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Challenges and Opportunities in Developing Up-to-Date USP–NF Excipient Monographs

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Tong (Jenny) Liu, Ph.D.
Kevin Moore, Ph.D.
Catherine Sheehan, MS, MS
Senior Director, Science –Excipients

- United States Pharmacopeia Convention

Abstract

As the second part of this series, this article focuses on the harmonization activities related to excipients under the work plan of the Pharmacopeial Discussion Group (PDG) that are also part of the USP Up-to-Date Initiative. As described in the first article, among the 19 FDA priority excipient monographs requested by FDA to be updated, fifteen (15) of them are in the PDG work plan among which eight (8) of these will be discussed in this article.[1] Three expert panels were formed under the 2010-2015 Excipient Expert Committee to address FDA's request to update five excipient monographs for Glycerin, Talc, and Povidones (Povidone, Crospovidone and Copovidone). The significant progress made through the efforts of these expert panels is discussed in this review and the impact on their harmonization within PDG. In addition, three cellulose-based excipient monographs, Microcrystalline Cellulose (MCC), Carboxymethylcellulose Sodium (CMC Na), and Croscarmellose Sodium (CROS Na), have been identified by FDA as high priority for updating. USP's comprehensive approaches for identification and assay update in these cellulose-based excipient monographs are also discussed in this review.

Introduction

The Pharmacopeial Discussion Group (PDG) was formed in 1989 with representatives from the European Directorate for the Quality of Medicines in the Council of Europe (the European Pharmacopoeia); the Ministry of Health, Labor, and Welfare (the Japanese Pharmacopoeia); and the United States Pharmacopeial Convention (the U.S. Pharmacopeia). In May 2001, PDG welcomed the World Health Organization as an observer. The purpose of PDG is to harmonize pharmacopeial standards (excipient monographs and selected general chapters) in these three regions of the world. Harmonization within PDG reduces the burden on manufacturers of having to perform analytical procedures in different ways and using different acceptance criteria in order to satisfy pharmacopeial requirements that vary across regions. Harmonization within PDG also can help strengthen the individual pharmacopeias by building scientifically robust monographs. This is accomplished by a global set of experts setting standards with specifications (test methods and acceptance criteria) representative of the global supply chain, which also minimizes duplication of testing requirements and inconsistencies.

Definition of Harmonization

PDG has defined harmonization of a pharmacopeial monograph or general chapter as follows:

> *"A pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept/reject decision is reached."*

When using a fully harmonized pharmacopeial monograph or general chapter, an analyst will perform the same procedures and reach the same accept/reject decisions irrespective of which PDG pharmacopeia is referenced. This is called interchangeability, and each pharmacopeia will identify, in an appropriate manner, each fully harmonized monograph and general chapter.

When full harmonization of a pharmacopeial monograph or general chapter is not possible, the PDG uses an approach termed harmonization by attribute. In this approach, the main elements of a monograph or general chapter are harmonized, while others are not, most typically due to different regulatory requirements in the respective regions. When a monograph is harmonized by attribute, interchangeability is achieved only with respect to the harmonized elements. For nonharmonized attributes, compliance with the individual pharmacopeial requirements in each region is necessary.[2]

The PDG harmonization process consists of seven stages outlined in *Figure 1*.[3] The process is followed for harmonization of general chapters and monographs on the PDG work plan.

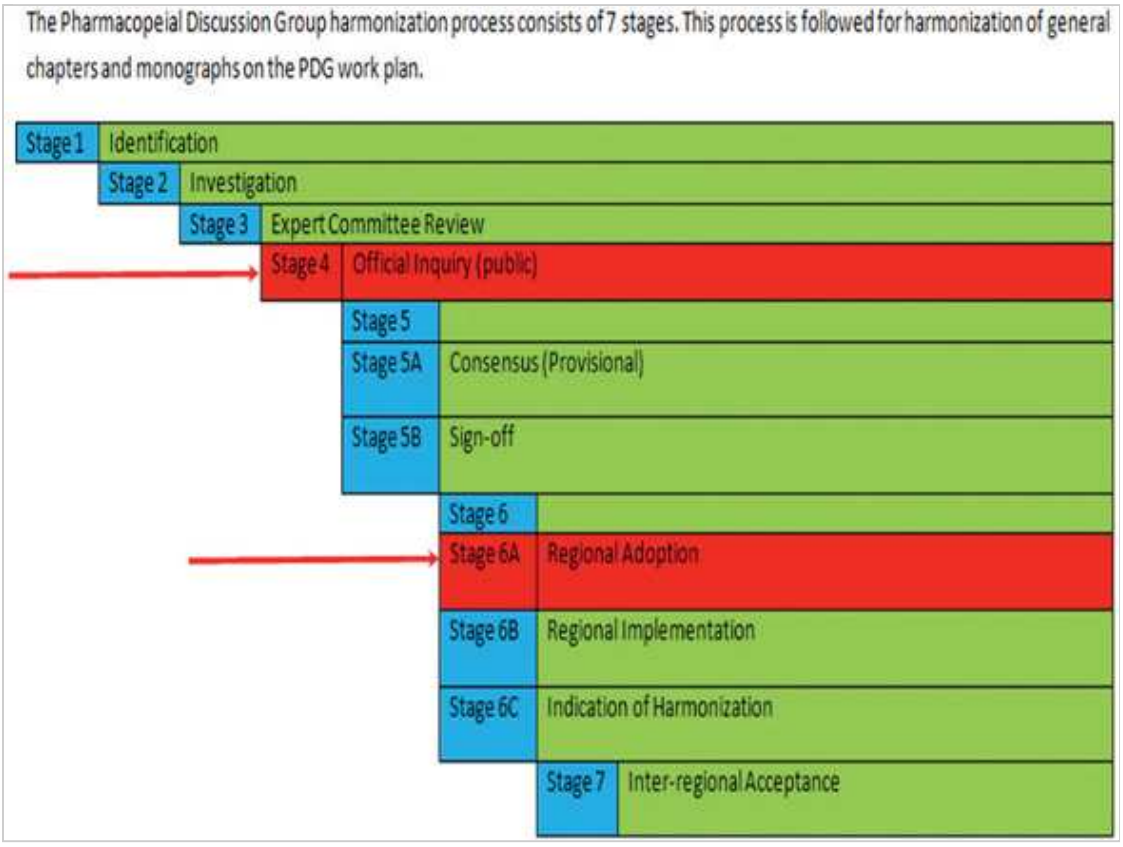

Figure 1. PDG Harmonization Process – 7 Stages

For example, the PDG harmonized standard for Carboxymethylcellulose Calcium reduced 37 non-harmonized tests to 10 tests (*Table 1*), which greatly helps industry save resources and improve efficiency.

Table 1.

USP Monograph	JP Monograph	EP Monograph	Harmonized Monograph
Total Tests = 13	Total Tests = 13	Total Tests = 11	Total Tests = 10
Identification A	Identification A	Identification A	Identification A
Identification B	Identification B	Identification B	Identification B
Identification C	Identification C	Identification C	Identification C
Identification D	Identification D	Identification D	Identification D
Alkalinity	Alkali	Alkalinity	Alkalinity
Chloride	Chloride	Chlorides	Chloride
Sulfate	Sulfate	Sulphates	Sulfate
Silicate	Silicate	Silica	
Heavy Metals	Heavy Metals	Heavy Metals	Heavy Metals
	Arsenic		
Starch	Starch		
Loss on Drying	Loss on Drying	Loss on Drying	Loss on Drying
Residue on Ignition	Residue on Ignition	Sulphated Ash	Residue on Ignition
Organic Volatile Impurities			
Global marketing test requirements = 37 without harmonization; 10 with harmonization.			

The PDG pharmacopeial harmonization efforts are progressing steadily, but relatively slowly, due to the challenges resulting from different regulatory requirements and expert opinions from different PDG regions. However, the risks to product quality in an increasingly globalized supply chain are pushing pharmacopeias around the world to speed up their efforts to harmonize and update the compendial standards that support these regulatory processes.

The PDG work plan covers 36 general chapters and general methods, as well as 62 excipients including 15 cellulose-based excipients. All excipients in the PDG work plan are widely used in the three major regions.[4] The work of the PDG results in the publi-cation of harmonized excipient monographs in the *European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), and United States Pharmacopeia–National Formulary (USP–NF)*.

FDA's Monograph Modernization Task Group (MMTG) and the Office of Regulatory Affairs (ORA) expressed their concerns that certain USP–NF excipients are at an elevated risk of adulteration because of the lack of Identification or proper Assay and Impurity tests.[5-7] Glycerin, Talc, and Povidones are used extensively and the standard of quality for these excipients has significant impact on the pharmaceutical industry. Therefore, three expert panels were formed by the 2010- 2015 USP Excipient Expert Committee to support the updates of these monographs. The progress made by the expert panels and the comprehensive approaches for updating cellulose-based excipients monographs are described below.

Expert Panels on Glycerin, Povidones, and Talc

In the case of Glycerin, Povidones, and Talc, the 2010-2015 USP Excipient Expert Committee did not have the extensive expertise needed to address FDA's concerns, and thus expert panels were created to provide technical recommendations to the Excipient Expert Committee on these respective topics. Expert panels allow for global participation of excipient users, manufacturers, distributors, governments, and academia working together on the method development, validation, and testing. In addition, expert panels gain stakeholder input and buy-in early in the process, providing an excellent means of engaging interested stakeholders.

The overarching goal for these expert panels is to develop harmonized, up-to-date global quality standards for these high-impact excipients. In the process, the outdated, non-specific technologies and methodologies are replaced with more current, specific procedures; critical tests such as identification and assay are added to the monographs; and tests that do not add value are deleted.

The Glycerin Expert Panel is charged with creating a PDG Stage 3 draft for developing a harmonized quality standard. The Expert Panel is considering 1) modifying the current gas chromatography (GC) method being used for the Limit of Diethylene Glycol (DEG) and Ethylene Glycol (EG) for use as an assay method, in order to replace the current non-specific titration assay 2) setting the appropriate acceptance criteria for the GC assay and 3) evaluating other methods being considered as part of the Stage 3 draft standard for PDG.

The Povidones Expert Panel is charged with finding a suitable replacement method for the Nitrogen Assay (Kjeldahl method) in the three Povidone monographs due to FDA concerns about potential adulteration with nitrogen-containing substances (i.e., melamine).[6] Gel permeation chromatography (GPC) is being considered as a viable method for Assay of Povidone, and work is continuing to determine its utility for use in profiling impurities. The Expert Panel is optimizing chromatographic conditions for a GPC procedure for Povidone and Copovidone. In addition, the Expert Panel is looking into modifying sample conditions to use this method to determine levels of impurities for Crospovidone. GPC is not a viable method for the assay for Crospovidone due to its insolubility in water and organic solvents.

The Talc Expert Panel is charged with modernizing the USP Talc monograph to ensure that the test for Absence of Asbestos has adequate specificity.[6] The Expert Panel published a Stimuli article in *Pharmacopeial Forum (PF) 40(4)* entitled "Modernization of Asbestos Testing in USP Talc" highlighting these recommendations. The Expert Panel members discussed several methods for improving the existing methods and limits in the Talc monograph. The Expert Panel's recommendation for revision of the test for Absence of Asbestos includes omission of the infrared spectroscopy

test and inclusion of a revised x-ray diffraction procedure (XRD), in combination with one or more microscopic evaluations (polarized-light microscopy, transmission electron microscopy, or scanning electron microscopy).

In addition, the Expert Panel recommended updating statements in the definition and/or labeling sections to indicate that talc containing (detectable) asbestos is not pharmaceutical grade. USP received public comments on the Stimuli article and will officially respond to the comments in an upcoming *PF*. The Talc Expert Panel concluded at the end of the 2010-2015 revision cycle. The newly formed Talc Methods Expert Panel will have a new charge and focus on analytics and associated Reference Standards.

Cellulose-Based Excipients

Cellulose is a linear polysaccharide polymer that is insoluble in water and most common solvents. After chemical modifications of cellulose by esterifications or etherifications at the hydroxyl groups of cellulose, the original physicochemical properties of the cellulose are significantly changed. Most water-soluble and organic solventsoluble cellulose derivatives are prepared by using the above chemical modifications. These chemically modified celluloses are widely used in the formulation of pharmaceutical products, for example as the binder, enteric coating, film coating, disintegrant, thickener, or stabilizer, as well as other applications. In response to FDA's request, the USP 2010-2015 Excipient Expert Committee made significant progress to establish up-to-date quality standards by adding or revising specific Identification and/or assay tests for the 15 cellulose excipient monographs in the PDG work plan. The USP 2015-2020 Excipient Expert Committee 2 will continue working on updating these monographs.

Pharmacopeial Identification

According to the FDA MMTG, development of specific identification tests for excipients are critical to determining the suitability for intended use in a pharmaceutical application, and also to screening for potential cases of intentional adulteration. At FDA's request, three cellulose-based excipient monographs have been identified as high priority for updating as these excipients may have an elevated risk of adulteration due to lack of specificity of the Identification test. Compendial tests for identification should be specific and rigorous, because under FDA current Good Manufacturing Practice (cGMP) regulations, manufacturers of finished pharmaceuticals must perform at least one test to verify the identity of each component used to make the finished pharmaceutical product; where available, a specific identity test must be used.[8]

Significant challenges exist in developing compendial specifications for cellulose-based excipients, given the known contributions to variability based on 1) grade (i.e., degree of polymerization, particle size, solubility, etc.); 2) manufacturer's processing parameters (site, processing, potential mixtures/additives); and 3) raw material origin. The compendial identification test should establish the identity of an excipient and should also be specific, such that compounds of closely related structure, Carmellose, Microcrystalline Cellulose (MCC), Carboxymethylcellulose Sodium (CMC Na), Carboxymethylcellulose Calcium (CMC Ca), and Croscarmellose Sodium (CROS Na), etc., can be distinguished from each other. For some excipients as described below, one identification test may not suffice and it may be necessary to include orthogonal test(s) under the Identification to address FDA's concern.

During the USP 2010-2015 revision cycle, the Excipient Expert Committee reviewed the list of cellulose-based excipients on the PDG work plan and began implementing a comprehensive process to develop specific identification tests for these chemically similar cellulose-based excipients based on infrared spectroscopy in combination with simple orthogonal methods. The first eight monographs (shaded yellow) have identification by infrared spectroscopy, and are either official in the USP–NF monograph or proposed in *PF*, as shown in *Table 2*. The USP staff and the 2015-2020 Excipient Expert Committee 2 are currently reviewing the identification section for the remaining seven cellulose-based excipient monographs. The Excipient Expert Committee concluded that for chemically and structurally similar compounds, such as the Carmellose family (Carmellose, CMC Ca, CMC Na, and CROS Na), orthogonal tests, such as ion identification and/or solubility, may be necessary to distinguish between the individual materials. In addition, the degree of polymerization can potentially be used to discriminate MCC from Powdered Cellulose; likewise, the content of

the hydroxypropoxy group and methoxy group in the assay analysis may be useful for distinguishing hypromellose (HPMC) from methylcellulose. To assist the current 2015-2020 Excipient Expert Committee 2, stakeholders are encouraged to sponsor and submit the method development/validation for cellulose-based excipients to USP.

Table 2. Progress on Updating Identifi cation for Cellulose-based Excipient Monographs

#	Monograph Name	Identification by Infrared Spectroscopy (Official/or in *PF*)
1	Cellulose Acetate	Yes
2	Cellulose Acetate Phthalate (Cellacefate)	Yes
3	Ethylcellulose	Yes
4	Hydroxyethyl Cellulose	Yes, proposed in Stage 4, *PF 40(5)*
5	Hydroxypropyl Cellulose	Yes
6	Hydroxypropylcellulose, low-substituted	Yes
7	Hypromellose Phthalate	Yes
8	Carmellose	Yes
9	Carboxymethylcellulose Calcium	No
10	Carboxymethylcellulose Sodium	No
11	Croscarmellose Sodium	No
12	Hypromellose	No
13	Microcrystalline Cellulose	No
14	Powdered Cellulose	No
15	Methylcellulose	No

Pharmacopeial Assay

As shown in *Table 3*, among the 15 cellulose-based excipient monographs in the PDG work plan, six monographs (shaded yellow) have an assay by GC, either official in the USP–NF monographs or published as a Stage 4 harmonization proposal in *PF*. Five monographs (shaded orange) have an assay by titration. The MCC and Powdered Cellulose monographs (shaded grey) currently lack an assay, as they do not have substitution groups. The Stage 6 harmonized monograph for CROS Na contains titration(s) along with the calculation of degree of substitution for Assay. The USP staff and Excipient Expert Committee 2 are considering applying a similar approach for the remaining Carmellose and CMC Ca monographs (shaded maroon). This approach may provide the opportunity for a harmonized assay among the Carmellose family monographs. Stakeholders are encouraged to assist the Excipient Expert Committee 2 with the update of these cellulose-based excipient monographs.

Table 3. Progress on Updating Assay for Cellulose-based Excipient Monographs

Progress on Updating Assay for Cellulose-based Excipient Monographs		
#	Monograph Name	Assay - Official/or in *PF*
1	Ethylcellulose	Yes (Capillary GC column), proposed in Stage 4, *PF 38(6)*
2	Hydroxyethyl Cellulose	Yes (Capillary GC column), proposed in Stage 4, *PF 40(5)*
3	Hydroxypropyl Cellulose	Yes (Capillary GC column)
4	Hydroxypropylcellulose, low-substituted	Yes (Capillary GC column)
5	Hypromellose	Yes (Packed GC column)
6	Methylcellulose	Yes (Packed GC column)
7	Carboxymethylcellulose Sodium	Yes (Titration)
8	Croscarmellose Sodium	Yes (Titration, Degree of substitution)
9	Cellulose Acetate	Yes (Titration, Content of Acetyl)
10	Cellulose Acetate Phthalate (Cellacefate)	Yes (Titration, Content of Acetyl and Phthalyl content)
11	Hypromellose Phthalate	Yes (Titration, Phthalyl content)
12	Microcrystalline Cellulose	No
13	Powdered Cellulose	No
14	Carboxymethylcellulose Calcium	No
15	Carmellose	No

- **PDG Harmonization and Update of Hydroxypropyl Cellulose (HPC) and Low-substituted Hydroxypropyl Cellulose (LS-HPC)**
- **Case Study: Assay by capillary GC**

Hydroxypropyl Cellulose (HPC)

– Stage 4 harmonization proposal in *PF* 35 (3), May-June, 2010

– Stage 6 sign-off by PDG in June 2013 at Rockville, MD, USA

Low-substituted Hydroxypropyl Cellulose (LS-HPC)

– Stage 4 harmonization proposal in *PF* 40(3), May- June, 2014

– Stage 6 sign-off by PDG in November 2014 at Strasburg, France

Hydroxypropyl Cellulose (HPC)

As proposed by PDG, Hydroxypropyl Cellulose (HPC) was used in the initial development and validation of a test method for the assay of alkyloxy groups, which may be applied to other cellulose-based excipients, including ethylcellulose, hypromellose, methylcellulose and low-substituted hydroxypropyl cellulose and hydroxyethyl cellulose. The new specific assay procedure by capillary GC based on the general principle for determination of alkyloxy groups in substituted celluloses (Zeisel reaction followed by GC) was initially presented by the IPEC Japan. It had been evaluated by several companies globally and the data were used by PDG for the Stage 4 proposal published in *PF* 35(3). The previous titration method for assay of hydroxyproxy groups in HPC required the highly toxic reagent chromic acid and was not specific. The challenges during the method development and validation of the assay were:

a. Defining a conversion factor that would correlate the assay results from the GC method with those from the existing titration method. Based on the data from validation and robustness studies, it was found that the response factor of 1.15 was necessary to correlate the assay values from the two methods.

b. Defining the assay specification. Based on the GC assay results, along with the consideration of feedback/comments from expert committees and stakeholders, the acceptance criteria were changed from the previous “NMT 80.5% of hydroxypropoxy groups” to “NLT 53.4% and NMT 80.5% of hydroxypropoxy groups”.

The PDG update and harmonization process for HPC has evolved at the global level with the participation of many excipient manufacturers, pharmaceutical companies, and other pharmacopeias. After about seven years of effort, a harmonized Stage 6 monograph was signed off by PDG in June 2013 at Rockville, MD.

Low-Substituted Hydroxypropyl Cellulose (LS-HPC)

The harmonization and modernization of the assay in the LS-HPC monograph followed the same approach used for HPC by using the Zeisel-GC method. In the Stage 4 proposal for LS-HPC in *PF* 40(3), a capillary GC column replaced the previous packed GC column because the packed columns are not typically commercially available and have to be manually prepared by analytical chemists. The validation results, in terms of specificity, linearity, accuracy/recovery, range, intermediate precision, robustness, limit of detection, and limit of quantitation, demonstrated that the newly developed capillary GC assay method is a suitable replacement for the currently official packed GC method. The GC conditions described in the proposed *PF* method provide good resolution between methyl iodide, ethyl iodide, and isopropyl iodide and are suitable for the Zeisel-GC assay analysis. The harmonized Stage 6 monograph for LS-HPC was signed off by PDG in November 2014 at Strasburg, France.

USP continues to work with sponsors, as well as EP, JP, and the FDA, to further strengthen the assay method for the cellulose-based excipient monographs.

Conclusions

Resolution 2 and 3 of USP’s resolutions for the 2015-2020 Cycle directly relate to excipients. Resolution 2 - USP–NF Monograph Modernization:

USP supports Up-to-Date monographs that meet the needs of FDA, industry, and other stakeholders for modern monographs within USP–NF. Resolution 3 supports establishing Globally Harmonized Standards that includes PDG harmonization and expand its commitment to harmonization of compendial standards by working with pharmacopoeias, the World Health Organization, and other stakeholders to determine optimal ways to advance and sustain globally harmonized standards.[9]

Excipient monograph updating is critical – especially given global supply chain threats. Updated excipient test methods help to eliminate the opportunity to substitute or falsify excipient ingredients thus facilitating the qualification of excipients and regulatory compliance. New approaches to creating up-to-date quality excipient monographs, especially the use of the USP laboratory facilities to develop up-to-date procedures and the use of global expert panels and collaborations, have the potential to provide additional support to excipient harmonization through the PDG process and stimulate additional avenues for harmonization and monograph update. Challenges currently faced are difficulties in obtaining samples, procedures and acceptance criteria from users and makers of excipients. Collaboration with FDA, industry and other stakeholders is a key factor to advancing the work.

USP's commitment to both resolution 2 for an up-to-date quality standard and resolution 3 for a harmonized standard will benefit all stakeholders in an excipient global supply chain and ultimately provide higher-quality medicines to patients. In addition to the harmonization and up-to-date initiative regarding Glycerin, Povidones, Talc, and cellulose-based excipient monographs, USP strives to update several other important monographs, many of which are also under the PDG harmonization work plan. The complete list of excipients monographs in need of update can be found on the USP website.[10]

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Author Biographies

Dr. Tong (Jenny) Liu *is a Scientific Liaison in Science—Excipients at U.S. Pharmacopeial Convention. She is currently responsible for development, updating and harmonization of Excipients Monographs under the work plan of Pharmacopeial Discussion Group (PDG). She has more than 10 years' experience of analytical method development and validation for pharmaceutical products. She received her Ph.D. in chemistry from Boston University, Boston, USA. Supported by NIH Fellowship, she performed post-doctoral research in Susan L. Cullman Laboratory under Department of Chemical Biology, Ernest Mario School of Pharmacy in Rutgers University, New Jersey, USA.*

Dr. Kevin Moore *is the Manager, Pharmacopeial Harmonization with responsibilities as the USP technical lead for all of USP's global harmonization activities. This includes leading the US delegation to the Pharmacopeial Discussion Group, which works to harmonize General Chapters and Excipient Monographs with representatives from the United States Pharmacopeia, the European Pharmacopeia, and the Japanese Pharmacopeia. In addition, Kevin works to coordinate the technical activities within USP for USP's prospective harmonization initiatives for drug substance, drug product, and excipient monographs, as well as support USP activities in collaboration with WHO in the development of the Good Pharmacopeial Practices (GPhP). Kevin holds a Ph.D. in Inorganic Chemistry from the University of Pennsylvania and a B.S. in Chemistry and Biology from LeMoyne College.*

Catherine Sheehan *is Senior Director in Science — Excipients at U.S. Pharmacopeial Convention. In her current role, she supports the standard setting activities of the USP Council of Experts for excipient monographs and related chapters development and update. She is part of the USP delegation to the Pharmacopeial Discussion Group's compendial harmonization of excipient monographs and general chapters. Ms. Sheehan received an M.S. Regulatory Science degree and M.S. Molecular Biotechnology degree from The Johns Hopkins University, Baltimore, USA.*

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