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ELEMENTAL IMPURITIES

Meeting Compliance with USP <232>, ICH Q3D, FDA and GMP Requirements

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USP & ICH's Current State of Implementation

In an effort to improve and modernize the USP General Chapter for Heavy Metals <231>, United States Pharmacopeia has proposed the addition of two new General Chapters and one Supplemental General Chapter.

- <233> Elemental Impurities – Procedure
- <232> Elemental Impurities – Limits
- <2232> Elemental Contaminants in Dietary Supplements

Changes to heavy metals test procedures for the analysis of pharmaceuticals and dietary supplements were approved for publication in the Second Supplement to USP 35 June 1, 2012, with an official date of December 1, 2012. However, because the General Notices provision making these applicable to all USP–NF articles is of a General Notices revision that appeared in USP 37–NF 32, compliance with these chapters was to take effect on May 1, 2014.

In June 2013, the ICH Q3D Elemental Impurities Working Group issued Step 2b of its Guideline for Elemental Impurities. In September 2013, the USP Elemental Impurities Expert Panel reviewed the Step 2 limits of the ICH Q3D step 2b and recommended revisions to General Chapter <232>. On December 27, 2013, the USP announced the approval of General Notices section 5.60.30 Elemental Impurities in USP Drug Products and Dietary Supplements with an official date of December 1, 2015.

Subsequently, in January 2015, USP announced that it intended to establish January 1, 2018 as the new date of applicability of Elemental Impurities Limits General Chapter <232>, and General Chapter <2232> Elemental Contaminants in Dietary Supplements. This new date served to align the implementation of General Chapter <232> more closely with that of the ICH Q3D Guideline, which was issued in final form in December 2014.

Time Lines for Compliance

With the USP establishing January 1, 2018, as the new date of applicability of the Elemental Impurities Limits General Chapters, and FDA setting December 2018, as the expected date of compliance for existing products, it appears there is some time to prepare. But there are other dates that can have a significant impact, especially in the global marketplace, and for new drug products. In both Europe and the US, the EQDM/EMA and FDA deadlines for compliance of new marketing authorization and new drug applications, respectively, with ICH Q3D are each set for June 2016.

What's Required by the USP

All drug products produced and sold in the U.S. will have to comply with the limits set by USP<232>, and drug substances and excipients will have to be tested and reported for elemental impurities. Likewise, all nutraceutical products will have to comply with limits set by USP<2232>, which includes guidelines for speciating organic and inorganic forms of various elements. USP<232> sets permitted daily exposure (PDE) limits for 15 elemental impurities.

Under <232>, the USP will require individual quantification of arsenic, cadmium, lead and mercury. If the presence of additional elemental impurities are suspected, then those additional metals would have to be tested. Screening will be required for all toxic metals that have been shown to be present, regardless of whether or not they are included in the USP impurities list. However, the USP will not mandate methodology. Each manufacturer and supplier will be able to choose the procedure(s) that best fits their processes.

ICH Q3D and FDA's Requirements

In September 2015, the FDA issued its Q3D Elemental Impurities Guidance for Industry. The guidance represents FDA's current thinking on elemental impurities as it applies to new finished drug products and new drug products containing existing drug substances, thus having a direct impact on new drug applications. Bear in mind that the ICH Q3D requirements for NDA/ANDA/BLA take effect on June 2016. Also, the ICH Q3D requirements cover 24 elemental impurities, the 15 listed in USP<232> plus 9 others. The following are what will most likely be FDA's expectations with regards new drug applications:

- The risk assessment for elemental impurities (Summation option) - the contribution of components of the drug product to be included in the "Pharmaceutical Development Report", section P2.3 of the application.

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- Specifications for elemental impurities, including "Heavy metals" are to be set according to ICH Q3D limits.
- All test methods used to assess elemental impurities are to be fully validated analytical methods.
- Testing methods and validation for controlled elemental impurities to be included in the corresponding drug substance and product sections of the application, sections S4.2 and 3, P5.2 and 3.
- Excipient contributions to be included in their controls, or to be referenced to a Drug Master File (DMF) of the supplier, Type IV.

GMP Requirements

While the USP has established January 1, 2018, as the new date of applicability of the Elemental Impurities Limits General Chapters, the FDA has set December 2018, as the expected date of compliance for existing products. Under GMP drug quality and regulatory requirements, elemental impurities will have to be monitored for all existing drug products, APIs, and excipients - not just for the 15 elemental impurities of USP<232>, but for the full 24 elemental impurities of Q3D. It appears that FDA's expectations for elemental impurities, relative to GMP requirements will include:

- Availability of the on-site Risk Assessment Report, in accordance with the ICH Q3D recommendations, or an alternate approach that may be equal to, or better than, Q3D, and deemed acceptable.
- Scientific data supporting the inclusion and/or deletion of elemental impurities from the specification limit(s)/ specifications for the elemental impurities of concern based on process knowledge.
- All test methods used to assess elemental impurities are to be fully validated analytical methods, i.e. data demonstrating suitability of the test methods for intended use.
- Test methods, and their validation, are to be available at the manufacturing site during GMP inspections, and also included in the drug application and annual reports.
- Availability of product/process data demonstrating capability and reliability of the manufacturing process steps to remove or control elemental impurities consistently at, or below specified levels.
- Change control management for potential impact on elemental impurities profile.
- Routine vs. full testing, and frequency of full testing for elemental impurities.
- If any additional testing, i.e. skip lot testing, etc., was/is performed to confirm "minimal levels" of elemental impurities, the results and test methods used are to be available during GMP inspections

Other Key Considerations for Compliance

In addition to timelines and requirements above, there are other timelines that can have a significant impact with compliance. In many cases, the two "Referee Procedures" in USP<233> may need to be modified in some way to address specific matrix issues. Such modification would then need a full validation rather than a much more abridged verification. Also, many have found the "Referee Procedures" in <233> to be too generic, or not suitable for their matrix. Subsequently, method development and validation have become necessary more often than not.

This additional time spent developing and validating the methods, as well as allocating analytical resources must also be factored in, as many labs simply do not have internal ICP-OES, ICP-MS, or microwave digestion capabilities readily available. Also, bear in mind that while there are a number of contract laboratories capable of GMP analytical work using these analytical techniques, their capacity is not infinite, and they may already be scheduled at maximum usage. Thus, as a cautionary measure, all these issues should be factored into the plan for developing and validating analytical methods to support risk assessments for elemental impurities.

About Quantex Laboratories

Quantex Laboratories has extensive experience utilizing microwave digestion, ICP-OES and ICP-MS in a wide variety of matrices. We have many years of experience analyzing heavy metals and other trace impurities in USP drug products, dietary supplements, medical device products, personal care products, cosmetics, excipients and raw materials. We have developed and validated numerous matrix specific methods to meet the compliance requirements of USP <232>, <233>; ICH Q3D and FDA GMP requirements for elemental impurities.

Whether you need help with ICP analysis or a strong partner to help you with method validation, turn to Quantex Laboratories, and our ICP experts to help you prepare to meet the new requirement.

About the author:
Jim Menoutis is Senior Laboratory Director at Quantex Laboratories. In addition to being an analytical chemist and a toxicologist, he is both a Certified Professional Chemist and a Certified Professional Chemical Engineer. Over the past 30 years he has been heavily involved with the development of methods to assess trace and heavy metals in APIs, drug products and excipients. He is an expert in the areas of microwave sample digestion, and the application of atomic absorption, ICP-OES and ICP-MS to the measurement and quantitation of elemental impurities. In addition he is a member of the executive board of the New Jersey Pharmaceutical Quality Control Association, and a member of its compendial committee actively involved with elemental impurities.