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Modernization of Organic Impurities Testing in USP Drug Substance and Drug Product Monographs

Impurities in Drug Substances and Drug Products Expert Panel^a

ABSTRACT Impurity measurements and control processes continue to evolve significantly as a result of scientific and technological innovations. These innovations, in combination with advancements in the field of toxicology, have contributed to the evolution of compendial standards for control of impurities in drug substances and drug products. As part of an ongoing monograph modernization initiative, U.S. Pharmacopeial Convention (USP) is updating general chapter *Impurities in Drug Substances and Drug Products* 〈 1086 〉 as it relates to the organic impurities tests for monographs in *United States Pharmacopeia–National Formulary (USP–NF)*. In this issue of *Pharmacopeial Forum*, USP also proposes a new general chapter, *Organic Impurities in Drug Substances and Drug Products* 〈 476 〉. In late 2011, USP established the Impurities in Drug Products Expert Panel, with oversight from the Physical Analysis Expert Committee, to evaluate the current content of USP's impurities general chapters, 〈 1086 〉 and *Ordinary Impurities* 〈 466 〉, and *General Notices and Requirements 5.60, Impurities and Foreign Substances*. The Expert Panel was charged with making recommendations on updating the general chapters to align them with current standards and to help ensure the appropriate control of organic impurities in drug substances and drug products. The proposals of the Expert Panel are published in this same issue of *Pharmacopeial Forum* for public comments. The purpose of this *Stimuli* article is to (1) provide the rationale behind the revision of general chapter 〈 1086 〉 as it relates to organic impurities, (2) provide the rationale for the creation of general chapter 〈 476 〉, and (3) describe the scope of revision and the strategy for implementation.

INTRODUCTION

In a USP/FDA-sponsored workshop held in 2011, attendees explored some key challenges posed by over-the-counter (OTC) products with regard to quality. One critical factor discussed was the large number of drug product monographs associated with single or multiple drug substances. With the modernization of *USP–NF* monographs in process, and also based on work of the Acetaminophen and Diphenhydramine Expert Panels in working with multiple drug product monographs with reference to both drug substances, USP created

the Impurities in Drug Products Expert Panel, which met for the first time in December 2011. The original charge of the group was to revise general chapter *Impurities in Drug Substances and Drug Products* 〈 1086 〉 in the context of current regulatory thinking with regard to OTC and generic product testing.

After several meetings, the Panel decided to expand the scope of its efforts and was renamed the Modernization of Organic Impurities Testing in Drug Substances and Drug Products Expert Panel. The Panel proposed to use the current ICH Q3A/Q3B and FDA guidances as starting points, with associated regulatory documents. The Panel also used additional strategies such as a survey, updates on websites, articles, and other approaches to gather feedback and also to inform stakeholders about this effort. Based on an impact analysis, the Expert Panel decided to begin its review with general chapter *Ordinary Impurities* 〈 466 〉, and organic impurities tests in individual monographs. Based on this review, the Panel determined that general chapter 〈 466 〉, while outdated for modern control of impurities in drug substances and drug products, should be retained in certain settings. The final decision of the group was to perform three key activities: (1) create a new general chapter, which became *Organic Impurities in Drug Substances and Drug Products* 〈 476 〉, and appears elsewhere in this issue of *Pharmacopeial Forum (PF)*; (2) perform a revision of the informational chapter 〈 1086 〉; and (3) provide suggestions to update *USP–NF General Notices and Requirements 5.60*. A survey was launched in June 2013 to obtain feedback and comments from stakeholders regarding this initiative. The main goal was to help shape development of USP written standards and reference standards on organic impurities in drug substances and drug products. The results were positive and were supportive of the decisions made by the Expert Panel.

RATIONALE FOR REVISION OF CHAPTERS

Public and regulatory expectation is that all products, including OTC products and legacy prescription products, will be safe and of high quality, and that pharmacopeial requirements in *USP–NF* should promote this level of quality. In September 2011, a workshop sponsored by USP and FDA focused on the development of standards for OTC products. USP had received from the FDA a list of drug substances and products prioritized for modernization. Ongoing modernization of the monographs for these drug substances and corresponding drug products is addressing missing or outdated tests for impurities and the replacement of nonspecific identification tests with more specific analytical procedures.

Survey Results

A survey was launched in June 2013 to obtain feedback and comments from stakeholders

regarding the USP modernization initiative. The main goal of the survey was to help shape development of USP standards on organic impurities in drug substances and drug products. Specific survey objectives were to: (1) identify overall needs and challenges regarding the current written standards on organic impurities, (2) assess the level of satisfaction with the written standards on organic impurities, (3) gauge opportunities for improvement, (4) analyze reactions to modernizing written standards on organic impurities, and (5) determine potential challenges to implementing the new approach. The survey was sent to a list of around 20,000 valid email addresses including *USP–NF* customers, *USP–NF* online users, *PF* users and USP Reference Standards customers.

A total of 991 complete responses from industry representatives were received. The three figures below show responses to several key messages derived from the survey. The percentages represent a response of 6 or 7 (combined) on a 7-point scale where 7 equals “Extremely Satisfied”, 6 equals “Very Satisfied”, and 1 equals “Not at all Satisfied”.

[Figure 1](#) shows that in general, there is only a moderate level of satisfaction (less than 60% responding very or extremely satisfied) with existing USP information for testing organic impurities. The scores may reflect the fact that only about half of respondents say *USP–NF* written resources are easy to follow.

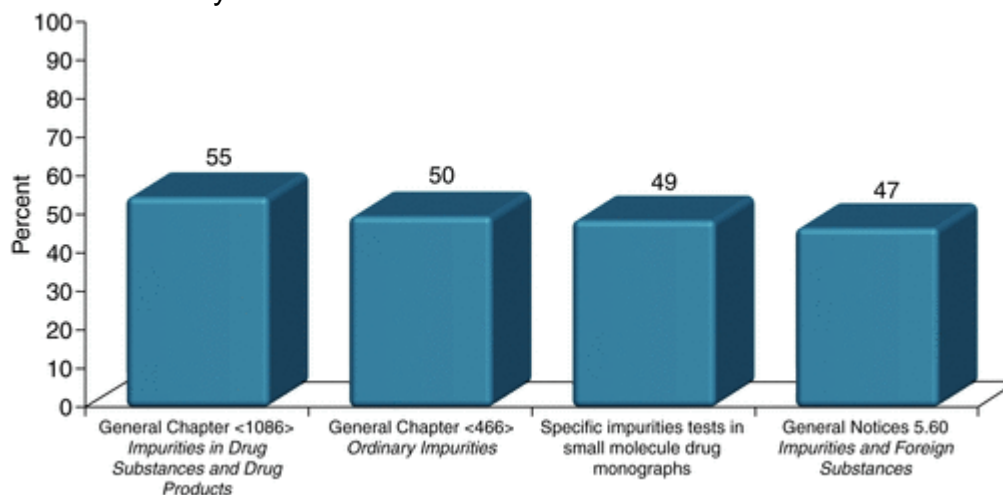


Figure 1. Percentage responding “Very Satisfied” or better with current *USP–NF* resources for testing organic impurities.

In [Figure 2](#), the data show a strong perceived need to modernize the *USP–NF* written standards for impurities. The percentage saying modernization is very needed is similar to the percentage that is less than very satisfied with current written resources.

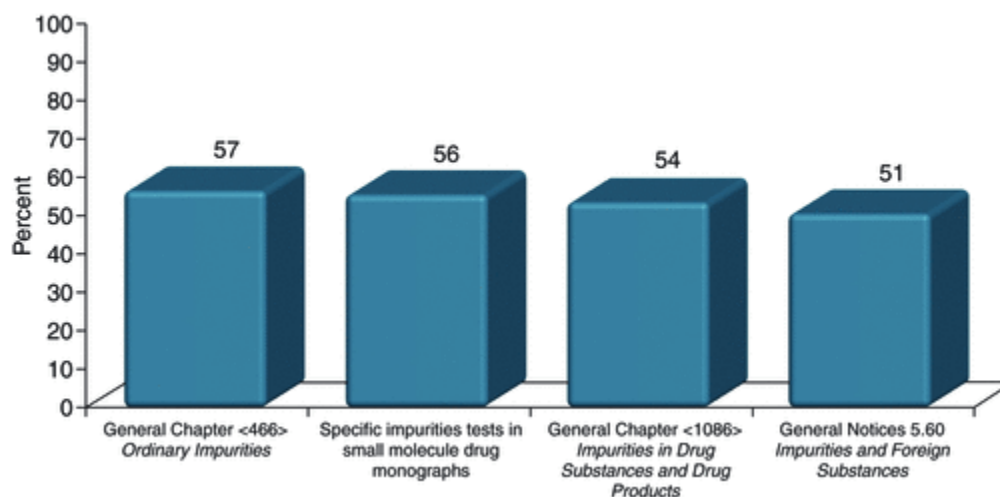


Figure 2. Percentage saying modernization of *USP–NF* resources for testing organic impurities is very needed.

[Figure 3](#) shows that the most supported areas for modernization (by about three in four respondents) are revising monographs, achieving harmonization with ICH, and offering alternative testing options.

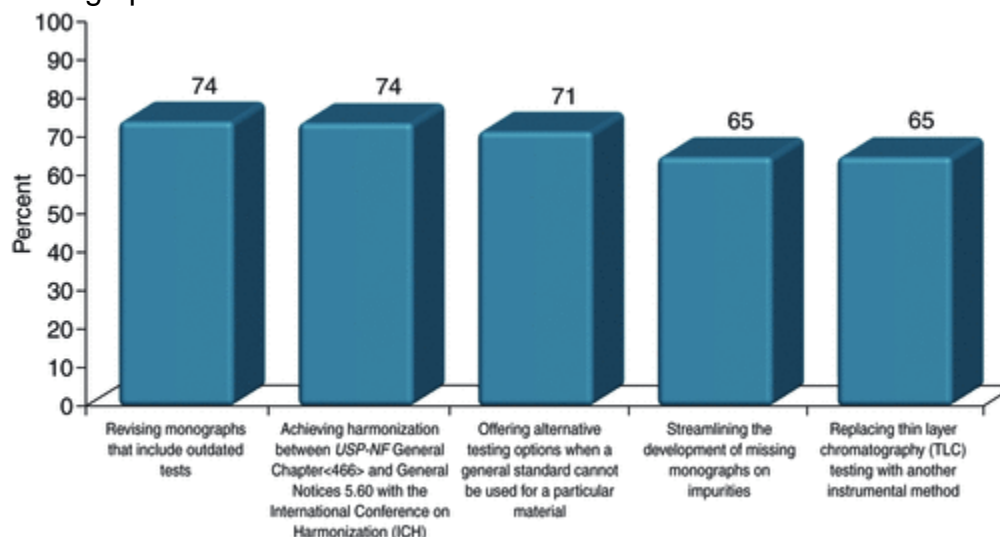


Figure 3. Percentage very supportive of modernizing *USP–NF* written standards on organic impurities in selected ways (top areas for modernization).

GENERAL CHAPTERS < 476 > AND < 1086 >

Results obtained from the survey confirmed the preliminary decisions made by the Expert Panel: (1) create a new descriptive chapter < 476 >, (2) update the informational chapter < 1086 > in order to synchronize it with the new chapter < 476 >, and (3) provide a recommendation to update *General Notices 5.60*. The Panel addressed some recommendations based on the survey findings. For example, respondents showed interest

in conceptual/informative elements and schematics, including tables showing thresholds and decision trees/flow charts, and some of these resources were included in both chapters. The Panel created a new general chapter 〈 476 〉 to align with current scientific and regulatory standards and to help ensure the appropriate control of organic impurities in drug substances and drug products. The goal is to provide a science-based approach for the control of impurities in relevant monographs, in order to ensure the quality of the product as it relates to safety and efficacy. Chapter 〈 476 〉 will support those monographs that do not include specific organic impurity tests and those monographs that are in need of additional guidance in this area.

General chapter 〈 1086 〉 has been updated to align it with current scientific and regulatory standards and to support the development of appropriate control of organic impurities in drug substances and drug products. In addition to the updated general guidelines, chapter 〈 1086 〉 introduces definitions, threshold tables, and a decision tree for use when needing to address or report impurities associated with drug substances and drug products; these new resources should assist the user who may have questions related to implementation of the newly created chapter 〈 476 〉.

In addition, the Panel proposes to update *General Notices 5.60* to clearly describe the intention of the two chapters: 〈 476 〉, which will not be enforced as the default standard for organic impurities in all monographs but instead on a case-by-case basis, and chapter 〈 1086 〉, which will provide complementary information that should be useful to stakeholders, irrespective of whether they are relying on chapters 〈 466 〉 or 〈 476 〉.

GENERAL CHAPTER ORDINARY IMPURITIES 〈 466 〉

The new descriptive chapter 〈 476 〉 is not intended to replace the procedural chapter 〈 466 〉. However, the ongoing monograph modernization process for *USP–NF* is eliminating references to chapter 〈 466 〉 by an independent process. USP has performed an evaluation of impact and identified about 100 monographs in *USP 36* that are in need of replacement of tests described in chapter 〈 466 〉 with specific organic impurities tests. The monographs were posted on the USP website under the priority list and are being updated. As of mid-October 2013, the references to chapter 〈 466 〉 had been deleted from 14 monographs; another 54 monographs were in the process of revision, and 32 monographs were still in need of modernization. Starting January 1, 2014, monographs posted to revise chapter 〈 466 〉 have been taken down, and the process of modernization is underway. When this monograph modernization project is complete, chapter 〈 466 〉 will become obsolete and will be omitted. Any new monograph should refer to chapter 〈 476 〉, if appropriate.

IMPLEMENTATION

New chapter 〈 476 〉 and revised chapter 〈 1086 〉 will provide greater alignment with current applicable regulatory guidance and scientific thinking. The implementation of chapter 〈 476 〉 is expected to utilize a phased-in approach. This means that this chapter may be used when it first appears (i.e., becomes official) in *USP–NF*, but the final implementation date will be based on the time needed for manufacturers to achieve compliance. The implementation plan will allow time to identify and resolve issues for specific monographs caused by introduction of chapter 〈 476 〉.

The Expert Panel anticipated, and the survey results confirmed, that users perceive that implementation of new chapter 〈 476 〉 may be challenging. In contrast to the challenges of implementing general chapters *Residual Solvents* 〈 467 〉, *Elemental Impurities—Limits* 〈 232 〉, and *Elemental Impurities—Procedures* 〈 233 〉, which affected many monographs, the new chapter 〈 476 〉 will be referenced only in monographs that are new, are missing tests, or are in need of complementary testing for organic impurities.

The Expert Panel requests feedback from stakeholders regarding the following questions. Stakeholder input will enable the design of a seamless and successful implementation path:

1. Do the newly revised/created chapters adequately address impurity control in drug substances and drug products? If not, what needs to be changed?
2. Would it be helpful to hold a workshop to inform the user community of the upcoming changes in USP written standards for impurities and to discuss the potential impact of these changes?
3. What length of time would be reasonable for implementing chapter 〈 476 〉 in new OTC drug products, OTC products that do not have a USP monograph, and existing OTC monographs that do not refer to chapter 〈 466 〉?
4. Would it be useful for USP to hold pharmacopeial education classes to provide training in how to use chapter 〈 476 〉?

^a Correspondence should be addressed to: Antonio Hernandez-Cardoso, Senior Scientific Liaison, United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. +1.301.816.8308; e-mail ahc@usp.org.