USP Excipients Open Forum
Setting Compendial Specifications for Excipient Composition, Organic and Inorganic Impurities

February 11–12, 2021

Executive Summary

Overview of the event

An Open Forum about Excipients, "Setting Compendial Specifications for Excipient Composition, Organic and Inorganic Impurities," was hosted by the United States Pharmacopeia (USP) on February 11 and 12, 2021. More than 650 people registered for the virtual event, where USP provided up-to-date information and engaged stakeholders to obtain their input, perspectives, and feedback. The attendees included stakeholders from industry, regulatory agencies, trade organizations, and academia.

The purpose of this meeting was two-fold: 1) to level-set the audience in their understanding of USP's standard-setting processes for excipients, thereby achieving better awareness, and 2) to highlight the many ways that stakeholders can get involved in setting excipient standards and managing their impact through USP's Stakeholder Engagement Model (SEM). For the past 10+ years, USP has been striving to boost stakeholder engagement via surveys, Stakeholder Forums, workshops, round tables, prospectus, Compendial Notices, stimuli articles, Excipient Newsletter, Pharmacopeial Forum (PF), and other opportunities to provide input. Still, despite these efforts, stakeholder involvement has been less than optimal.

Background, history, and challenges

USP's work on excipient standards is consistent with the goals of the U.S. Food and Drug Administration (FDA). Both FDA and USP seek to advance the science of excipient selection and regulatory evaluation. Recent USP collaboration occurred with the FDA Monograph Modernization Task Group to update 19 high-priority excipient monographs. These revision efforts are continuing, with three USP Expert Committees dedicated to excipients for the 2020–2025 cycle. Stakeholder input is always sought and carefully considered via the public comment process, and other USP engagement tools before any new or revised monographs become official.

The complexity, variability, and origin of excipients create challenges for both users and pharmaceutical makers in manufacturing and selecting the right excipients. This can lead to challenges in setting compendial specifications for excipient composition and impurities. Recently

USP published a Stimuli article in 2018 [insert link] to help stakeholders understand the complex issues involved, and most importantly, to request their input and participation. At the Open Forum, USP emphasized that the Stimuli article content is not new. The USP Excipient Expert Committees have been following the principles and approaches described in the article for the past three revision cycles (about 15 years) since USP collaborates with the FDA, industry, and all stakeholders to update excipient compendial standards.

While the Stimuli article is not new, stakeholder input is still needed. USP encouraged stakeholders to read and utilize the article, which serves as an open invitation to engage in the compendial standard-setting process. In the Stimuli article, readers will find:

- A simplified classification system for organizing excipients and prioritizing them for modernization.
- Principles and approaches for setting specifications for excipient components, with examples of challenges included.
- Proposed definitions for key terms that, if accepted and used going forward, could improve consistency and avoid confusion.

Another challenge is the lack of clear guidance and direction from the USP on how to specify excipient composition, including control of impurities. USP plans to address these gaps through this open forum and future stakeholder engagement opportunities with their input and collaboration.

Excipients are critical to medicine quality, but historically, quality-control efforts have focused primarily on active pharmaceutical ingredients (APIs) rather than excipients. During the early 2000s, case reports of excipient adulteration were rising, leading to recognition that excipient adulteration was a growing problem.

Major themes for consideration and continuing stakeholder engagement

- **Clear guidance should be developed, possibly in the form of an informational General Chapter/guideline** where USP seeks stakeholder input and collaboration on this. The chapter/guideline could fill a void by addressing how to specify excipient composition, including control of impurities. Excipient composition is especially important for some of the new drugs coming onto the market. Poor control of excipient quality can lead to the loss of a million-dollar drug.
    - Concepts of "safety" versus "quality" of the excipient are described in Case Study 2 in the 2018 Stimuli article that discusses the toxicological assessment of any identified component as a critical step for excipient standard development.

  - Definitions for excipient components must be clear and accurate. Otherwise, it is not possible to describe excipient composition.

- **A *Roadmap* for addressing element-specific chapters** and stand-alone tests in excipient monographs was published by USP in 2020. USP decided to take the approach of the *European Pharmacopoeia* on elemental impurities tests, which involves keeping elemental impurity tests in monographs for excipients of natural origin but removing them from monographs for those of synthetic origin. Many stakeholders who completed USP surveys agreed that harmonization is very important for the industry.

USP Stakeholder survey engagement results

USP conducted two surveys, 2018, Excipient Impurity Survey and 2021, to collect information.

- Highlights of the 2018 Excipient Impurities Survey include:
  - Most respondents (87%) believe that updating USP specifications for excipient composition and impurities is important.
  - A majority of respondents agreed with the proposed definitions in the Stimuli article for Simple Excipient, Nominal Component, and Added Substances in Official Substances.
  - More than 60% of respondents said General Notices 5.60.10 Other impurities in *USP* and *NF* articles should be updated/clarified.
  - Pharmacopeial methods were the most commonly cited methods used by respondents to test excipients for specific impurities specifications, followed by in-house procedures.
  - Two-thirds (65%) of respondents support the development of an informational General Chapter (above 1000) on excipient impurities with test procedures. If such a chapter is developed, 75% of respondents would be interested in training from USP.

- Highlights of the 2021 Survey include:
  - Almost half (46%) of respondents said they think testing for excipient organic impurities is necessary for analytical testing.
  - Three-quarters (77%) of respondents consider compositional testing important for controlling the risk of contamination and adulteration.
  - Almost three-quarters (71%) of respondents consider testing that helps understand excipient composition necessary analytical testing.
  - Excipient testing is most commonly performed by the excipient maker (42%) or the pharmaceutical manufacturer (30%).

How to engage with USP

There are many ways that stakeholders can engage with USP to express their views, get involved, and inform or influence standards.

- USP continues to encourage stakeholders to submit comments via *Pharmacopeial Forum* (*PF*) during the public comment period for new and regular revisions. *PF* is the official tool for providing input on proposals; however, the USP survey showed that more than 50% of stakeholders do not use the online *PF* comment feature, and about 75% have never commented on Compendial Notices.
- A new, comprehensive approach – the Standards Engagement Model (SEM) – is now launching and includes formal and informal communications, information sharing, and convening of stakeholders, among other options.
    - The SEM and its tool complement the *PF* process and are intended to inform standards and the standards-setting process. Official comments on new and revised standards are only accepted through *PF*.
    - Open Forums: This new event format has recently been introduced to increase stakeholder engagement. See "What is an Open Forum?" below.
    - Stakeholder Forums: These are USP's original stakeholder events, which will continue.
    - Numerous other options for stakeholder engagement are available, including surveys, project teams, roundtables, e-newsletters, blog posts, white papers, education courses, Stimuli and journal articles, and trade organization outreach.
- Contact USP staff anytime with your questions, comments, and input [sf@usp.org]

Next steps

- USP staff will share all stakeholder input with the Excipients Composition and Impurities Joint Subcommittee (JS) and the Excipients Expert Committees, which will then develop a work plan and identify appropriate tool(s) to use going forward, such as a project team, roundtable, stakeholder forums, and/or expert advisors.

What is an Open Forum?

- Virtual meetings, like Open Forums, focus on a timely topic (suggested by USP, Industry, or Regulatory Agencies complement other flexible approaches.
- Open Forums do not have a Planning Committee; they are facilitated by an Expert Committee member or a USP Facilitator.

- Open Forums focus on one topic generally, are 1-2 hours in duration, 60% of the scheduled time is allocated for dialogue from stakeholders.
- Proactive, issue-driven, intended to help inform USPs' work.

About USP

U.S. Pharmacopeia (USP) is an independent, nonprofit, scientific organization that sets quality standards for medicines, dietary supplements and food ingredients worldwide. USP's quality standards are legally recognized in the U.S. and elsewhere, and are used in more than 150 countries. These standards are continuously developed and revised by more than 800 volunteer experts in science, industry, healthcare and academia. Learn more at www.usp.org.