

Metal Impurities Frequently Asked Questions

Q. Why is USP revising its standards for metal impurities?

A. USP is revising its standards for metal impurities in the interest of protecting public health. The revisions focus on two areas of work:

- Updating the methodology that regulators, manufacturers, and other parties use to test for metal impurities in medicine and food products to include procedures that rely on modern analytical technology; and
- Setting limits for acceptable levels of metal impurities (including, but not limited to, lead, mercury, arsenic, and cadmium) in medicine and food products.

Q. Why is any level of metal impurities considered “acceptable”? Shouldn’t the level always be zero?

A. The human body requires trace elements of many substances to function properly. For example, iron is a metal that would be harmful or toxic beyond certain levels, but is frequently taken as a dietary supplement to help ensure healthy blood. For metals that should not ever be present in medicines or foods (such as lead, mercury, arsenic, cadmium, and others, which are present in many places in the environment in tiny amounts) modern analytical methods are so sensitive that even traces can be detected. A limit is necessary to ensure that levels are well below that known to cause any toxicity.

Q. What is wrong or deficient about the current test methodology?

A. The test methodology currently in wide use, which is described in the *USP-NF*, was first introduced over one hundred years ago. It is not sufficiently sensitive to detect a number of metals at levels known to be toxic. In addition, it can fail to detect some important metals such as mercury.

Q. Why has USP waited until now to revise standards for metal impurities? Was there a specific event that prompted the revision?

A. USP undergoes regular re-evaluation and revision of all its standards to update their currency and accuracy. There was no specific event that triggered the revision of metal impurities standards, but our scientific experts felt that the standards should be updated before there was any public health crisis. As we have gained a clear understanding of the limitations of the current methods, it has become clear that they must be revised now.

Q. How is USP approaching the revision?

A. USP is taking a risk-based approach that focuses on the *likelihood* of a given impurity being found in a drug or food article; and on the *toxicity* of the impurity at levels that may be found. For example, it makes no sense to assay every pharmaceutical for cadmium, because that impurity is only likely to be present in certain substances and not others. Similarly, many dietary supplements made from kelp will contain some level of arsenic, but in its organic form arsenic has very low toxicity – so testing for it provides no public health benefit.

USP’s current revision takes a new approach in that we’re looking at metals exposure not only from drugs, but also from food ingredients and dietary supplements. This is a much more comprehensive approach that provides greater and more realistic protection to the consumer. For example, exposure to mercury in medicines may be very limited, but the likelihood of exposure from food ingredients or dietary supplements

may be much greater. By looking across the spectrum of sources, USP is taking a broader-based view of the typical consumer's risk. To that end, we have included toxicologists as well as chemists in the group of experts revising the standards.

Q. Some in the pharmaceutical industry believe that USP is creating unrealistic, unworkable requirements for testing, which could lead to non-compliance and shortages of key medicines. For example, the article published in USP's *Pharmacopeial Forum* (*PF*) (2008, 34, 1345) includes a list of 31 substances to be tested for. And the proposed limits for each individual metal may be unworkable across the many quality assurance labs that would be affected.

A. USP does not intend to burden industry with unwieldy and unnecessary testing requirements. The list in the *PF* article was intended as a proposal for discussion. As the revision and comment period moves forward, that list will almost certainly change, most likely getting shorter. Nor will we mandate the methodology that each lab must use. Manufacturers will have the flexibility to choose a test that best fits their processes.

Setting rational limits for individual metals is admittedly complex. Considerations must include whether a drug is taken for a brief period (such as an antibiotic) or for a chronic condition (such as a statin for high cholesterol); whether the drug is taken orally, is injected, or is inhaled; what the differing toxicities might be for sensitive populations such as children or those with compromised immune systems; and what other sources of exposure such as food and water that an individual might have. USP seeks and welcomes input to the discussion on how to balance these public health considerations with the need for a deployable standard.

Q. The proposed leeway for manufacturers to choose their own test methods is attractive because of the added flexibility. But doesn't that expose manufacturers to added risk of FDA rejection?

A. Potentially, but USP is going to great lengths to work with both FDA and industry to ensure widespread agreement on interpretation of the revised standard. And the revision will include a default method, which manufacturers can use if they want to ensure complete compliance to the standard.

Q. How long will it take USP to revise the metal impurities standards? What should consumers do in the meantime?

A. USP's standards-revision process involves international collaboration among USP experts, industry, regulators, and the general public. When there is particular urgency this deliberative process can be accelerated, as was done in 2008 when the heparin supply was adulterated with a life-threatening substance for economic gain. When there is no specific medical emergency, as is the case with metal impurities, it is beneficial to allow careful deliberation and scientific dialog to reach conclusions that are supported by all stakeholders. USP anticipates that revised metal impurities standards will be published sometime in 2010 and become official at a later date to allow manufacturers sufficient time to incorporate changes in their processes.

In the interim, consumers can protect themselves in a number of ways:

- Talk to your physician or other health care providers about medications and dietary supplements to understand what you are taking, and why; and
- When buying dietary supplements, look for the "USP Verified" mark to ensure that what is on the label is what is in the bottle (see www.usp.org/verified for more information).

Q. Have imports from China and India posed an increased problem with metal impurities? How is USP dealing with this?

A. To date, there have been no known incidents in which metal impurities were detected in pharmaceuticals. This illustrates the high quality of manufacturers, both in the United States and overseas. However, the quality and safety concerns about materials coming from Asia are not unfounded. Ultimately, manufacturers are responsible for testing ingredients, no matter what the source. But as more ingredients are sourced from Asia (it is estimated at 60-80%), the presence of modern, scientifically sound quality standards will help protect both manufacturers and patients in the United States. USP's facilities in China and India are working with the manufacturers and governments of both countries to raise quality standards of medicines and food ingredients intended for export and for domestic consumption.