USP ELEMENTAL IMPURITIES TO REPLACE USP <231> HEAVY METALS

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Our last article on the replacement of USP <231> Heavy Metals (October 2008) focused primarily on Inductively Coupled Plasma (ICP) and limits under consideration at that time. Since then, the USP has completed its revision on how heavy metals testing will be performed for drug products, drug substances, excipients and dietary supplements. The classical wet chemistry methods will be replaced by more specific methodology including ICP Spectroscopy, Atomic Absorption (AA) Spectroscopy and X-Ray Fluorescence (XRF) Spectroscopy. This has been a hot topic in the last few years with various Pharmacopeial Forum publications and industry commentary taking place. Outlined here are the main points and outcome of this highly anticipated change.

The USP has proposed three new general chapters to replace the current Heavy Metals procedure in general chapter <231>:

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

<232> ELEMENTAL IMPURITIES – LIMITS

USP <232> provides limits for Class 1 and Class 2 elemental impurities in drug substances, drug products and excipients. The limits are based upon toxicity and the hazard these impurities may cause to the environment. The focus is on the Class 1 elemental impurities Arsenic, Cadmium, Lead and Mercury. All drug products must comply with Class 1 elemental impurity specifications. Class 2 elemental impurities are metal catalysts, which include Chromium, Copper, Iridium, Manganese, Molybdenum, Nickel, Osmium, Palladium, Platinum, Rhodium, Ruthenium and Vanadium. Testing for Class 2 elemental impurities is required only if these metals are added during manufacturing.

Specifications are based upon the route of delivery for the drug product, and the USP has proposed limits for oral and parenteral dosage forms. The specifications are based upon the following assumptions: 10 grams/day drug product dose, 50 kg body weight, 70 year lifetime, 10% bioavailability for oral dosage forms and 100% bioavailability for parenteral dosage forms. USP has provided three methods for calculating elemental impurities in drug products:

1. The first calculation method multiplies the impurity results from a typical dosage unit by the maximum daily dose to determine if it is less than the permissible daily exposure (PDE).

2. The second calculation method evaluates each individual component in the drug product. If the drug substance(s) and all excipients meet the proposed component limits, then these components may be used in any proportion in the drug product. This calculation may only be used if the maximum daily dose is not more than 10 grams.

3. The third calculation method is used when the daily dose is more than 10 grams/day or if any individual component exceeds the component limit. This calculation is performed on each individual elemental impurity. The sum of the elemental impurity in each component of the drug product must be less than the PDE.

<233> ELEMENTAL IMPURITIES – PROCEDURES

USP <233> provides methodology for analyzing elemental impurities in drug substances, drug products, excipients, dietary supplements and dietary ingredients. Alternate methods may be used, but must be validated for each elemental impurity. Validation procedures are described for limit tests and quantitative tests.

Limit test validation includes performing accuracy and repeatability at the

limit, and specificity. Quantitative test validation includes performing accuracy at 50%, 100%, and 150% of the limit, repeatability at the limit, specificity, and limit of quantitation (at 50% of the limit). USP has proposed two referee procedures. These procedures use ICP-OES and ICP-MS methodology. Sample preparation can be performed by diluting the test article in an aqueous solution (dilute acid), diluting in an organic solvent or by closed vessel microwave digestion. Two working standards and a blank are analyzed. System suitability using check standard recovery is outlined within each method. Prior to analyzing any test articles, method verification according to USP <1226> Verification of Compendial Procedures must be performed.

<2232> ELEMENTAL CONTAMINANTS IN DIETARY SUPPLEMENTS

USP <2232> provides limits for Class 1 elemental contaminants in dietary supplements and dietary ingredients. Limits for individual components and permissible daily exposure (PDE) are provided for Arsenic (inorganic), Cadmium, Lead, Mercury (total), and Methylmercury. The limits are based on the assumptions described under <232> for oral dosage forms.

Speciation for Arsenic and Mercury are addressed in this general chapter with testing methodology provided for inorganic Arsenic and Methylmercury. The test for inorganic Arsenic would not be required if the results from a non-speciated Arsenic test method met the PDE limit. The test for Methylmercury would not be required if the results for total Mercury met the Methylmercury PDE limit.

Calculating elemental contaminants in dietary supplements can be done using the same three scenarios described under <232>.

Trust SGS for Your Elemental Impurity Testing

The USP changes should become official within the next 12 months. SGS has extensive experience with the proposed USP methodology and is ready to implement the new USP requirements to make a smooth transition for our clients. Contact SGS Life Science Services to help you plan your strategy to remain in compliance with Heavy Metals Testing.

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