New quality standards limiting elemental impurities in medicines announced

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As part of its ongoing efforts to help ensure the quality of medicines, the U.S. Pharmacopeial Convention (USP) has announced two new standards related to elemental impurities: General Chapters Elemental Impurities—Limits and Elemental Impurities—Procedures. The new standards provide procedures for the detection of selected impurities in drug products based on modern analytical methods, as well as acceptable limits for their presence based on toxicity data and exposure levels. Conformance to the new standards will be required starting May 1, 2014.

A nonprofit scientific organization, USP develops standards for the identity, strength, quality and purity of prescription and over-the-counter medicines. USP's written standards for drugs and drug ingredients are expressed in monographs, general chapters, and General Notices published in USP's compendia, United States Pharmacopeia and National Formulary (USP–NF). General chapters may contain tests, procedures and/or specifications that apply across multiple medicines or ingredients. Those designated as above-1000 are considered interpretive and informational, and are not required unless referenced in a monograph, General Notices or a general chapter numbered below 1000. General chapters designated as below-1000—such as and —contain tests that may apply to items recognized in USP or NF, and may also be required by the Food and Drug Administration (FDA) to demonstrate conformance to Good Manufacturing Practices (GMPs).

General chapters and have been approved for publication in the Second Supplement of USP 35–NF 30, which will be official on December 1,

2012. However, the general chapters will have a deferred application date of May 1, 2014. Thus, while and will become official on December 1, 2012, the date on which conformance with these chapter is required will be May 1, 2014. More information on the implementation requirements is at http://www.usp.org/usp-nf/hot-topics/elemental-impurities.

FDA and other public health officials have monitored the presence of elemental impurities in products intended for human consumption for some time. Elemental impurities can occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment). Elemental impurities include catalysts and environmental contaminants such as lead or mercury that may be present in drugs.

Until the development of and , USP's standards for elemental impurities were included in USP–NF's General Chapter Heavy Metals and applied only to active pharmaceutical ingredients and excipients. The test methodology included in —while widely used—is based on a longstanding technique not sufficiently sensitive to detect a number of impurities at levels known to be toxic. Once general chapters and are implemented, all references to USP General Chapter will be omitted from monographs in USP–NF.

"Given the broad-reaching impact of these standards on multiple drug products, USP has established a clearly-defined timeline for pharmaceutical manufacturers and regulators to prepare for these changes," said Anthony DeStefano, Ph.D., USP's senior vice president for compendial sciences. "We feel that these new standards have struck a good balance between the need to maintain the quality of medicines for the protection of patients and rational testing procedures and limits that can be readily applied by industry."

General Chapter specifies limits for the acceptable amounts of elemental impurities in drug products. Of the 15 elemental impurities identified for testing in , 11 are catalysts. As such, their presence in a given drug product would be known through an assessment of the manufacturing process. The remaining four elements—arsenic, cadmium, lead and mercury—are naturally occurring or environmental impurities, thus making it necessary to assess the likelihood of their presence. The analytical procedures in General Chapter apply inductively coupled plasma–atomic (optical) emission spectroscopy (ICP-AES) or inductively coupled plasma–mass spectroscopy (ICP-MS) to detect elemental impurities. The general chapter also describes criteria for validation/verification of the procedures and for the establishment of acceptable alternative procedures. Both general chapters can be accessed at http://www.usp.org/usp-nf/hot-topics/elemental-impurities.

The revised General Chapter Elemental Contaminants in Dietary Supplements appeared in the May-June 2012 issue of Pharmacopeial Forum. The deadline for submitting feedback on the general chapter is July 31, 2012.

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