United States Pharmacopeia-National Formulary.

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Editorial

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Many people use the United States Pharmacopeia-National Formulary (USP-NF), but how many understand the organization and processes behind the book? This editorial will begin by explaining some of the workings of the USP-NF as they impact pharmaceutical excipients, and will finish with a simple request.

The USP-NF may be unique among the world's pharmacopeias in that it is legally two separate compendia, that is, the United States Pharmacopeia (USP) and the National Formulary (NF) which are published in the same set of volumes. The USP and NF, together with the Homeopathic Pharmacopeia of the United States are the three compendia specifically referenced in the US Food, Drug and Cosmetic Act.

The USP-NF is published by the Unites States Pharmacopeia Convention, Inc. which is also unusual for a national pharmacopeia in that it is not part of government, but is an independent non-governmental organization (NGO) operating as a not-for-profit corporation. The USP-NF is a member of the Pharmacopoeial Discussion Group (PDG) along with the European Pharmacopoeia (Ph.Eur) and Japanese Pharmacopoeia (JP).

2015 is an important year for the USP-NF. July 1st saw the start of a new 5-year revision cycle; the first under its new CEO, Dr. Ronald Piervincenzi (who succeeded Dr. Roger Williams in January 2014). The USP-NF operates on 5-year revision cycles, and thus every 5 years there is a meeting of the USP Convention to elect the members of the Council of the Convention, approve amendments to by-laws, elect chairs for the different Expert Committees, and approve policies in the form of Resolutions passed by the members of the Convention for the next cycle. This year the Convention meeting was held in April in Washington, DC. The changes resulting from the convention votes will impact the excipient world, as the Expert Committees for excipients have changed.

In this new revision cycle, there are two Expert Committees for excipients, i.e., Excipient Monographs 1 and 2 (in the previous Revision Cycle there was one combined Excipient Committee). There are two new Chairs, Dr. Eric Munson, University of Kentucky is Chair, Excipients Monographs 1, and Dr. Cate Houck,

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Astellas Pharmaceuticals, Inc is Chair, Excipients Monographs 2. The remits of the two committees are given in Table 1. There is a third Expert Committee whose work will likely impact excipients: the General Chapters–Physical Analysis Expert Committee chaired by Dr. Xiaorong He, Boehringer-Ingelheim Pharmaceuticals, Inc.

Table 1 The responsibilities of the USP Excipient Expert Committees for the 2015 to 2020 Revision Cycle.

EXCIPIENT COMMITTEE 1	EXCIPIENT COMMITTEE 2
The Excipient Monographs 1 Expert Committee is responsible for developing new and revising existing monographs and their associated reference standards for pharmaceutical excipients. The committee is also responsible for new excipient related general chapters development and excipient general chapters update. **Focus areas include**: • Monograph modernization • New monograph development with associated RS • Monograph modernization with associated RS • New excipient related chapters development • Excipient General Chapters update	The Excipient Monographs 2 Expert Committee is responsible for global harmonization activities that include: Retrospective harmonization of excipient monographs, excipient-related general chapters for the PDG work plan, and working closely with other Expert Committees (GCCA, GCPA, B&B) on general chapters, B&B general chapters and ICH Q6A general chapters. The Expert Committee is also responsible for developing new and revising existing excipient monographs, their associated reference standards for pharmaceutical excipients, new excipient-related general chapters development, and excipient general chapters updates. The Expert Committee works with global pharmacopeias on bilateral harmonization and is responsible for prospective harmonization of API, DP and excipients. **Focus areas include**: • Monograph Modernization • New monograph development with associated RS • Monograph modernization with associated RS • New excipient related chapters development • Excipient General Chapters update • International harmonization ‣ Pharmacopeial Discussion Group (PDG) ‣ Bilateral Harmonization ‣ Prospective harmonization of API, DP, and Excipients

As can be seen from Table 1, there is a lot of work to be done in this new revision cycle for both Committees.

The work of the committees is broadly divided into three main areas:

1. Preparation and approval of new monographs
2. Updating existing monographs:
   - Updated statements regarding additives
   - Updated analytical technologies and methods
   - New specifications and tests which are better reflect the composition of commercially available material.
3. Continuing work on the international harmonization of excipient monographs via the Pharmacopoeial Discussion Group (PDG) (Committee 2).

The Excipient Monograph Expert Committees are each comprised of 15-16 individuals. These individuals are considered experts in their fields and they have extensive experience in the technical aspects of excipients. USP-NF also insists that, whenever the Expert Committee members are taking part in the work of the USP-NF, in whatever capacity, they operate as independent experts, i.e., they leave their other hats, e.g. corporate hat, outside the door, so to speak. This can be difficult, and it is sometimes difficult for employers to understand this. To this end, when the Expert Committee members are asked to vote on a particular topic, they are required to recuse themselves and abstain on topics where they have a potential conflict of interest, e.g., a person employed by a company manufacturing a particular excipient must recuse themselves in the voting to approve any changes to the monograph for that excipient. They can, however, still take part in the discussion since their experience is still relevant and needed.

In addition to the elected members of the Expert Committee, there are other participants in the work of the Committee. The appropriate USP members of staff are present, including scientific liaisons and administrative staff. In addition there are also observers from the US Food and Drug Administration (FDA). The involvement of FDA staff in the committee deliberations started during the previous revision cycle and has been very useful. The

FDA has an effective right of veto on anything in the USP-NF. By having FDA staff taking part in the discussion, they have been able to provide advice on what might or might not be acceptable in a particular monograph. This has helped to reduce the time taken to develop new monographs or make changes because the number of changes that need to be re-issued for public comment has reduced.

When preparing new excipient monographs or revising existing ones, the USP-NF prefers to work with industrial sponsors (most often excipient manufacturers, but they can also be excipients users) to develop the methods and specifications for the excipient. There are several reasons for this. Sponsors generally will have an understanding of the excipient, the required specifications and the available test methods. This saves a lot of time. In addition, the USP-NF understands that any new monograph, or an amendment to an existing monograph, must be relevant to the commercially available excipients.

In some instances, the USP-NF will initiate a broader project covering several related excipients, or a more fundamental assessment of a particular material. Under such circumstances, the USP-NF may set up an Expert Panel to undertake a more thorough and wide-ranging assessment of the issues. The Expert Panels are *ad hoc* and will continue until their work is complete, even into a further revision cycle. The Expert Panels will report back to the appropriate Expert Committee. Expert Panels can be formed at any time. They will be disbanded once their work is complete.

One issue that continues to be debated is the question of performance related tests. The Ph.Eur has adopted the concept of a non-mandatory section of their excipient monographs entitled Functionality-Related Characteristics (FRCs). This has caused several problems in the harmonization process because legally, neither the USP-NF nor the JP, can have non-mandatory sections in their monographs. The monograph is the specification and all tests are mandatory. These problems have now been resolved, although there was a delay of about two years in the harmonization process.

The USP-NF has not included a general category of performance-related tests in the monographs because the excipient characteristics that are linked to performance will vary from application to application (formulation to formulation). The tests in the USP-NF monographs for excipients are designed to verify the identity and safety of the excipient. The USP-NF experts consider that the specification and nature of performance-related tests are properly topics for negotiation between the excipient user and the excipient manufacturer. However, the USP-NF experts have recognized that a defined set of tests which may be relevant for performance-related testing would be useful. The USP-NF now contains a non-mandatory General Chapter <1059> Excipient Performance in which the different types of excipient are reviewed, and a list of General Chapters which might apply to such excipients is given. It is up to the individual excipient user to establish which of the tests described in the General Chapters is relevant to their particular application.

Another issue that continues to be raised is the adoption of new analytical methods. In the last twenty years or so, we have seen the development of new analytical methodologies which can be applied to excipients, such as, near infra-red spectroscopy (NIR), Raman spectroscopy, terahertz spectroscopy, inverse gas chromatography, etc. Some of these methods may be of benefit in providing more specific ID tests, which is a concern of the FDA. Other methods may be more relevant to performance-related tests. There are other considerations which impact the debate on new analytical methodologies including: cost of the equipment, operating costs, availability of equipment, etc. The debate on the introduction

of new analytical technologies will doubtless continue through this new revision cycle.

People often ask why it takes so long for a monograph to be developed. Part of the answer is that it sometimes takes a long time to identify a sponsor. Another factor is that as a public standard, any proposals for change must be published for public comment (on-line in Pharmacopeial Forum) and this all takes time. Even if the comment deadline is missed USP-NF is still required to consider all comments and the Expert Committee must justify any decision not to accept a comment. If the proposed and accepted changes are of a sufficient magnitude, the document may be published a second time in Pharmacopeial Forum with a further public comment period. Finally, it is USP-NF policy that a new monograph or an update to a monograph which requires a new Reference Standard material cannot be implemented until the official USP Reference Standard is available.

Having described some of the workings of the USP-NF, my request is quite simple. If you, or your organization, is approached and asked to assist the USP-NF, please provide as much help as you can and, as quickly as you can. This will allow the USP-NF to complete its projects in a timely manner and thus strengthen the protection of the patient that the USP-NF seeks to achieve. Let's not forget that all our endeavors as pharmaceutical scientists should be directed to helping the patient, and the USP-NF monographs and General Chapters are an important piece of that effort. Better monographs will lead to better finished drug products and lessen the potential for harm to the patient.