REGULATION OF ELEMENTAL IMPURITIES IN MEDICINES: IMPLEMENTATION OF ICH Q3D AND ANALYTICAL CHALLENGES

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Abstract: The purpose of this study is to emphasize the importance of controlling elemental impurities in pharmaceutical products to protect patient health and ensure product quality. Medicines must be as pure as possible because the presence of elemental impurities, which are traces of metals introduced during production, purification, transportation, or storage, can have toxic effects and pose significant health risks. The methodology used in this study involved a detailed review of international guidelines, published research, and analytical techniques related to detecting and regulating elemental impurities. Special focus was placed on the guideline of the International Council for Harmonization on elemental impurity control, which establishes toxicologically based limits for permitted daily exposure. This guideline promotes a scientific and risk-based approach to impurity management. The results show that adherence to Good Manufacturing Practice and thoughtful process design can reduce, but not completely eliminate, elemental impurities. Modern analytical technologies such as inductively coupled plasma mass spectrometry and atomic absorption spectroscopy provide more accurate detection and quantification than classical heavy metal tests. The conclusions highlight that understanding the potential sources of contamination — including raw materials, equipment, water, and packaging — is essential to maintaining safe impurity levels. It is recommended that pharmaceutical manufacturers develop and apply thorough risk assessment strategies throughout production. Continuous monitoring of impurity levels and strict compliance with international standards are crucial for ensuring safety. Additional data from reviewed literature confirm that a systematic, science-driven approach significantly improves impurity control. Such strategies enhance both the reliability of pharmaceutical products and the safety of patients. Ultimately, effective control of elemental impurities represents a cornerstone of modern pharmaceutical quality assurance.
Keywords: elemental impurities, heavy metals, pharmaceutical quality, risk assessment, toxicology, regulatory compliance

1. INTRODUCTION

Metal residues in pharmaceutical substances or drug products can originate from multiple sources (i.e. metal catalysts and reagents used during the synthesis of active pharmaceutical ingredients (APIs) and excipients), manufacturing equipment and piping, bulk packaging, environmental contamination, and cleaning solvents (European Medicines Agency [EMA], 2008). Because these elemental impurities do not provide any therapeutic benefit and may pose health risks, product specifications may need to include limits and validated analytical methods to ensure acceptable quality and safety (EMA, 2008).

Impurities introduced or formed early in the manufacturing process are generally more amenable to removal during purification, and are therefore less likely to persist in the final drug substance. In contrast, impurities generated later in the process are more difficult to eliminate and may be carried forward into the finished product (ICH Q11, 2012).

The ICH Q3D guideline focuses on evaluating the toxicity of potential elemental impurities, establishing Permitted Daily Exposure (PDE) limits for each element of toxicological concern, and applying a risk-based approach for their control in drug products (ICH, 2022). Manufacturers are advised to perform a comprehensive product risk assessment by identifying all potential sources of elemental impurities, including those intentionally added, those present in materials used to prepare the product, and those introduced from equipment or container-closure systems. Observed or predicted impurity levels are then compared against the established PDE values to determine necessary control measures (U.S. Food and Drug Administration [FDA], CDER & CBER, 2018).

ICH Q3D applies to new finished drug products and products containing existing APIs, including purified proteins, polypeptides, polynucleotides, and oligosaccharides. It does not cover herbal products, whole blood, cellular blood components, dialysate solutions not intended for systemic circulation, or elements intentionally included for therapeutic purposes (ICH, 2022).

The ICH Q3D guideline on elemental impurities has been effectively implemented in the European Union since June 2016 for new marketing authorization applications and since December 2017 for authorized medicinal products (European Directorate for the Quality of Medicines & HealthCare [EDQM], 2021). Compared to the earlier CHMP

Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents (EMA, 2008), ICH Q3D expands the scope of elemental impurity control. While the CHMP guideline focused primarily on metals intentionally introduced during drug substance synthesis, ICH Q3D addresses a broader range of sources, including elements not used as catalysts or reagents, and considers contributions from manufacturing processes such as equipment, water, and container-closure systems (CHMP, 2019; EDQM, 2021).

The guideline emphasizes that the drug product manufacturer or Marketing Authorization Holder (MAH) should establish a control strategy based on a comprehensive risk assessment, forming an integral part of overall risk management. ICH Q3D outlines two approaches: the Drug Product Approach and the Drug Product Components Approach (CHMP, 2019). The requirements for implementing ICH Q3D are consistent whether the assessment is conducted via an Active Substance Master File (ASMF) or a Certificate of Suitability (CEP) dossier. A summary of the drug substance risk assessment, including potential intentionally added elemental impurities and mitigation steps, must be included in the ASMF/CEP and made accessible to the drug product manufacturer and regulatory authorities (CHMP, 2019). Union legislation mandates submission of detailed information on drug substance synthesis, including any metal catalysts or reagents used. When elemental impurities are routinely controlled by the drug substance manufacturer, the quality assessor reviews the analytical procedures but defers final compliance evaluation to the drug product assessment (CHMP, 2019).

To support international harmonization, the European Pharmacopoeia integrates ICH Q3D standards into general chapter 5.20 (Elemental Impurities) and relevant monographs, emphasizing risk-based assessment and establishing PDE values for 24 elements (EDQM, 2021). In the United States, drug products with USP monographs must comply with USP General Chapters <232> and <233>. Non-compendial products follow ICH Q3D guidance (CDER & CBER, 2018). A notable advancement is the phase-out of the classical heavy metals test <231>, replaced by modern analytical techniques such as ICP-MS (*Inductively Coupled Plasma – Mass Spectrometry*) and ICP-OES (*Inductively Coupled Plasma – Optical Emission Spectroscopy)* for precise measurement. While Chapter <232> sets limits for acceptable elemental impurity levels in finished products, routine testing may be conducted on components rather than the final dosage form (USP, 2022).

2. ICH Q3D ELEMENT CLASSIFICATION

ICH Q3D (2022) classifies elemental impurities into three categories based on their toxicity, expressed as permitted daily exposure (PDE), and their likelihood of occurrence in pharmaceutical products. The probability of occurrence is determined by factors such as their potential use in manufacturing processes, their presence as co-isolated impurities in raw materials, and their natural prevalence in the environment.

Class 1 elements—arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb)—are highly toxic to humans and are therefore restricted or prohibited in pharmaceutical manufacturing. Their presence in drug products often results from contamination in commonly used excipients. These four elements must always be included in risk assessments for all potential sources of contamination and all routes of administration. Based on the assessment outcomes, additional controls may be required to ensure safety.

Class 2 elements are route-dependent toxicants and are subdivided into Classes 2A and 2B.

Class 2A elements, cobalt (Co), nickel (Ni) and vanadium (V), have a relatively high probability of occurrence and require comprehensive risk assessment across all potential sources and routes.

Class 2B elements, silver (Ag), gold (Au), iridium (Ir), osmium (Os), palladium (Pd), platinum (Pt), rhodium (Rh), ruthenium (Ru), selenium (Se), and thallium (Tl), have a lower likelihood of occurrence and may be excluded unless intentionally introduced during manufacturing.

Class 3 elements, barium (Ba), chromium (Cr), copper (Cu), lithium (Li), molybdenum (Mo), and antimony (Sb), exhibit low oral toxicity and are primarily considered for parenteral and inhalation routes.

Other elements—such as aluminum (Al), boron (B), calcium (Ca), iron (Fe), potassium (K), magnesium (Mg), manganese (Mn), sodium (Na), tungsten (W), and zinc (Zn) —are not addressed by ICH Q3D due to their low toxicity and are managed under regional or alternative guidelines (ICH Q3D, 2022).

3. METHOD FOR ESTABLISHING EXPOSURE LIMITS AND SAFETY ASSESSMENT

For most elemental impurities, acceptable exposure levels are defined by calculating the PDE. This value represents the maximum acceptable intake of an impurity per day without posing a significant health risk (ICH Q3D, 2022). The PDE calculation is based on toxicological data obtained from animal or human studies, using either the No-Observed-Adverse-Effect Level (NOAEL) or the Lowest-Observed-Adverse-Effect Level (LOAEL) from the most relevant study. A correction, or safety factor, is then applied to account for various biological and toxicological uncertainties, including interspecies variability, study duration, data quality, and severity of effects. These factors (denoted F1 through F5) adjust for potential differences between test species and humans, variability among individuals, and limitations in available data. Mass adjustment is also applied to correct for body weight differences between the test species and an average human.

For example, the oral PDE for cobalt was determined using data from a human toxicity study summarized by Tvermoes et al. (2014). In this study, the NOAEL for polycythemia was identified as 1 milligram per day. Applying appropriate safety factors (F1 = 1 for human data, F2 = 10 for human variability, F3 = 2 for a 90-day study, F4 = 1 due to absence of severe toxicity, and F5 = 1 as a NOAEL was available), the resulting PDE was calculated as 50 micrograms per day. This value represents the safe daily intake of cobalt for oral exposure (ICH, 2022).

$$PDE = 1\ mg/day / (1 \times 10 \times 2 \times 1 \times 1) = 0.05\ mg/day = 50\ \mu g/day$$

The ICH Q3D guideline provides a summary safety assessment for each element, identifying the critical studies used to set PDE values. For certain elements such as Ir, Os, Rh and Ru, insufficient data exist to establish PDE values for any administration route. In such cases, PDEs are inferred from structurally similar elements, such as Pd. Each element is assigned separate PDEs for oral, parenteral, and inhalation exposure, as toxicity often varies with the route of administration. Factors considered include the element's oxidation state, human and animal toxicological data, bioavailability, and route-specific effects.

When data for parenteral or inhalation exposure are limited, the oral PDE serves as a reference, adjusted by a modifying factor based on oral bioavailability. For elements with oral bioavailability below 1%, the oral PDE is divided by 100; for bioavailability between 1% - 50%, it is divided by 10; for 50% - 90%, by 2; and for bioavailability above 90%, by 1. If no data are available, a default factor of 100 is applied (ICH, 2022).

As an example, due to limited data on parenteral cobalt exposure, the parenteral PDE was estimated by dividing the oral PDE of 50 micrograms per day by a factor of 10, resulting in a value of 5 micrograms per day. Similarly, the inhalation PDE, based on chronic exposure studies by the Agency for Toxic Substances and Disease Registry, was estimated at approximately 2.9 micrograms per day, underscoring cobalt's potential toxicity even at low airborne concentrations.

$$PDE = \frac{0.0001\ mg/m^3}{1000\ m^3/L}\ x\ 28.800 L/day\ = 2.9 \mu g/day$$

Table 1: Permitted Daily Exposures for Elemental Impurities

Element	Class[2]	Oral PDE µd/day	Parental PDE, µd/day	Inhalation PDE, µd/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	6
Tl	2B	8	8	8
Au	2B	300	300	3
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	15	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

Source: ICH Q3D Guideline for Elemental Impurities

4. RISK ASSESSMENT AND CONTROL OF ELEMENTAL IMPURITIES

The risk assessment process for elemental impurities comprises three key stages. The first stage involves identifying all potential sources of elemental impurities that may be present in a pharmaceutical product. The second stage includes evaluating each impurity by determining its observed or predicted concentration and comparing it with the established PDE value. The final stage consists of summarizing and documenting the results to determine whether existing control measures are sufficient or if additional actions are necessary to ensure the safety of the final drug product (ICH Q3D, 2022).

Potential sources of elemental impurities should be carefully considered during the identification stage. These include intentionally added substances such as catalysts and inorganic reagents, as well as unintentionally introduced

elements from raw materials, excipients, and water. Manufacturing equipment can also contribute to contamination, especially during aggressive technological processes that may extract or release trace metals. Packaging closure systems represent another potential source, although their risk depends on the pharmaceutical dosage form. For solid products, the likelihood of elemental leaching is minimal, while for liquid and semi-solid formulations, there is an increased risk of migration during storage. Therefore, extractables and leachables studies should be conducted on container closure systems after washing, sterilization, or irradiation (ICH Q3D, 2022). This approach aligns with the *FDA Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics* (FDA, 1999), which identifies solid-to-solid contact as a low-priority risk.
Table 2 provides recommendations for the inclusion of elements in the risk assessment. This table can be applied to all potential sources of elemental impurities.

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	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Source: ICH Q3D Guideline for Elemental Impurities

A key component of the risk assessment process is comparing observed or predicted impurity levels with the established PDE. Setting a control threshold at 30% of the PDE enables early detection of potential risks and helps determine the need for additional control measures (ICH Q3D, 2022). If total impurity levels from all sources remain consistently below this threshold, no further controls are required. When impurity levels may exceed the threshold, additional actions such as process modification, implementation of in-process controls, setting specification limits, and selecting suitable packaging systems must be applied. (CHMP, 2019).

5. STRATEGY TO FOLLOW FOR ELEMENTAL IMPURITIES

The PDE, expressed in micrograms per day (µg/day), defines the maximum allowable quantity of a specific element that may be present in the maximum daily intake of a medicinal product. To simplify the evaluation, the PDE can be converted into a concentration limit. Four approaches (Options 1, 2A, 2B, and 3) are used to ensure that the total amount of impurities does not exceed the established PDE value (*ICH Q3D*, 2022).
Option 1 establishes a fixed maximum concentration of impurities (µg/g) that applies to each component of the drug product, assuming a maximum daily intake of 10 grams. The concentration is calculated by dividing the PDE (µg/day) by 10 g/day. For example, if the PDE for a specific metal is 100 µg/day, then the maximum permitted concentration in each component would be 10 µg/g. This means that every raw material used in the preparation of the medicinal product must contain a concentration of that element below 10 µg/g.
Option 2A allows the calculation of a common concentration limit based on the actual Maximum Daily Intake (MDI) of the drug product. For each elemental impurity, the concentration limit is calculated by dividing the PDE value by the actual Maximum Daily Intake (MDI) of the drug product. All components must remain below this uniform limit.
Option 2B provides flexibility by allowing different impurity concentrations among components, provided that the total daily intake of each element does not exceed its PDE value. This method requires precise knowledge of each component's quantity and composition.
Option 3 evaluates impurities in the finished product itself, using validated analytical methods to verify that the total elemental content remains within PDE-based safety limits (*ICH Q3D*, 2022).

6. ANALITICAL TESTING FOR ELEMENTAL IMPURITIES

The determination of these impurities must be conducted using validated analytical methods appropriate for their intended purpose and specific to each element identified during the risk assessment (*ICH Q3D*, 2022). This may involve method validation for non-pharmacopeial procedures or system suitability testing for compendial methods (ICH Q2(R1), 2005; *ICH Q11*, 2012).

For pharmaceutical products governed by a United States Pharmacopeia (USP) monograph, the recommended analytical approaches for elemental impurity testing are outlined in USP Chapter <233> (Elemental Impurities—Procedures), unless otherwise specified. This chapter describes two principal techniques: Procedure 1, based on Inductively Coupled Plasma–Atomic (Optical) Emission Spectroscopy (ICP-AES or ICP-OES), and Procedure 2, which employs Inductively Coupled Plasma–Mass Spectrometry (ICP-MS) (USP, 2022). The Target Limit or Target Concentration defines the maximum permissible impurity level in a sample; exceeding this limit indicates non-compliance. Similarly, the Ph. Eur. applies Chapter 2.4.20 for elemental impurity determination (Ph. Eur., 2022).

Accurate sample preparation is vital for analytical precision. Solid samples must be dissolved before nebulization, commonly using dilute nitric acid or aqueous media to minimize interference. Resistant samples require thermal or microwave-assisted digestion, while volatile metals necessitate closed-vessel digestion to prevent loss. High-purity solvents and control of matrix effects are essential for reliable ICP-based measurements. When analytical performance falls outside acceptable ranges, internal standards or matrix-matching corrections are applied. Advanced microwave digestion–ICP-MS techniques provide superior sensitivity and accuracy for trace elements such as Cd, Pb, As, Hg, Co, V, and Ni (Hao et al., 2024), supporting compliance with ICH Q3D (2022) impurity standards.

7. CONCLUSION

The regulation of elemental impurities in medicines represents a critical advancement in ensuring pharmaceutical safety, efficacy, and quality. Implementation of the ICH Q3D guideline has harmonized global standards and established a science-based, risk-oriented framework for managing toxic metal residues. Through defined PDE limits and comprehensive risk assessments, manufacturers can identify and mitigate contamination sources across all stages of production—from raw materials and equipment to packaging systems. Modern analytical techniques such as ICP-MS and ICP-OES have replaced outdated heavy metal tests, providing highly sensitive and accurate quantification of trace elements. Although adherence to Good Manufacturing Practice and robust process control cannot entirely eliminate impurities, continuous monitoring and method validation significantly minimize associated risks. Ultimately, integrating ICH Q3D principles into pharmaceutical quality systems promotes consistency, transparency, and patient safety. Maintaining vigilance and innovation in analytical testing will remain essential as regulatory expectations evolve and new impurities are identified.

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