**REVIEW ARTICLE**

# Review of Elemental Impurities in Pharmaceuticals Arena

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**ABSTRACT**

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in the synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/ closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. The main objective of the International Conference on Harmonization (ICH) (Q3D) guideline applies to new finished drug products and new drug products containing existing drug substances. The drug products containing purified proteins and polypeptides. This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, or blood derivatives, including plasma and plasma derivatives. The evaluation of the toxicity data for potential elemental impurities; the establishment of a permitted daily exposure (PDE) for each element of toxicological concern; application of a risk-based approach to control elemental impurities in drug products. Different analytical techniques for elemental impurities detection: flame atomic absorption spectrometry (FAAS), graphite furnace atomic absorption spectrometry (GFAAS), atomic fluorescence spectrometry, X-ray fluorescence spectrometry (XRF), instrumental neutron activation analysis (INAA), inductively coupled plasma-atomic emission spectroscopy (optical emission spectroscopy, ICP-OES), inductively coupled plasma mass spectrometry (ICP-MS), and microwave plasma atomic emission spectrometry (MP-AES).

**Keywords:** Elemental impurities, International Conference on Harmonization (ICH), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma-atomic emission spectroscopy (optical emission spectroscopy, ICP-OES, Permitted daily exposure (PDE), X-ray fluorescence spectrometry (XRF).

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## INTRODUCTION

The ICH finalized the ICH Q3D Guideline for Elemental Impurities[1] in December 2014. Regulators are now implementing the requirements worldwide. The U. S. Federal Drug Administration[2] and the European Medicines Agency,[3] both adopted a start date of June 2016 for new drug products and December 2017 for authorized drug products. Health Canada has announced that applications submitted after 31st December 2016 must include a risk assessment for elemental impurities. Japanese regulators will begin implementing the guideline for new drug products in April 2017.

The ICH Q3D introduces risk assessment approaches, and limits for the maximum PDE based on safety assessments for chronic exposure. However, ICH Q3D does not provide specific daily limits for major components of final drug products, bringing excipient in particular under scrutiny.[4] Unlike APIs, excipient does not have established daily doses, leaving manufacturers with less information for calculating concentration limits. This article discusses an ICH Q3D-compliant control strategy model for risk assessment.

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in the synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/ closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. There are three parts of this guidance:

- The evaluation of the toxicity data for potential elemental impurities;
- The establishment of a PDE for each element of toxicological concern;
- Application of a risk-based approach to control elemental impurities in drug products.

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An applicant is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs. The PDEs established in this guidance are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted, when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, for elements with high PDEs, other limits may have to be considered from a pharmaceutical quality perspective, and other guidance should be consulted (e.g., ICH Q3A).

The main objective of the Q3D guideline applies to new finished drug products and new drug products containing existing drug substances, the drug products containing purified proteins, and polypeptides. This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, and cellular blood components or blood derivatives, including plasma and plasma derivatives.[5]

The ICH Published Guidance For Impurities[6-10]

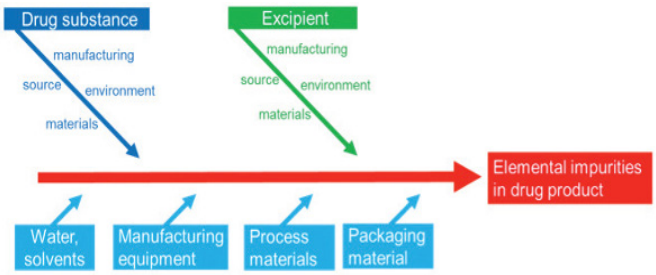


**Figure 1:** Potential source of elemental impurities

**Table 1:** ICH guidance for impurities

| *ICH guidance* | *Title* |
|---|---|
| ICH Q3A (R2) | Impurities in New Drug Substances |
| ICH Q3B (R2) | Impurities in New Drug Products |
| ICH Q3C (R7) | Impurities: Guideline for Residual Solvents |
| ICH Q3D | Guideline for Elemental Impurities |
| ICH M7 (R1) | Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. |

## ELEMENT CLASSIFICATION[9]

Different classes based on their toxicity (PDE) and likelihood of occurrence in the drug product.

An element with low natural abundance = reported natural abundance of < 1 atom/106 atoms of silicon.

## POTENTIAL SOURCE OF ELEMENTAL IMPURITIES

Potential source of elemental impurities are shown in Figure 1.

## DRUG PRODUCT AND COMPONENT ASSESSMENT APPROACH[11]

Preferred by manufacturers, the component assessment approach assesses individual components for their contributions to impurities. The combined contribution of an element is compared with the PDE, and a control strategy is established, if necessary. When using this approach, drug product manufacturers should ensure that impurities from the manufacturing process are not significant contributors to the overall level of elemental impurities. This approach benefits greatly from supplier information to help analyze data. Figure 2 compares the approaches.

The risk assessment process can be described in three steps:

- Identify known and potential sources of elemental impurities that may find their way into the drug product.
- Evaluate the observed or predicted level of the impurity and comparing with the established PDE.
- Data to support may be from:
  - » Prior knowledge;
  - » Published literature;

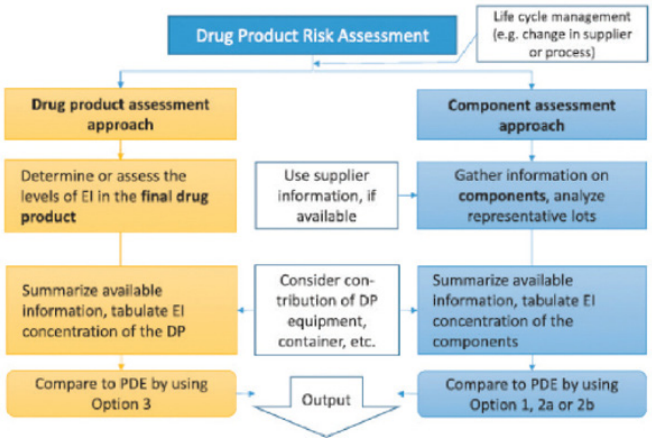


**Figure 2:** Product and component assessment approach

**Table 2:** Element classification

| *S. No.* | *Class* | | *Elements* |
|---|---|---|---|
| 1 | 1 | Route independent human toxicants, high probability of occurrence | As, Cd, Hg, and Pb |
| 2 | 2A | Route-dependent human toxicants and relatively high probability of occurrence | Co, Ni, and V |
| | 2B | Route-dependent human toxicants and relatively reduced probability of occurrence | Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl |
| 3 | 3 | Relatively low toxicity by oral route but may be considered in the risk assessment for inhalation and parenteral routes | Ba, Cr, Cu, Li, Mo, Sb, and Sn |
| 4 | Others | PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations | Al, B, Ca, Fe, K, Mg, Mn, Na, W, and Zn |

  - » Data generated from similar processes;
  - » Supplier information or data;
  - » Testing of the components of the drug product;
  - » Testing of the drug product.
- Summarize and document the risk assessment: develop, document, and implement a plan to limit the elemental impurities in the finished dosage form.

## CONTROL OF ELEMENTAL IMPURITIES[9]

To assure that elemental impurities do not exceed the PDEs. The following approaches can be applied to control of elemental impurities:

- Modification of the steps in the manufacturing process;
- Implementation of in-process or upstream controls;
- Establishment of specification limits for excipients or materials (e.g., synthetic intermediates);
- Establishment of specification limits for the drug substance;
- Establishment of specification limits for the drug product;
- Selection of appropriate container closure systems.

The following information to be provided in a regulatory submission:

- A summary of the risk assessment, and
- A description of the controls established to limit elemental impurities.

ICH Q3D provides PDE limits in µg/day for elemental impurities. However, concentration limits in µg/g are more useful for evaluating impurity content in a sample. Chapter 7 of ICH Q3D offers several options for translating between the two:

- Option 1 assumes the daily intake of the drug product is 10 grams (or less)
- Option 2A uses an actual maximum daily intake (*vs.* assuming 10 grams)
- Option 2B calculates a sum based on known component impurity levels
- Option 3 measures the concentration of elements in the final drug product

## DRUG PRODUCTS[9]

Not all 24 elements are expected to be detailed in every risk assessment. A number of these elements will be determined as unlikely to be present, and, after documentation, no further action is required. Other elements, such as those in class 1 and class 2A, need to be considered in all risk assessments. The control threshold is a decision tool that can aid in determining elements at risk of exceeding the PDE. If the observed level of elemental impurity is consistently below the control threshold, defined as 30% of the PDE, existing controls are considered to be adequate.

If the threshold is exceeded, manufacturers should consider additional controls, including upstream controls. Alternatively,

**Table 3:** Elements to be considered in the risk assessment

| | | | *If not intentionally added* | | |
|---|---|---|---|---|---|
| *Element* | *Class* | *If intentionally added (all routes)* | *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 |

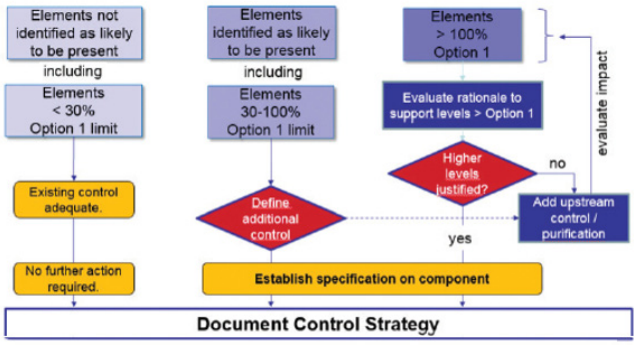


**Figure 3:** Control strategy for components, based on the option 1 limit as the default[12]

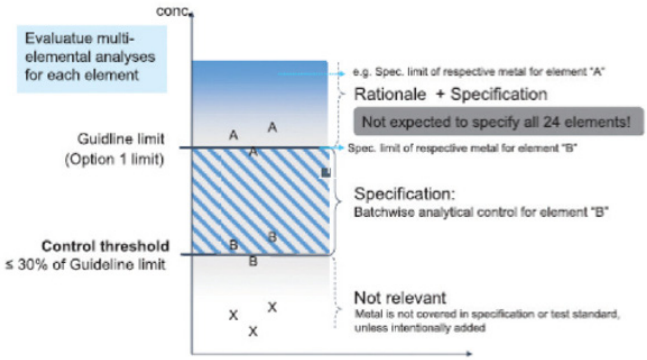


**Figure 4:** Control strategy for elements not added intentionally[13]

purification methods may be added at the source of impurities. Specifications should also be established for these elements. For elements exceeding the PDE, a safety assessment can be prepared with a rationale to support higher levels of exposure (i.e., short-term usage, intermittent dosage, a life-threatening disease, etc.). If this additional justification is not available or acceptable, controls should be implemented at the source of contamination, and upstream control or purification methods should be added.

## DRUG SUBSTANCES AND EXCIPIENTS[9]

While the limits provided by ICH Q3D are specified for final drug products, the same guidelines do not apply to excipients and drug substances. Because excipients do not have a daily dose, there is no established concentration limit, which is generally applicable to excipient manufacturers. Furthermore, compliance of APIs and excipients to a pharmacopoeial substance monograph does not guarantee suitable control of elemental impurities.

As a result, establishing limits for components is a matter of negotiation between drug product manufacturers and their suppliers. To support the negotiations, option 1 (10 grams daily dosage) is typically used as the default concentration limit. Please note that the PDEs in ICH Q3D differ depending on the route of administration (i.e., oral, parenteral, and inhalation).

If all components have levels below the option 1 limit for all target elements, these components may be used in any proportion in the final drug product. Figure 3 illustrates this approach.

### Elements Intentionally Added[12]

Metals or elements intentionally added to the manufacturing process should be considered in every risk assessment. This requires information about which elements have been added, including the relevant production steps and the purge potential of subsequent steps. These elements should be included in the drug substance specification unless the element is controlled by a suitable limit in a synthesis intermediate.

### Elements Not Intentionally Added[13]

Elements not added intentionally must also be evaluated. Multi-element analyses are conducted to determine the typical elemental impurity level in APIs, excipients, or chemical process materials.

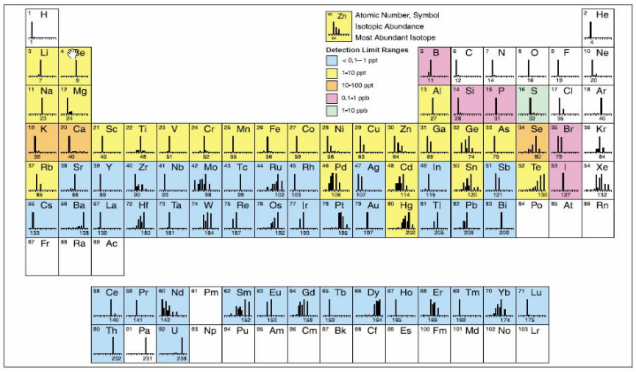

**Figure 5:** Periodic table of elements[14]

*Figure 4* illustrates an approach to evaluating the results of a multi-element analysis. The y-axis depicts the concentration of the individual elements, the guideline limit, and the respective control threshold. The guideline limit (by default, the option 1 limit) is dependent on the route of synthesis and the maximum daily dose of the drug product. To apply the control threshold as a decision tool, the sources of variability should be understood, both in terms of the analytical method and the variability of the metal level in the specific sources.

If the results of metal X testing consistently do not exceed the control threshold, the metal can then be excluded from the specification. If metal B is higher than the control threshold, but below the guideline limit, the element should be subject to analytical control and covered in the specification. Any pharmaceutical substance with element results higher than the guideline limit (option 1 limit by default) for the drug product may still be used in final drug products. However, a rationale will be appropriate to support higher levels. For pharmaceutical substances at this level, a suitable specification limit should be defined.

## ANALYTICAL TECHNIQUES FOR ELEMENTAL IMPURITIES DETERMINATION[15-19]

- Various techniques are available for analysis of elemental impurities. The previously heavy metal limit test is being used wherein the intensity of the colour of precipitate resulting from ten sulfide forming elements is compared

visually with 10 ppm lead standard.

- This test is inadequate in terms of sensitivity, specificity, and accuracy to monitor the level of the elements that should be controlled based on toxicity. Hence, to address these deficiencies, regulatory bodies have published modern techniques to monitor elemental impurities, and acceptance criteria are replaced by element-specific PDE.
- On the same note, general chapter USP <231> Heavy Metal Analysis is replaced by USP <232> Elemental Impurities–Limits and USP <233> Elemental Impurities–Procedures.
- Modern techniques for elemental impurities are listed below.[19]
  - » FAAS
  - » GFAAS
  - » Atomic fluorescence spectrometry
  - » XRF
  - » INAA
  - » Inductively coupled plasma-atomic emission spectroscopy (optical emission spectroscopy, ICP-OES)
  - » ICP-MS
  - » MP-AES
- Techniques listed here above vary in terms of features, performance, and cost. Out of these techniques, only ICPOES and ICP-MS are capable of detecting all 24 elements listed in ICH Q3D in a single measurement. Thus, looking at the pros and cons of all the techniques available, the USP panel has listed ICP-OES, and ICP-MS as preferred methods in USP <233>.

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