

Patient Safety & Elemental Impurities ICH Q3D

From 1st January 2018, the European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP) have replaced the old methods for testing of heavy metals (USP <231> and Ph.Eur. 2.4.8) in raw materials with a new harmonised guideline “ICH Q3D”. Drug product manufacturers are responsible for providing a risk-based assessment of the elemental impurities, justifying that the contents for each of the 24 elements are below the exposure limit as described in ICH Q3D. The elemental impurity level and variability must be established by validated analytical methods specific for each matrix to avoid biased results.

Elements

All matter on Earth is composed of elements. The four elements common to all living organisms are oxygen (O), carbon (C), hydrogen (H), and nitrogen (N), which together make up about 96% of the human body¹. Elements like mercury (Hg), lead (Pb) and cadmium (Cd) are toxic. For patient safety, ICH Q3D states a permitted daily exposure of 24 specific elemental impurities in drug products². The risk-based approach, as defined by ICH Q3D, is established to limit the level of elemental impurities in pharmaceuticals for humans. The elemental Impurities may originate from multiple sources; catalysts and inorganic reagents intentionally added, impurities present in drug substances and excipients or elements released from manufacturing equipment and packaging.

Risk Assessment

The scope is patient safety – patients should not risk being poisoned with elemental impurities when dosing their medicine. Drug product manufacturers are responsible for ensuring and documenting that the elemental impurities are below the permitted daily exposure (PDE) levels. The processes must be based on scientific knowledge and should; (1) identify known and potential sources of elemental impurities (2) evaluate

their presence and (3) summarise and document the analytical data used for the risk assessment. Using such risk-based assessment, the drug manufacturers can reduce the requirement for full testing of all 24 elemental impurities.

Compliant Testing

The analytical determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. As long as the test is specific for each elemental impurity, any analytical procedures can be used². The previously required pharmacopoeia tests for heavy metals USP <231> and Ph.Eur. 2.4.8 were both non-specific and were not developed to detect elements at low concentration levels, and are therefore not useful for the new risk-based approach for evaluation of possible critical content of elemental impurities in drug products. Instead multi-elemental detection techniques are recommended, e.g. ICP-OES (inductive coupled plasma with optical emission spectrophotometry), or ICP-MS (inductive coupled plasma with mass spectrometry), where the latter, i.e. ICP-MS can cover all 24 elements, with superior selectivity and sensitivity.

Sample preparation is typically performed by digestion of the sample in a microwave oven using a mineral acid under high pressure and heat. This technique ensures that all matrix components are being dissolved and all elements are released into solution, making it possible for analysis of the resulting solution by ICP/OES or ICP/MS. In order to perform a thorough risk evaluation of the content of elemental impurities, any analytical approach needs to be validated. All matrices behave differently when exposed to mineral acid digestion, which clearly shows that necessary caution must be exercised when determining which digestion technique is chosen when performing the analytical work. *For proper evaluation of the performance of*

the analytical technique used, a method validation must in all cases be performed for each specific matrix analysed. Only in this way is it ensured that the method is suitable for the intended use. Results based on methods that are not validated for a specific matrix type cannot be trusted as the results can be biased by negative matrix effects including precipitation, signal suppression or interferences. It is therefore critical that a thorough focus on digestion technique is always taken into consideration for all analytical work on elemental impurities.

Laboratory Requirements

Analytical determination of low level content of elemental impurities requires a super clean laboratory, equipped with special instrumentation and experienced staff. The majority of the contract laboratories (CROs) that offer testing for elemental impurities are not GMP approved or inspected by FDA. In addition, most CROs do not offer adequate testing services required for ICH Q3D. This service involves expertise in achievement of low detection limits and sufficient validation work, together with the required GMP documentation. Some of the typical pitfalls for most CROs, when analysing elemental impurities, are to document complete dissolution of silica, talc and other difficult matrices. For these matrices, special acids need to be used for complete digestion, e.g. hydrofluoric acid. Some CROs also experience problems in obtaining precise recovery of volatile elements such as mercury and osmium that need special care during analysis.

Eurofins Metal Competence Center – Centre of Excellence

The Metal Competence Center in Denmark has more than 40 years' combined experience within metal testing and offers GMP testing for elemental impurities to support risk assessment, validations and routine testing of drug substance, excipients and final products.

The lab is fully equipped with state-of-the-art ICP/MS and ICP/OES instrumentation. Furthermore, in order to ensure that the background level of any elemental impurity is kept at an absolute minimum, a high-pressure room facility with airlocks and mandatory garment change for the staff before entering the room is used routinely. Combined with highly experienced lab technicians and chemist, it is possible to test for elemental impurities at the absolute lowest obtainable level with a high degree of precision and accuracy in most pharmaceutical products.

Analytical Approaches at Eurofins Biopharma Product Testing Denmark

Self-validating Test

For the purpose of performing risk

evaluation of content of elemental impurities, Eurofins BPT-DK A/S has developed a self-validating test procedure.

This procedure can be used for analysis of the 24 ICH elements on several samples of the same matrix in the same test series. Aliquots from one of the samples are used for the determination of the method characteristics (accuracy, precision and LOQ). This is done by spike recovery tests combined with a repeatability study.

This type of test is useful for the risk evaluation for a limited number of samples (different batches of the same sample material) that can be tested in one analytical series and is as useful as an alternative to a full

validation, that in most cases is much more time-consuming and costly.

Full validation will be a preferred choice when the risk assessment has shown that specific elements are to be tested on a routine basis for each batch that needs to be released. The full validation approach can also be used for the risk assessment if more detailed information to the method uncertainty is required.

For More Information

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ICH Q3D – Elemental Impurities – Are you ready?

Eurofins BioPharma Product Testing is a global CRO offering biopharmaceutical product testing services for the biopharmaceutical industry. Eurofins is the largest contract laboratory in the world with more than 400 labs and >32,000 employees, and operates in 41 countries.

REFERENCES

1. Russell PJ, Hertz PE, McMillan B. *Biology: The Dynamic Science* 4th ed. Cengage Learning 2016.
2. ICH Q3D Guideline for Elemental Impurities <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>, Online 05. Dec 2017.



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Dr. Rie Romme Rasmussen has a M.Sc in Environmental chemistry (2002) and a Ph.D. in Analytical chemistry (2010) and more than 15 years of experience in the analytical field; hereof 7 years focusing on trace element detection. Rie has co-authored 15 peer reviewed publications, >20 posters and 3 European Standards. Since 2017 Rie has focused on environmental impurities at Eurofins including validation, GMP analysis and quality control.

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