

White Paper: Modernization of Organic Impurities Testing in USP Drug Product Monographs

As part of an ongoing modernization initiative, USP is updating its general chapters related to organic impurities testing for articles subject to USP–NF standards. Due to scientific and technological innovations, impurity measurements and control processes continue to evolve significantly. These, in combination with advancements in the field of toxicology, have contributed to the evolution of the regulatory standards for control of impurities in drug substances and drug products. USP has established the Impurities in Drug Products Expert Panel (EP) to evaluate the current content of USP’s impurities general chapters. The EP will make recommendations on updating the general chapters to align them with modernized standards and to help ensure the appropriate control of organic impurities and degradation products in drug products. Public and regulatory expectation is that all products, including over-the-counter (OTC) products and legacy prescription (Rx) products, will be safe and of high quality, and that pharmacopeial requirements in USP–NF are adequate to ensure this level of quality. While committed to this goal, USP anticipates challenges associated with the process, especially for OTC products. This is because many OTC medicines, which are subject to existing USP quality standards, are available in a wide variety of dosage forms and formulations. Such diversity in formulations, which includes numerous colors, flavors, and other aesthetic ingredients, poses complexities in developing analytical procedures and specifications.

In September 2011, [a workshop sponsored by USP and FDA focused on the development of standards for OTCs](#). USP has received a list of OTCs from the FDA prioritized for modernization. Modernization of these products will address missing or outdated tests for impurities and the replacement of non-specific identification tests with more specific analytical procedures. Because of the diversity of OTC dosage forms and drug strengths, the use of alternative approaches for developing USP monographs and general chapters related to OTCs was a major area of discussion at the 2011 workshop. As manufacturers respond to the growing needs and demands of OTC consumers and as more products enter the market, USP also must respond in a manner that keeps pace with these changes. Suggestions that emanated from the workshop included consideration of more efficient approaches to modernization such as updating families of monographs associated with one drug substance. For example, currently in the USP–NF there are 37 different monographs for acetaminophen dosage forms alone. Acetaminophen is among FDA’s list of OTCs targeted for modernization. Modernization of the acetaminophen monograph family could encompass analytical procedures that apply to multiple active ingredients (e.g., cough and cold products) as well as interfering inactive ingredients (e.g., colors and flavors).

As USP explores novel approaches to help streamline the development of missing monographs and the revision of outdated monographs, it will continue discussions with FDA and industry stakeholders in order to establish an optimal path forward. General Chapter <1086> Impurities in Drug Substances and Drug Products includes key definitions associated with impurities that are aligned with those established by other pharmacopeias and the International Conference on Harmonization (e.g., ICH Q3A and Q3B), as

well as current FDA guidance. This chapter refers to General Chapter <466> Ordinary Impurities and General Notices 5.60, both of which may need updating as part of USP's modernization program. Consequently, in late 2011, the Impurities in Drug Products EP, reporting to the Physical Analysis Expert Committee (EC), was established and charged with developing recommendations for revising General Chapter <1086> and its associated general chapters and General Notices references. The EP is comprised of pharmaceutical and OTC industry representatives; members from the Physical Analysis, Small Molecules and Toxicology ECs; and FDA liaisons. The EP is identifying potential gaps in the impurities testing for both OTC medicines and Rx products. This initiative is also leading to the development of a new General Chapter <476> intended to replace current General Chapter <466> for the inclusion of harmonized mandatory requirements regarding identification and reporting thresholds of organic impurities. In a complementary approach, general guidelines, terminology and decision trees for use when needing to address or report impurities associated with drug products will be introduced during the revision of the chapter <1086>. Thus far, the EP has convened at two face-to-face and six teleconference meetings; discussions will continue at additional meetings in the future in order to complete this task, including providing input to the Expert Committees that will decide on the adoption of new or revised General Chapters. Input from stakeholders is strongly encouraged.