This edition of the column discusses the updates to and harmonization of excipient USP-NF standards and the importance of stakeholder engagement.

Since 1820, the US Pharmacopeial Convention (United States Pharmacopeia, or USP) has published drug standards used in the USA and in more than 140 countries [1]. Additionally, USP produces and supplies more than 3,500 reference standards used in testing for drug substances, biologics, excipients, and many other items.

Given the broad application of excipients in drug products, dietary supplements, and food ingredients, USP has resolved to update the USP-National Formulary (USP-NF) excipient standards by adding or revising specific identification, assay, and impurity tests. These tests help improve testing controls and provide tools to qualify an excipient for its intended use. The complete list of excipient monographs in need of updating can be found on the USP website, along with guidelines for sponsors to submit a request for revision to USP-NF [2-4].

USP employs several approaches that include:
- The traditional donor model (externally sourced from a sponsor);
- USP laboratories (internally sourced through our USP-China compendial development lab);
- USP expert committees and expert panels (which use industry expertise and gain early stakeholder input), and
- Harmonization initiatives through the Pharmacopeial Discussion Group (PDG) in partnership with the European Pharmacopoeia (PhEuR) and Japanese Pharmacopoeia (JP) [5,6].

USP has made steady and significant progress in updating methodologies in the USP-NF through collaborative efforts with the FDA and its stakeholders [1,7,8].

**USP Excipient monograph Expert Committees’ updates and progress**

USP Expert Committee (EC) work plans are posted on the USP website. The two Excipient Monograph ECs’ (EM1 and EM2) work plans provide a summary of their work during the 2010-2015 revision cycle that includes the area of focus and key issues [9].

Major topics of the 2015-2020 EM2 work plan include reconvening the USP Expert Panel to revise General Chapter <1059> Excipient Performance [10]. This chapter provides an overview of the key functional categories of excipients and tests or procedures that can be used by both the user and maker of the excipient to monitor and control critical material attributes or properties of the excipient. This is important because not all the critical physical and chemical properties may be identified in excipient monographs via compendial tests and specifications. The use of excipients in specialized drug delivery systems—such as in biologics and injectables—has highlighted the need to control critical excipient properties that contribute to excipient variability in a dosage form.

The expert panel’s area of focus for revision includes:
- Adding missing USP-NF functional categories to include excipients used in specialized dosage forms per <1151> Pharmaceutical Dosage Forms, such as biologics,
- Identifying methods that can be introduced into <1059> to support the new NF categories, and
- Updating the USP reference table “USP and NF Excipients, Listed by Functional Category.”

Major topics of the 2015-2020 EM2 work plan include the formation of the new Talc Methods expert panel, which held its first meeting in March 2016. The charge of the expert panel is to address the request from the FDA Monograph Modernization Task Group (MMTG) to modernize the high-priority USP-NF talc monograph requesting that, “Labeling should be revised to match the statements that are provided in the Talc FCC monograph, thereby assuring that talc is not sourced from mines that are known to contain asbestos.” Also, USP should consider revising the current tests for asbestos to ensure adequate specificity [11]. This expert panel was formed based on the recommendation of the previous talc expert panel under the 2010-2015 Excipient EC, which was charged with identifying the scope of the updates to the USP Talc monograph to ensure that the test for absence of asbestos has adequate specificity. This scope was published in a Stimuli article, which addressed the challenges faced in updating the test for absence of asbestos and provided recommendations for the Talc monograph update [12]. Based on these recommendations, the current Talc Methods expert panel was formed to
identify appropriate analytical methods and reference standards to test for the absence of asbestos in talc. The specification will be shared with the PDG members for consideration as a revision to the currently harmonized Talc monograph [13].

Global excipient harmonization initiatives

To help meet the challenges of global excipient manufacturing and supply chains, USP collaborates with other pharmacopeial organizations worldwide to harmonize excipient monograph specifications, such as test procedures and acceptance criteria. Recent progress on these initiatives includes:

• In September 2016, USP signed a Memorandum of Cooperation with JP establishing a framework for collaborative work between the two organizations that includes excipients.
• In October 2016, USP renewed a Memorandum of Understanding (MOU) with the Chinese Pharmacopoeia (ChP), to establish a framework for collaborative projects between the two organizations over the next 3 years. Under this MOU, we will collaborate to strengthen standards in our respective pharmacopoeias and participate in joint standard-setting and harmonization activities that include excipients. Following the MOU signing, USP and ChP held a joint workshop focused on advancing quality in regulatory science.
• Since 1989, USP has participated in the PDG, which aims to harmonize excipient standards among USP, PhEur and JP. PDG has harmonized 30 of 36 General Chapters and 49 of 67 excipient monographs on its work plan [6]. USP attended the PDG meeting in Tokyo, Japan on October 24-26, 2016, to discuss the PDG work plan, including signing off on the new Color General Chapter [14]. Progress has also been made on four of the recently added items: isostearyl alcohol, myristyl myristate, polysorbate 65, and sodium cetyl sulfate. JP has been confirmed as the coordinating pharmacopoeia for these monographs, and the draft texts provided to USP will also be provided to PhEur for comment in accordance with the PDG procedure.

USP excipient stakeholder engagement

USP continued to expand opportunities to engage with global excipient stakeholders by hosting its third Excipients Stakeholder Forum in September 2016, which discussed progress and stakeholder achievements on the USP Excipient Up-to-Date initiative. The forum was created to foster exchanges of information and perspectives between USP and users of USP standards to improve those standards. It provides opportunities for manufacturers, distributors, and users of excipients to discuss topics in an open setting. USP found that the Stakeholder Forum encourages excipient constituencies to work openly and directly with USP and to collaborate with fellow stakeholders [15].

USP workshops are another activity designed to promote the exchange of ideas across a wide range of current scientific findings, regulatory trends, and public health topics. Workshops are open to all interested parties. USP and FDA co-sponsored a workshop on standards for pharmaceutical products, “Critical Importance of Excipients in Product Development: Why Excipients are Important Now and In the Future” in late February [16]. The workshop discussed how the quality and variability of excipients impact medicines. The workshop helped participants:

• Develop a strategy on excipient selection for complex drug products [17, 18];
• Understand the FDA’s position on Q1/Q2/Q3 in terms of risk assessment for product quality and clinical performance; and
• Recognize and understand the importance of excipient selection suitable to the drug product and process.

Conclusions

USP’s up-to-date monograph quality specifications help improve testing controls and provide tools to use in qualifying an excipient for its intended use. In combination with other suitable controls on excipient quality, compendial testing plays a very important role in ensuring the quality of pharmaceutical products [1]. Supported by the FDA, and by public and industry outreach efforts, the USP monograph up-to-date and harmonization initiatives continue to increase the relevance and quality of excipient standards in furtherance of USP’s stated mission of improving global public health. USP welcomes participation and contribution—including revisions to monographs, donation of bulk material to be developed into reference standards, and shared expertise—from interested parties in our collaborative standards-setting activities [19].

References

5. Expert panels provide support to the expert committees by contributing additional expertise beyond that of the Expert Committee (which is global in make-up) and present recommendations to the expert committees upon completion of their charge.
13. USP-NF Talc Monograph. 2015.

Catherine Sheehan is senior director of science and John A. Giannone is senior director of strategic marketing and program operations at USP, 12601 Twinbrook Parkway, Rockville, MD 20852. Tel. 301 881 0666. Website: www.usp.org.