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science on demand

ICH Q3D for Elemental Impurities Testing

Lessons learnt from the adoption of ICH Q3D for Elemental Impurities Testing

Since the United States Pharmacopeia (USP) adopted the General Chapters on Elemental Impurities in 1st January 2018, closely followed by the EP and JP in adopting ICH Q3D.

Butterworth Laboratories have worked with a number of pharmaceutical manufacturers, helping them perform their risk assessments by analysing Finished Products, API's and Excipients, many of whom had already started the process in anticipation of these changes. So what are the lessons that have been learned?

ICH Q3D provides a means of assessment and control of 24 elemental impurities using the principles of risk management as detailed in ICH Q9. It establishes permitted daily exposure (PDE) limits for each element, expressed in µg/day, calculated using published toxicity data and set according to the route of administration.

The elements are divided into three classes based on their toxicity and likelihood of occurrence with limits applicable to finished formulations based on a maximum dosage of 10g/day. Compliance is not directly applicable to excipients or the drug substance, however, USP <232> does state "elemental impurity levels present in drug substances and excipients must be known, documented, and made available upon request".

In order to appropriately complete product risk assessments there is obviously a heavy emphasis on knowledge of the manufacturing process and the raw materials used in the formulation. The benefits of Quality by Design (QBD) can't be ignored, particularly with respect to New Drug Applications (NDA)/ Marketing Authorisation Applications (MAA). Control of elemental impurities should be fundamental in the design of the formulation and manufacturing process, removing, where possible, or at least reducing the requirement for routine analysis.

However, in the case of existing marketed products, manufacturers were in many cases requesting information on the levels and variability of elemental impurities from their material suppliers for use in the risk assessment exercise. The reality is that not all suppliers had this information and the manufacturer was often left with gaps in their information. Hence the requests for analysis of API's and Excipients, in addition to Finished products from manufacturers.

Both ICP-OES and ICP-MS offer multi element analysis over a large linear range, making them ideal choices for screening. From a practical perspective, however, ICP-MS can determine concentrations 1000 times lower

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than that of ICP-OES and as sample preparation will involve dilution, ICP-OES struggles to meet the required specification limits for some of the elements in Q3D, particularly Arsenic and Mercury. Consequently ICP-MS is the method of choice at Butterworth for elemental impurity screening.

The Butterworth approach to quantitative screening involves looking at the 24 elements listed in ICHQ3D. Given the linearity of the technique, a calibration using two standards set at an order of magnitude apart are produced for each of the 24 elements, with the lower standard being equivalent to the target quantitation limit. A further standard is produced from alternative sources to act as a QC Standard. Samples are usually prepared in duplicate, with an additional preparation being spiked with a known quantity of all the elements, to provide recovery information. The data obtained from the standards, spike and duplicate preparations provide a significant amount of verification data demonstrating that the method used is fit for its intended use with a particular material or formulation.

So what are some of the lessons we have learned at Butterworth?

- Perhaps the most remarkable feature of the results we have obtained is that elemental impurity concentrations in API's and Excipients are generally very low, often well below the quantitation targets set to meet the recommended Potential Daily Exposure (PDE) limits. As such minimising risks from contamination in sample preparation is essential.
- The exceptions are often associated with minerals that are mined such as Titanium Dioxide or Calcium Carbonate.
- Where materials are produced from plant based materials grown in countries where the groundwater has high levels of Arsenic in the groundwater used for irrigation etc.
- The most commonly found elemental impurities in API's and excipients are those originating from where the element associated with a catalyst in the manufacturing process, which is usually a sign of catalytic breakthrough.
- Although ICP-MS is the industry standard approach, there are some elements that suffer from known interferences, but most of these can be overcome using known techniques.
- Sample preparation of drugs used in inhalation products, which are often received in sealed aluminium containers, is difficult, as in opening the container to obtain a sample aliquot is prone to contamination.
- Validation of methods where identified impurity measurements is essential.

Having been involved in Elemental Impurity testing by ICP-MS since before it was formally adopted by the National Pharmacopoeias, we have had to make ongoing changes to our practices and procedures.

We have introduced a Fume Hood specifically designed for Trace Metals Preparations, which has very few metal components and has a laminar flow system similar to a Safety Cabinet to protect the analyst as well as sample preparations, which has seen a reduction in levels of contamination. Provided the analysts with their own dedicated DI Water supply. Adopted new procedures on Calibration Standard production to reduce possibility of cross contamination.

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Author Biographies

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David started his career at Sandberg LLP before joining Butterworth Laboratories as an Analytical Chemist in 1986 in the Microanalytical Department performing CHN analysis and has progressed through various roles to his current position as Technical Director.

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John started at Butterworth in 1987 as an Analytical Chemist and has had various roles including Quality Assurance Manager and Business Development Manager before becoming Associate Director of Business Operations in 2018.

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