Understanding USP General Chapter <232> — Elements and Limits of Elemental Impurities in Pharmaceutical Products, Substances and Excipients

The United States Food and Drug Administration (FDA) and similar international health agencies have had long-standing regulations in place for controlling harmful impurities in pharmaceutical products marketed for human consumption.

Since the early 1900s, the United States Pharmacopeia (USP) has operated under a procedure known as General Chapter <231> - Heavy Metal Limit Test. With this current standard now more than a century in use, regulatory agencies have established new mandatory guidelines that will utilize more modern testing methods and instrumentation, and thus provide a higher level of control of potential toxic impurities in drugs.

These new guidelines are to be established in two new General Chapters: USP <232> and USP <233>. The first, USP <232>, addresses the specific elements — or heavy metals — to be evaluated, and the limits of these elemental impurities that may be found in drug products.

We understand that each client and each product is different. Our goal at RD Laboratories is to make adhering to these new mandates as simple and straightforward as possible for you. We are ready to begin working with you to help your company implement compliance in accordance with your particular needs.

USP <232> — Which Metals Should Be Tested?

The new Elemental Impurities chapters in the USP subdivide the metals desired for testing into several groups.

The first group consists of what is commonly referred to as "The Big Four":

- Arsenic (As)
- Cadmium (Cd)
- Mercury (Hg)
- Lead (Pb)

These elements will be tested for in all drug products and constitute the minimum requirement for testing.

At RD Laboratories, we have performed method verification studies on selected finished dosage forms, excipients, and active pharmaceutical ingredients, thereby demonstrating our expertise at successfully performing studies for this most critical group.

The second group consists of the following materials:

- Iridium (Ir)
- Osmium (Os)
- Palladium (Pd)
- Platinum (Pt)
- Rhodium (Rh)
- Ruthenium (Ru)
- Chromium (Cr)
- Molybdenum (Mo)
- Nickel (Ni)
- Vanadium (V)
- Copper (Cu)

These metals are to be tested for based on risk of exposure due to components (excipients or drug substances), manufacturing process, or route of exposure. For instance, USP <232> imposes limits on Chromium in inhalational products only, as it is not considered to be a safety concern in oral or parenteral drug products. We have successfully performed several limited verification studies on members of this group.

While some have misinterpreted the testing requirements for these metals, it is not necessary, nor will it become necessary, to test for all the members of this group in every product. Subsequent information provided in the guidelines drafted by the FDA in their Elemental Impurities Q3D document make this point clear.
What Are The New Elemental Impurities Testing Requirements?

The FDA has released their final Guidance for Industry to Q3D Elemental Impurities. Much of the information in the final release has not changed from the previous draft but what has changed is the inclusion of the FDA’s expected applicability timeline. In the guidance, it states, “Application of Q3D to existing products is not expected prior to 36 months after publication of the guidelines by ICH.” ICH Q3D was finalized in December 2014, thus the 36 month applicability timeline coincides with the omission of USP <231> Heavy Metals and the application of USP’s <232> Elemental Impurities on January 1, 2018.

The FDA guidance on the Q3D Guideline clarifies the testing requirements with regard to elemental impurities in new drug applications and abbreviated new drug applications.

Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb) are designated as Class 1, which must be evaluated under all circumstances. There are three primary reasons for this: There is no significant use of these elements in the Approved Pharmaceutical Ingredient (API) or in excipient manufacture, all four are highly toxic, and they cannot be easily removed from many materials.

Class 2 consists of elemental impurities considered to be toxic to a greater or lesser extent, based on route of administration. The guideline then subdivides Class 2 into two groups, 2A and 2B. These elements are less toxic than those in Class 1.

Subclass 2A consists of the elements Cobalt (Co), Nickel (Ni) and Vanadium (V). These elements must also be included in all assessments due to their ubiquity and relative toxicity. RD Laboratories is currently evaluating the feasibility of adding Subclass 2B to “The Big Four” grouping to provide better value to our customers.

Subclass 2B consists of Gold (Au), Thallium (Tl), Palladium (Pd), Platinum (Pt), Iridium (Ir), Rhodium (Rh), Ruthenium (Ru), Osmium (Os), Selenium (Se) and Silver (Ag). These elements only need to be evaluated if they are intentionally added to the processes used to generate the product. An example would be an API that is produced using any one of these metals as a catalyst.

As referred to in the previous section, this underlines the fact that testing for all of the elements included in the USP Elemental Impurities General Chapter <232> is not necessary for every product. Only those USP elements that would be reasonably presumed to be present will be required, along with the “Th Big Four” — Arsenic, Cadmium, Mercury and Lead.

Class 3 elemental impurities have relatively low toxicity by oral administration, but require assessment if delivered through the parenteral or inhalational routes. This class includes Antimony (Sb), Barium (Ba), Lithium (Li), Chromium (Cr), Copper (Cu), Tin (Sn), and Molybdenum (Mo).

Class 4 elemental impurities include Boron (B), Iron (Fe), Zinc (Zn), Potassium (K), Calcium (Ca), Sodium (Na), Manganese (Mn), Magnesium (Mg), Tungsten (W), and Aluminum (Al).

These are elements for which a potential daily exposure (PDE) has not been established due to their low inherent toxicity and/or regional regulations. There is currently no assessment requirement for these elements.

In conclusion, it will be necessary to demonstrate compliance with NDA and ANDA for finished dosage forms for, at least, the elements Arsenic, Cadmium, Mercury, Lead, Cobalt, Nickel, and Vanadium. For manufacturers of currently approved finished dosage forms, you will need to evaluate what level of compliance you need, based on your knowledge of the FDA office in your area.

We at RD Laboratories are committed to providing for your analysis needs according to the latest guidance and information available regarding the Elemental Impurities <232> and <233> General Chapter requirements. We look forward to assisting you as you navigate these new FDA and USP guidelines. Click Here to request a quote for testing implementation to meet your needs.