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Mpurities in Pharmaceutical Elemental Impurities in Pharmaceutical Risk Assessment of Products: A Review Products a Review Elemental Impurities in Pharm

Ms Shahitha Afreen[1], Ms Shafna Tv[2], Ms Akhil NP[3]

[1,2,3]Student, Pharmaceutical Quality Assurance, Al Shifa College Of Pharmacy

Abstract

Elemental impurities are trace inorganic substances that may enter pharmaceutical products through Poonthavanam post, Perinthalmanna, Malappuram, Kerala – 679325 active pharmaceutical ingredients, excipients, catalysts, manufacturing equipment, water, environmental exposure, and container-closure systems. Their presence is important because toxicity depends on the specific element, dose, route of administration, and duration of exposure. This review summarizes the major sources and classes of elemental impurities, the principles of toxicological evaluation, and the risk-based approach used to assess and control them in pharmaceutical manufacturing. Particular emphasis is placed on the principles of ICH Q3D, including permitted daily exposures (PDEs), route-specific considerations, source identification, risk estimation, analytical verification, and control strategy. Common analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma optical emission spectrometry (ICP-OES) are discussed. The review also considers the role of pharmaceutical quality risk management in supplier qualification, process control, equipment selection, water quality, packaging assessment, and lifecycle monitoring. A structured risk-assessment framework and literature-comparison format are presented to support practical quality assurance applications.

Keywords: active pharmaceutical ingredients, excipients, catalysts, manufacturing equipment, water, environmentalElemental impurities; Risk assessment; ICH Q3D; Heavy metals; ICP-MS; ICP-OES; Permitted daily exposure; Pharmaceutical quality. exposure, and container-closure systems. Their presence is important because toxicity depends on the specific element, dose, route of administration, and duration of exposure. This review summarizes the major sources and classes of elemental impurities, the principles of toxicological evaluation, and the risk-based approach used to assess and control them in pharmaceutical manufacturing. Particular emphasis is placed on the principles of ICH Q3D, including permitted daily exposures (PDEs), route-specific considerations, source identification, risk estimation, analytical verification, and control strategy. Common analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma optical emission spectrometry (ICP-OES) are discussed. The review also considers the role of pharmaceutical quality risk management in supplier qualification, process control, equipment selection, water quality, packaging assessment, and lifecycle monitoring. A structured risk-assessment framework and literature-comparison format are presented to support practical quality assurance applications.

Keywords: Elemental impurities; Risk assessment; ICH Q3D; Permitted daily exposure; Heavy metals; ICP-MS; ICP-OES; Pharmaceutical quality; Quality risk management.

1. Introduction

Elemental impurities are inorganic elements that may be present in drug substances, excipients, finished pharmaceutical products, process streams, or packaging-related materials. Unlike organic process impurities, elemental impurities cannot be degraded by conventional chemical degradation pathways and therefore require source-based control and toxicological evaluation.

The increasing emphasis on lifecycle pharmaceutical quality has shifted elemental-impurity evaluation from simple end-product testing toward a science- and risk-based approach. The objective is not merely to demonstrate that a product passes a metal limit test, but to understand where elements can enter the manufacturing process, determine whether exposure can approach a toxicological concern, and establish controls proportional to the identified risk.

In this context, ICH Q3D provides the central framework for evaluating elemental impurities in drug products. The risk assessment considers the drug substance and excipients, manufacturing processes, water, equipment, and container-closure systems, together with the intended route and maximum daily dose.

2. Elemental Impurities in Pharmaceuticals

Elemental impurities can arise intentionally, incidentally, or naturally. Some elements are introduced as catalysts or reagents, while others are present as trace constituents of raw materials or may be introduced by contact with production equipment. The presence of an element does not automatically mean that a product presents unacceptable risk; risk depends on its concentration, daily patient exposure, toxicological profile, and route of administration.

The assessment therefore links analytical concentration to patient exposure. A useful quality-assurance perspective is to distinguish between hazard (the intrinsic toxicological potential of an element) and risk (the likelihood and magnitude of exposure under actual product conditions).

3. Classification of Elemental Impurities

For pharmaceutical risk assessment, elements are commonly grouped according to their toxicological concern and likelihood of occurrence. ICH Q3D uses classes to guide the depth of evaluation and the relevance of different potential sources. A simplified working classification is shown below.

4. Sources and Routes of Elemental Contamination

Potential sources should be evaluated systematically across the full manufacturing chain. Raw materials and excipients may contribute naturally occurring elements; catalysts may leave residual metals; manufacturing equipment may contribute metals through wear, corrosion, or contact surfaces; water systems may contribute inorganic contaminants; and packaging components may contribute elements through extractables or leachables.

The source assessment should consider the composition of each material, supplier information, manufacturing route, equipment train, water quality, and the ability of any impurity to accumulate or partition into the final product.

Table 1. Illustrative classification of elemental impurities

Category	Examples	Risk-assessment emphasis
Class 1	As, Cd, Hg, Pb	High toxicological concern; routinely evaluate plausible sources
Class 2A	Co, Ni, V	Toxicological concern with occurrence requiring systematic assessment
Class 2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl	Consider when a plausible source exists in the process or materials
Class 3	Ba, Cr, Cu, Li, Mo, Sb, Sn	Generally lower concern by oral route; still assess when relevant to route/source

Table 2. Potential sources and typical controls

Source	Potential contribution	Typical control
API/raw materials	Trace elements from synthesis or natural origin	Supplier qualification; specifications; risk assessment
Excipients	Elemental residues or naturally occurring metals	Supplier data; periodic verification; incoming controls
Catalysts/reagents	Residual catalyst metals	Process purge/purification; targeted testing
Equipment	Metal release, wear or corrosion	Material selection; maintenance; cleaning; process review
Water	Inorganic contaminants	Water-system qualification and routine monitoring
Container-closure	Elemental extractables/leachables	Packaging assessment and compatibility studies

5. Toxicological Significance of Elemental Impurities

Elemental impurities differ substantially in toxicity. Arsenic, cadmium, mercury, and lead are of particular concern because of their established systemic toxicity and potential chronic effects. Other metals may present organ-specific or route-dependent risks. Toxicity can involve the kidney, liver, nervous system, cardiovascular system, reproductive system, or other organs depending on the element and exposure.

The toxicological assessment is therefore element-specific and dose-dependent. A concentration that is acceptable for one element cannot be interpreted as acceptable for another solely because the analytical concentration is similar.

6. Regulatory Perspective

ICH Q3D is the principal international guideline for elemental-impurity assessment in pharmaceutical dr-

ug products. It establishes permitted daily exposure values for specified elements and promotes risk-based evaluation rather than a universal one-limit approach. The evaluation considers the route of administration, daily dose, likely sources, and the overall control strategy.

Pharmacopoeial and regional requirements may provide complementary analytical or quality expectations. In practice, the quality system should align the risk assessment, analytical methods, specifications, supplier controls, and change-control procedures so that elemental-impurity management remains consistent throughout the product lifecycle.

7. Risk Assessment of Elemental Impurities

Risk assessment begins with identification of all credible sources. Each material and processing step is reviewed for elements that could reasonably enter the drug product. The potential contribution is then estimated using supplier information, historical analytical data, process knowledge, published information, or testing where needed.

The estimated elemental contribution is compared with the applicable PDE after accounting for the product maximum daily dose and route of administration. Where the predicted contribution is well below the PDE and the source is stable and controlled, routine monitoring may be sufficient. Where uncertainty is high, the contribution is close to the PDE, or the source is variable, additional controls or analytical verification are warranted.

Risk assessment should be documented, scientifically justified, and revisited when suppliers, raw materials, processes, equipment, formulations, or packaging components change.

Table 3. Practical risk-ranking framework

Risk level	Severity	Probability / uncertainty	Suggested QA action
Low	Low toxicity or exposure far below PDE	Low and stable	Routine controls; periodic review
Moderate	Potential toxicological relevance	Possible variability or incomplete data	Enhanced supplier/process controls and targeted verification
High	High toxicity or exposure approaching PDE	Likely source, high variability, or significant uncertainty	Immediate mitigation; validated analytical control; documented CAPA/change control as appropriate

8. Analytical Techniques for Elemental Impurities

Analytical verification is commonly performed using highly sensitive elemental-analysis techniques. ICP-MS is particularly useful for trace-level determination because of its broad elemental coverage and low detection capability. ICP-OES provides robust multi-element analysis and is widely applicable when concentrations are within its working range. Atomic absorption spectrometry may also be suitable for selected elements, while other techniques can support specific sample types or screening applications.

Sample preparation is a critical part of the analytical procedure. Complete and reproducible digestion or dissolution is necessary for accurate recovery. Method validation should address specificity, accuracy, precision, range, detection limit, quantitation limit, robustness, and recovery as appropriate to the intended use.

9. Risk-Based Control Strategy

Control should be distributed across the manufacturing system rather than relying only on finished-product testing. Useful measures include qualified suppliers, appropriate raw-material specifications, validated process controls, suitable equipment materials, water-system monitoring, catalyst purge strategies, packaging evaluation, and targeted finished-product testing where justified.

A lifecycle approach is important because a previously acceptable risk profile can change after supplier changes, process scale-up, equipment modification, formulation changes, or packaging changes. Change control should therefore trigger reassessment of potential elemental-impurity sources when relevant.

10. Quality Risk Management Tools

FMEA can be used to rank potential elemental-impurity failure modes by severity, occurrence, and detectability. Fishbone diagrams can help organize source categories, while risk-ranking matrices can support prioritization of analytical testing and mitigation. The chosen tool should fit the complexity of the process and should not replace scientific judgement.

11. Literature-Based Comparative Evaluation

A literature review is most useful when individual studies are compared using a consistent framework. The following format can be used to summarize published evidence relevant to a pharmaceutical product, formulation, or manufacturing process.

Table 4. Suggested format for literature comparison

Author / year	Product / material	Elements studied	Method	Major finding	Risk conclusion
Study 1	API / excipient	As, Cd, Pb, etc.	ICP-MS / ICP-OES	Reported concentrations and source	Below / near / above relevant exposure limit
Study 2	Finished product	Selected elements	Validated ICP method	Batch-to-batch variability assessed	Acceptable with specified controls
Study 3	Packaging / process	Potential migrants	Elemental analysis	Source identified or ruled out	Additional control recommended

12. Research Gap

Published literature does not always provide complete source-to-exposure information for individual pharmaceutical processes. Further work is useful in areas such as low-level variability of excipients across

suppliers, contributions from specialized processing equipment, elemental leachables from modern packaging systems, and harmonized lifecycle approaches for periodic reassessment.

13. Future Perspective

Future elemental-impurity control is expected to emphasize better source characterization, improved trace-level analytical capability, more effective supplier data exchange, and stronger integration of analytical science with pharmaceutical quality risk management. Digital trend analysis may further support early detection of shifts in elemental profiles before they become specification or compliance issues.

14. Conclusion

Elemental-impurity control is a multidisciplinary activity involving toxicology, analytical chemistry, manufacturing science, supplier quality, engineering, and regulatory compliance. A robust risk assessment identifies credible sources, relates potential exposure to the relevant PDE, evaluates uncertainty, and implements proportionate controls. ICH Q3D provides the key framework, while sensitive analytical methods such as ICP-MS and ICP-OES support verification. A documented, lifecycle-based approach is therefore essential for maintaining the safety and quality of pharmaceutical products.

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