can be applied before the impurity reaches the finished product.

13. Toxicological Profiles of Selected Elements

Arsenic is a recognized human carcinogen and has been associated with both cancer and non-cancer effects. Lead primarily affects the nervous system and may also cause hematological and renal effects. Cadmium is particularly associated with renal and skeletal toxicity, while mercury is associated with neurological and renal toxicity. These toxicological differences explain why the ICH Q3D framework uses element-specific PDEs rather than a single generic heavy-metal limit [16,25].

14. Toxicological Significance of Major Elemental Impurities

Elemental impurities differ substantially in their toxicological profiles, and their potential clinical significance depends on the identity of the element, chemical form, dose, route of administration, and duration of exposure. ICH Q3D therefore classifies elements according to toxicity and likelihood of occurrence rather than treating all metals as a single group [16]. Class 1 elements—arsenic, cadmium, mercury, and lead—receive particular attention because of their established human toxicity and their potential occurrence through commonly used materials. The toxicological evidence underlying the PDE values is derived from relevant human or animal data and incorporates modifying factors to account for interspecies differences, variability, study duration, severity of toxicity, and data quality [16].

15. CONCLUSION

ICH Q3D has successfully modernized elemental control by emphasizing patient safety through toxicological data. The transition from testing to a risk-based science approach ensures that manufacturers build quality into the process rather than relying on final-product testing alone [1, 15].

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