



VIEW POINT

Approach to “The Elemental Impurities
Risk Assessment” in Pharmaceuticals



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What are Elemental Impurities?

The elemental impurities are the impurities which get introduced into the final drug product either directly through raw materials, residue by-products, or contact with environment, packaging material, manufacturing location, equipment's, etc.

These elemental impurities could affect the stability & efficacy of the finished product & also have hazardous effect on the patients and therefore they have to be monitored/controlled during the entire manufacturing process.

The need to create a uniform approach to assess Elemental impurities was dual fold a) to minimize concerns being raised due to toxicological effects from Elemental impurities and b) to create a global standards in drug manufacturing. From centuries pharmaceutical industries are using manual or simple laboratory instruments/methods to calculate elemental impurities and its risk assessment

These assessment or testing process were not advance enough to provide detailed analysis of the impurities. However, with the advancement in technology, few areas like toxicology assessment from excipients and APIs have become easier and accurate i.e. benefiting elemental impurities assessment.

Assessment of Elemental Impurities has 2 key benefits

- (a) Enable Global sourcing of the drugs -
In today's world, drug manufacturing is possible through global sourcing, where the drug substances are manufactured at different places and formulated in different location. If we have a global standards of elemental impurities assessment, then without further investigation the drug formulation could proceed, rather than re-testing the toxicology of the elements/substance
- (b) Build confidence with respect to standards of drug quality among people who are end consumers (For example: A particular drug bought by a consumer in India would be same as the one bought in New York).

To address Elemental Impurities assessment & monitoring, there are guidance from International Conference of Harmonization (ICH) Q3D guideline: elemental impurities and ICH Q9: Risk Based Quality Control Strategy.

This guideline applies to finished drug products and new drug products using existing drug substances. The key aspects of these guidelines are

- For each dosage and route of administration, the Permitted Daily Exposure (PDE) to be established for the elements
- Propose minimum levels of elemental impurities that is permissible based the Permitted Daily Exposure
- Analysis & Control of Elemental Impurities by risk based approach
- Provide Element Classification to facilitate decision making during risk assessment



Changes

How rules affect

Elemental Impurity Risk Assessment methodology

Elemental Impurity Risk based assessment is conducted by using various laboratory data and computing it against regulatory limits originated from Certificate of Analysis (CoA), historical data, Lab Reports, ICH/USP (United States Pharmacopoeia) limits and Product data to provide early insights on risk assessments to future batches. This process can help in understanding if the controls built are advanced enough to limit the elemental impurities in upcoming batches and documents the detailed risk assessment performed along with summary and conclusion.



The Crux of the risk assessment approach lies in understanding where and how the impurities into the stream



Fig 1: Fishbone Diagram showing sources of Elemental Impurities

Process steps

The Elemental Impurities risk assessment evaluation could be performed using the below approach.

Assess the elemental impurities contributed from each of the above sources to find the overall elemental impurities. Followed by creation of a **prioritization** matrix for impurities as per the guideline. For example: Class 1, 2, 3 and 4.

Design an algorithm to predict probability of occurrence of impurities in the final product
Evaluate and compare the impurities to that of established PDE (Permissible daily Exposure)

Lastly, **implement** a tool to provide holistic view on data analysis, monitoring, storage and visualization.

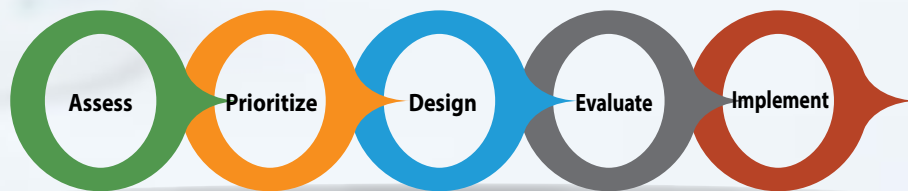


Fig 2: Elemental Impurities Risk Assessment process steps



Challenges in Elemental Impurities Risk Assessment

Disparate sources of elemental impurities – which all have to be considered?

Siloed data in different formats - requiring manual intervention

No standard algorithm to compute the data which is common across companies

How much data to be collated for sufficient conclusion and submission to regulatory body?

When and where to start assessing the elemental impurities risk?

Unanticipated change in regulatory guidelines





How Infosys can help Pharma companies

While drug substance manufacturing is a series of complex processes, employing certain scientific methods at appropriate level to plan and design efficient processes will help in identifying and managing elemental impurities.

Infosys can work hand in glove with Pharma companies to perform Risk Assessment of the Drug substances to meet the Regulatory standards.

Infosys has a strong understanding of the regulation & process around Elemental Impurities. Infosys and has the capability to help Pharma companies structure a tool with pre-defined inputs (Like Permissible Daily Exposure, Limit of Quantitation etc.), business rules and algorithms This would facilitate extraction & consolidation of unstructured lab data from disparate sources into a structured databases help to query/analysis and final reporting with conclusion for regulatory submission.

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