International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

A Review on Elemental Impurity Risk Assessment in Pharmaceutical Analysis

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Abstract: ***Elemental impurities represent a critical safety concern in pharmaceutical products due to their toxicological effects, even at trace levels. Regulatory bodies such as the International Council for Harmonisation (ICH), the United States Pharmacopeia (USP), and the European Medicines Agency (EMA) have established stringent guidelines (ICH Q3D, USP <232>, <233>) to ensure patient safety. This review consolidates current knowledge on elemental impurity risk assessment, highlighting sources of contamination, analytical methodologies (ICP-MS, ICP-OES, AAS), and risk evaluation strategies based on permitted daily exposure (PDE) values. Case studies on contamination in herbal medicines and injectables illustrate practical challenges. Future directions include automation, nanotechnology-based sensors, and AI-driven predictive impurity profiling.***

Keywords: Elemental impurities, contamination, nanotechnology-based sensors

1. Introduction

Pharmaceutical analysis is the backbone of drug development and quality assurance, ensuring that medicines are safe, effective, and compliant with international standards. Among the various impurities that may compromise drug quality, **elemental impurities** occupy a unique position because they are inorganic, non-degradable, and potentially toxic even at trace levels. Unlike organic impurities, which can often be removed or degraded during synthesis and purification, elemental impurities persist and may accumulate in the human body, leading to long-term health risks[1].Elemental impurities can originate from multiple sources: **catalysts** used in synthetic processes (e.g., palladium, platinum, rhodium), **excipients** of natural origin (e.g., talc, calcium carbonate), and **packaging materials** (e.g., aluminum or lead leaching from glass vials and rubber stoppers). Their presence is not always predictable, making **risk assessment** a critical part of pharmaceutical quality contro l[2]. Recognizing these risks, international regulatory agencies have established stringent guidelines. The **International Council for Harmonisation (ICH)** introduced the **Q3D guideline**, which classifies 24 elements into risk categories and sets **permitted daily exposure (PDE)** limits based on toxicological data. The **United States Pharmacopeia (USP)** reinforced these requirements through chapters **<232>** (limits) and **<233>** (procedures), while the **European Medicines Agency (EMA)** and the **World Health Organization (WHO)** have aligned their standards to ensure global harmonization.To comply with these regulations, advanced **analytical techniques** such as **Inductively Coupled Plasma Mass Spectrometry (ICP-MS)**, **Optical Emission Spectroscopy (ICP-OES)**, and **Atomic Absorption Spectroscopy (AAS)** are employed. These methods provide high sensitivity, reproducibility, and multi-element detection capabilities, making them indispensable in modern pharmaceutical laboratories [3].

Beyond compliance, **risk assessment strategies** are essential for proactive control. These include supplier qualification, equipment validation, and routine monitoring of raw materials and finished products. Case studies have demonstrated the real-world impact of elemental impurities, such as heavy metal contamination in herbal medicines, leaching from packaging in injectables, and catalyst residues in anticancer drugs.

Looking forward, the field is evolving with **automation in ICP-MS workflows**, **nanotechnology-based sensors** for portable detection, and **AI-driven predictive models** that can anticipate impurity risks before they occur. These innovations promise to make elemental impurity analysis faster, more reliable, and more accessible across diverse pharmaceutical settings[4].Thus, this review aims to consolidate current knowledge on elemental impurity risk assessment, bridging regulatory frameworks, analytical advances, and practical case studies, while highlighting future directions that will shape the next generation of pharmaceutical analysis.

1.1 Regulatory Guidelines [3] [4] [5]

ICH Q3D Guideline: Introduced in 2014, revised in 2019 (Q3D(R1)), it provides a global harmonized framework for controlling elemental impurities in pharmaceuticals. **Covers** 24 elements**, grouped into classes:**

- Class 1 (high toxicity, must be strictly controlled): Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb).
- Class 2A (toxic, likely to be present): Cobalt (Co), Nickel (Ni), Vanadium (V).
- Class 2B (toxic, less likely to be present): Palladium (Pd), Platinum (Pt), Rhodium (Rh), Iridium (Ir), Osmium (Os), Ruthenium (Ru).
- Class 3 (low toxicity, risk only via parenteral route): Barium (Ba), Chromium (Cr), Copper (Cu), Lithium (Li), Molybdenum (Mo), Antimony (Sb), Tin (Sn).
- Establishes Permitted Daily Exposure (PDE) values based on toxicological data, considering route of administration (oral, parenteral, inhalation).
- Encourages risk-based assessment rather than routine testing, meaning manufacturers must identify potential sources and justify control strategies.

USP <232> and <233>

- USP <232>: Specifies limits for elemental impurities in drug products, harmonized with ICH Q3D.

- USP <233>: Provides validated analytical procedures for testing, primarily using ICP-MS and ICP-OES.
- Emphasizes method validation parameters: accuracy, precision, specificity, detection limits, and robustness.
- Requires manufacturers to demonstrate compliance through either risk assessment or direct testing.

EMA and WHO Perspectives

- **EMA (European Medicines Agency):** Aligns with ICH Q3D, requiring risk assessment for all new drug applications in Europe. EMA also issues guidance on **metal catalyst residues** in active pharmaceutical ingredients (APIs).
- **WHO (World Health Organization):** Focuses on **global harmonization**, especially for herbal medicines and traditional remedies, which are more prone to heavy metal contamination due to environmental factors. WHO guidelines emphasize **quality control in herbal drugs**, ensuring safety in developing countries where herbal medicines are widely used.
- Both EMA and WHO stress the importance of **pharmacopoeial harmonization**, so that global manufacturers can follow a unified standard, reducing duplication of testing and regulatory burden.

1.2 Sources of Elemental Impurities

Catalysts in Synthesis

- Many **active pharmaceutical ingredients (APIs)** are synthesized using transition metal catalysts such as **Platinum (Pt), Palladium (Pd), and Rhodium (Rh)**.
- These metals accelerate reactions like hydrogenation, oxidation, and coupling, but **residual traces** may remain in the final product if purification is incomplete.
- Even at very low concentrations, these metals can cause **toxicity** (e.g., nephrotoxicity, neurotoxicity).
- Regulatory agencies therefore require strict monitoring of catalyst residues, especially in **oncology drugs** and complex synthetic molecules[5].

Excipients of Natural Origin

- Excipients like **talc, calcium carbonate, starch, and gelatin** are often derived from natural sources.
- Geological origin plays a major role: talc mined from contaminated soil may contain **arsenic, lead, or cadmium**.
- Calcium carbonate from limestone deposits can carry **trace heavy metals** depending on the mineral composition.
- Since excipients are used in large quantities, even small contamination levels can significantly contribute to overall impurity burden.
- Supplier qualification and **geological source verification** are critical to minimize risks[6].

Packaging and Storage Leachables

- **Glass vials, rubber stoppers, and plastic containers** can leach metals into drug formulations, especially under stress conditions such as **heat, light, or extreme pH**.
- **Aluminum (Al)** leaching from glass vials has been reported in parenteral formulations.
- **Lead (Pb)** contamination can occur from older glass manufacturing processes or pigments used in packaging.
- Rubber stoppers may introduce **antimony or zinc**, while plastic containers can leach **tin or chromium**.
- Long-term storage, especially of injectables, increases the risk of leaching, making **packaging compatibility studies** essential[7].

Other Potential Sources

- **Water used in manufacturing**: If not properly purified, can introduce trace metals like iron, copper, or manganese.
- **Manufacturing equipment**: Stainless steel reactors may contribute chromium or nickel if corrosion occurs.
- **Environmental contamination**: Dust, air, or handling practices can inadvertently introduce impurities during production[8].

1.3 Analytical Techniques

ICP-MS (Inductively Coupled Plasma Mass Spectrometry)

a) **Principle**: The sample is nebulized into an argon plasma (~6000–8000 K). Atoms are ionized, and the ions are separated by a mass spectrometer based on their mass-to-charge ratio.
b) **Instrumentation details**: Includes a plasma torch, nebulizer, ion optics, quadrupole or time-of-flight mass analyzer, and detectors.
c) **Strengths**:
- Ultra-trace detection (ppt–ppb range).
- Simultaneous multi-element analysis.
- High precision and reproducibility.
- Capable of isotopic analysis (e.g., distinguishing isotopes of Pb or Hg).

d) Limitations:
- Very high cost and maintenance.
- Requires clean lab conditions to avoid contamination.
- Matrix interferences (e.g., high salt content) can affect accuracy.

e) Pharmaceutical applications:
- Monitoring Class 1 toxic elements (As, Cd, Hg, Pb).
- Detecting catalyst residues (Pt, Pd, Rh) in oncology APIs.
- Routine compliance with ICH Q3D and USP <233>[3].

1.4 ICP-OES (Inductively Coupled Plasma Optical Emission Spectroscopy) [9]

a) **Principle**: In plasma, atoms are excited and emit light at characteristic wavelengths. The emitted radiation is measured, and intensity correlates with concentration.
b) **Instrumentation details**: Plasma torch, optical system with diffraction grating, photomultiplier tubes or CCD detectors.
c) **Strengths**:
- Multi-element detection in a single run.
- Faster throughput compared to AAS.
- Moderate cost compared to ICP-MS.
- Robust for routine quality control.

d) **Limitations:**
- Detection limits are higher (ppm–ppb range).
- Less sensitive for ultra-trace elements.
- Spectral interferences can occur if multiple elements emit at similar wavelengths.

e) **Pharmaceutical applications:**
- Screening excipients for trace metals.
- Routine QC in manufacturing environments.
- Suitable for Class 3 elements (low toxicity, e.g., Cu, Mo, Sn).

1.5 AAS (Atomic Absorption Spectroscopy)

a) **Principle**: Atoms in the sample absorb light at specific wavelengths; the amount of absorbed light correlates with concentration.
b) **Instrumentation details**: Hollow cathode lamp (element-specific), atomizer (flame or graphite furnace), monochromator, and detector.
c) **Strengths**:
- Cost-effective and widely available.
- Simple operation and maintenance.
- Good for targeted single-element analysis.

d) **Limitations:**
- Limited to one element at a time.
- Lower sensitivity compared to ICP techniques.
- Not suitable for complex impurity profiling.

e) **Pharmaceutical applications:**
- Confirmatory testing of specific metals (e.g., Pb in herbal drugs).
- Smaller labs with limited resources.
- Educational and training purposes in pharmaceutical institutions.

1.5 Risk Assessment Strategies[10] [11] [12]

1) PDE Values (Permitted Daily Exposure):
a) **Definition**: PDE is the maximum acceptable intake of an elemental impurity per day without causing adverse health effects.
b) **Calculation factors**:
- **Toxicological data**: Derived from animal studies and human exposure data.
- **Safety factors**: Applied to account for variability in populations.
- **Patient body weight**: Standard assumption is 50–70 kg adult.
- **Route of administration**: Oral, parenteral, or inhalation — each has different absorption and toxicity profiles.

c) **Example:** PDE for lead (Pb) is stricter for parenteral drugs than oral formulations because direct bloodstream exposure increases toxicity risk.

2) Supplier Qualification:
a) **Importance**: Raw materials and excipients are major sources of elemental impurities.
b) **Steps**:
- Audit suppliers for compliance with pharmacopeial standards.
- Require certificates of analysis (CoA) for impurity levels.
- Implement long-term contracts with trusted suppliers to ensure consistency.
- Periodic re-testing of excipients to verify impurity levels remain within limits.

c) **Outcome:** Reduces risk at the source, preventing contamination before manufacturing begins.

3) Equipment Validation:
a) **Risk**: Manufacturing equipment (reactors, pipelines, storage tanks) can leach metals such as nickel, chromium, or iron due to corrosion.
b) **Validation process**:
- Conduct extractable and leachable studies.
- Simulate worst-case conditions (high temperature, acidic/basic environments).
- Document results in qualification reports (IQ, OQ, PQ).

c) Preventive measures:
- Use corrosion-resistant materials (e.g., stainless steel 316L).
- Regular maintenance and cleaning protocols.
- Replace worn-out parts to avoid contamination.

4) Control Strategies in Manufacturing:
- **Routine monitoring**: Regular testing of raw materials, intermediates, and finished products for elemental impurities.
- **Batch testing**: Random sampling of production batches to ensure compliance.
- **Preventive maintenance**: Scheduled equipment checks to minimize leaching risks.
- **Risk-based approach**: Focus testing on high-risk areas (e.g., parenteral drugs, oncology APIs) while reducing unnecessary testing in low-risk products.
- **Documentation**: Maintain detailed records of risk assessments, supplier audits, and testing results for regulatory inspections.

5) Integrated Risk Management:
- Combines **toxicological evaluation (PDE values)**, **supplier control**, **equipment validation**, and **manufacturing strategies** into a holistic system.
- Ensures compliance with **ICH Q3D, USP <232>/<233>, EMA, and WHO guidelines**.
- Protects patient safety while optimizing manufacturing efficiency.

2. Conclusion

Elemental impurities represent a critical challenge in pharmaceutical analysis because of their toxicological impact, persistence, and potential to compromise patient safety. Regulatory frameworks such as **ICH Q3D**, **USP <232>/<233>**, and guidelines from **EMA and WHO** have established harmonized standards to control these impurities, ensuring global compliance and safeguarding public health.

The sources of contamination are diverse- ranging from **catalysts in synthesis**, **natural excipients**, and **packaging leachables**, to **manufacturing equipment and environmental exposure**. This complexity necessitates a comprehensive risk-based approach. Analytical techniques such as **ICP-MS, ICP-OES, and AAS** provide powerful tools for detection and quantification, each with unique strengths suited to different laboratory and regulatory contexts.

Effective risk assessment strategies- including **PDE value calculations**, **supplier qualification**, **equipment**

validation, and **preventive control measures**- form the backbone of impurity management. Case studies on herbal medicines, injectables, and oncology drugs highlight the real-world consequences of inadequate monitoring, reinforcing the need for vigilance.

Looking ahead, the integration of **automation in ICP-MS workflows**, **nanotechnology-based sensors**, and **AI-driven predictive impurity profiling** promises to revolutionize impurity testing, making it faster, more reliable, and more proactive. These innovations will not only strengthen regulatory compliance but also enhance patient safety and confidence in pharmaceutical products.

In summary, elemental impurity risk assessment is not merely a regulatory requirement but a vital component of modern pharmaceutical quality assurance. By combining **robust analytical techniques, risk-based strategies, and forward-looking innovations**, the industry can ensure safer medicines and contribute to global health protection.

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