

USP Heavy Metals Testing Methodologies Workshop

Held August 26-27, 2008

Summary¹

USP supported a workshop on August 26-27, 2008 that was organized by and conducted at the Institute of Medicine (IOM) of the National Academy of Sciences of the United States to address limitations of specifications for metals testing as described in Chapter <231> of the *USP*. The IOM independently formed a planning committee consisting of individuals with recognized expertise in the areas of risk assessment, analytical methodology, toxicology, and compendial science as related to metals testing and exposure. The planning committee was given a charge by USP to develop and conduct a workshop that would provide the basis for USP to advance its specifications for metals testing. In addition, the committee was asked to involve experts from the European Community and Japan, if possible, with the goal of coming to common specifications for metals testing among the USP, EDQM (PharmEurope), and the Japanese Pharmacopoeia.

The specifications for metals testing as stated in *USP-NF* <231> consist of a wet chemical screening method that has been in use for more than 90 years. It is a subjective visual test based on precipitation of metal sulfides. A number of evaluations during the past 13 years have shown that this method is frequently unable to detect the presence of metals of great interest such as mercury, and seriously underestimates the concentrations of other metals. A number of these metals are known to be toxic (lead, arsenic, cadmium, mercury) and are potentially present in pharmaceutical ingredients. Similarly, the presence of a number of these metals has been well-described in marketplace surveillance of dietary supplements and food ingredients.

A general consensus by speakers and planning committee experts at the workshop was that the current methodology for metals testing is inadequate and should be replaced by instrumental methods of greater specificity and sensitivity for a wide range of metals of interest. At the same time it was acknowledged that with current state-of-the-art methods metals can be detected at levels much below that of any clinical or toxicological importance. The challenge presented, therefore, is the coupling of method capability, risk assessment, and likelihood of presence of metals of interest in a manner that best protects the public health.

Metals of Interest

Due to known toxic effects and demonstrated potential for contamination in pharmaceutical ingredients, dietary supplements and food ingredients, there was general agreement that lead, mercury, arsenic, and cadmium should be detectable at toxicologically relevant concentrations. In addition, consistent with the EMEA "Guideline on the Specification Limits for Residues of Metal Catalysts", platinum, palladium, ruthenium, rhodium, and rubidium should be detectable based on the likelihood of presence and toxicity. A wider range of metals may be used as organometallic reagents. There was some discussion about the appropriateness of testing for these metals, with a common view that if they were used in a manufacturing process and therefore at risk for presence, that a limit for the specific metal in the specific process may be a good course.

Current analytical methods permit the simultaneous detection of a large number of metals and other elements; however, it is unclear how many of these other elements

should be included in a pharmacopeial specification. In some instances there is some likelihood of presence (e.g. iron, copper); however, the metal has low toxic potential. In other instances the element is known to be toxic (e.g. beryllium, uranium); however, the likelihood of it being present is very low.

An important consideration is the form of the metal. This is of particular importance for arsenic and mercury. Dietary supplements that contain kelp and some other constituents known not to be toxic have very high concentrations of organic arsenic. Similarly, metallic mercury is relatively nontoxic; however methyl mercury is highly toxic and is known to be concentrated in some foods such as fish. Lead in all forms is toxic; however tetraethyl lead is much more toxic than metallic lead. Unless separation of metal forms (speciation) is carried out prior to analysis, the total of all forms for a given metal will be detected. Speciation is a much more complex issue in the case of dietary supplements and perhaps food ingredients. Reports of metals in various dietary supplements describe both metals that should not be present in any form such as lead and mercury and metals that are well known to be present in nontoxic forms such as arsenic. The failure to make such a distinction simply confuses the public and is not in the public interest.

Conclusions

- The need for revision of *USP* <231> for metals testing was strongly advocated. Further consideration of limits for various metals will be required.
- Serious effort will be made to harmonize approaches to metals testing across the major pharmacopeias.
- These efforts will go forward as a public process, with input sought from the various stakeholders (the public, industry, and regulatory bodies) at each step.

¹ USP is developing a paper based on the IOM workshop and other sources, which will go into detail about specific metals, methodologies, etc.