PREPARING FOR THE NEW ELEMENTAL, HEAVY METAL, IMPURITIES REGULATIONS

Elemental, or heavy metal impurities are an increasingly hot topic for all manufacturers of drug products. While guidelines are in place for controlling organic impurities and residual solvents, a corresponding guideline has been missing for elemental impurities. This is the main reason why both the ICH and USP have been developing ICH Q3D and USP chapters <232 and <233> in the last few years.

The two main purposes of these initiatives are to:

1. Evaluate toxicological data for potential elemental impurities and based on these establish PDEs (Permissible Daily Exposures) for each element of concern;
2. Develop controls for limiting the levels of these elemental impurities in finished drug products.

HOW TO PREPARE FOR WHAT IS COMING

It now seems as if both ICH Q3D and USP <232> and <233> will be finalized during 2014 meaning it is high time for all manufacturers of drug products and ingredients to start preparing for the upcoming changes. A risk-based approach should be applied and there are numerous important questions to consider, for example:

- **Which products are affected by the new regulations?**
  Keep in mind that at this point, ICH Guideline Q3D only applies to new finished drug products while USP <232> & <233> will also apply to existing drug products.

- **Which elements, heavy metals may these products contain and at what concentrations?**
  There are several sources of elemental impurities, for example 1) those that are intentionally added, e.g. catalysts, 2) elements known or suspected to be found in starting materials, excipients, reagents, etc. and 3) elements that may be introduced through contact with equipment in the manufacturing stages of production. Naturally, the number of potential sources of elemental impurities will vary depending on each individual drug product.

- **Should method validations and analyses be carried out in-house or outsourced to a contract laboratory?**
  For manufacturers with in-house laboratories already equipped with multiple ICP-instruments and with personnel with experience of elemental impurity analyses, in-house analyses may be a convenient option. For others, outsourcing the analyses to a contract laboratory will be the best alternative in the vast majority of cases. A combination may also be a sound solution where a contract laboratory can function as a backup laboratory.

While it may be difficult to put a price tag on in-house capabilities to measure elemental impurities, the option of outsourcing method validations and analyses is in most cases a more cost-efficient approach.

Regarding the time perspective, setting up a metal testing laboratory is a very time consuming process. Upon ordering an ICP, it will often take 6-8 months before the instrument is fully operational. Therefore, in order to be able to prepare for the new regulations, there is no time to waste for anyone planning on setting up in-house capabilities.

For those who are planning on collaborating with a contract laboratory it is also recommended to initiate discussions in order to avoid getting behind your competitors.

HOW CAN ALS PHARMA HELP WITH THE PREPARATIONS AND TESTING OF ELEMENTAL IMPURITIES

ALS Pharma has operated ICP-MS instruments since 1996. As of today our instrumental park consists of 11 ICP-SFMS (High Resolution ICP-MS), 4 ICP-OES as well as 4 AFS and 2 MC-ICP-MS instruments.

Not only does this give us the capability to process a large number of GMP samples per day, it also gives us a solid backup capacity which is imperative under the circumstances.

Before performing metals testing it is of paramount importance to apply the appropriate sample preparation method(s), which can sometimes be challenging, particularly for an element like osmium. In some cases, it will also be necessary to apply 2-3 different sample preparation methods and instrumental runs on each sample matrix in order to achieve satisfactory recovery in the analyses of all elements covered in the various guidelines.

At ALS Pharma, we have the knowledge, experience and equipment necessary to dissolve almost any matrix under clean room conditions. In combination with our ICP-SFMS instruments, this means that ALS is uniquely-equipped to tackle any requirements on elemental setup or PDEs set by ICH, USP and EMEA.

All analytical tests used in demonstrating compliance with the new regulations should be carried out according to validated methods. To date ALS Scandinavia has delivered some 100 customer-specific method validations, most of them according to ICH Guidelines Q2 (R1) and USP <233>.

QUALITY AT ALS SCANDINAVIA PHARMA

EN ISO/IEC 17025 ACCREDITATION **GMP CERTIFICATE** **FDA APPROVED**

If you would like more information related to the new elemental impurities regulations, need assistance or wish to request a quote, please contact us!

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