

## GENERAL INFORMATION FOR ALL SUBMISSIONS

**Introduction** This document, and the accompanying Submission Guidelines, are intended to provide guidance to Sponsors submitting information to support creation of a new monograph, or a revision to a proposed or existing official monograph in the the *United States Pharmacopeia* and *National Formulary (USP–NF)*. All such requests are considered Requests for Revision. The purpose of this document and the Submission Guidelines is to promote optimal submissions by Sponsors and facilitate development and finalization of a Revision. Sponsors of Requests for Revision, whether for new monographs or revision of existing or proposed monographs, should understand that a Request for Revision will lead to a public standard that may incorporate comments from other parties and will ultimately be determined by the assigned USP Expert Committee. As a result, it may differ from the original Request for Revision and may no longer reflect the private standard of the submitting Sponsor. Sponsors are encouraged to understand and conform to the Submission Guidelines, and in particular this General Information for All Submissions, and also to be familiar with the *General Notices and Requirements* and General Chapters in *USP-NF* which contain terms and conditions applicable to official monographs.

Monographs are included in the *USP-NF* only for articles which are legally approved for marketing in the U.S (including biologics, which are considered a subset of drugs by FDA and USP). It is USP's position that every such article (drug product, drug substance, excipient, and dietary supplement) should have a *USP-NF* monograph accompanied, where appropriate by USP Reference Standards (RS). At the same time, USP recognizes that some manufacturers may be unwilling to submit information and materials to USP for the development of a monograph and RS in the early years following FDA approval, in part because of intellectual property concerns. To afford FDA-approved manufacturers ample opportunity to participate as submitting Sponsors, it is USP's policy to seek to actively collaborate with pioneer manufacturers for donation of monographs and RS materials until approximately five years prior to potential generic entry,<sup>1</sup> at which time USP will seek alternative Sponsors. This will help ensure that at a minimum, a public monograph and accompanying RS will be available by the time of generic entry (to provide public standards for multiple versions of the same drug), and at the same time help minimize any undue barriers to the approval of generic applications. In summary, ***USP will endeavor to work with the FDA-approved manufacturer during the period leading up to an estimated 5 years before patent expiration/generic entry to develop a monograph and accompanying RS. However, if the manufacturer is unwilling or unable to provide the necessary information or material, USP may begin***

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<sup>1</sup> As a general rule, although non-patent exclusivity is also considered, USP focuses on drug substance (active ingredient) patents listed in the FDA Orange Book, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. In cases of multiple drug substance patent listings, USP will generally focus on the patent with the later expiration date. Where sources are available to identify an earlier expiring drug substance or other patent as likely being key to generic entry, USP may use such earlier date.

*development working with a potential generic applicant under its “Pending Monograph” approach*, described below.

**Organization of the Submission Guidelines** Definitions for terms commonly used in the Submission Guidelines are provided in a Glossary at the end of this General Information document. There is a Submission Guideline for each class of compendial articles, as follows:

- (1) Small Molecule drug substances and products;
- (2) Excipients;
- (3) Biologics/Biotechnology drug substances and products:
  - (3A) Biologics – general
  - (3B) Biologics – Vaccines,
  - (3C) Biologics – Blood, Blood Components and Blood Products; and
- (4) Dietary Supplements.

Submission Guidelines for other classes of compendial articles may be added, as appropriate. Recommendations are duplicated in several of the sections to allow manufacturers of specific articles simpler and more direct access to applicable recommendations in their entirety. Following the Submission Guidelines are various **Templates**; these are provided to facilitate preparation of submissions for selected types of articles (e.g., Drug Substances; Tablets and Capsules; Excipients; Injections; Metered Dose Inhalers).

**Form of Submissions** USP requests that Sponsors provide a Request for Revision electronically, via e-mail or computer disc (CD), using either PDF or a Windows-based application , or as a printed copy. Because USP uses Microsoft Office products, submissions in these formats are preferred. Documents also may be submitted in HTML, SGML, or XML formats. Draft Requests for Revision should be complete and include all supporting information and software applications/versions used to prepare the Request for Revision.

**Procedures for Submitting Requests for Revision for a New *USP-NF* Monograph** Where no *USP-NF* monograph exists for an article, a Sponsor may submit a Request for Revision on its own initiative or be requested to provide a Request for Revision by USP staff. In either case, the provision of information by a Sponsor is voluntary. When received, USP assigns the Request for Revision to a Scientific Liaison who will work with the Sponsor to ensure that the Request for Revision contains the appropriate information and background materials.

Availability of timely, high quality revisions to *USP-NF* requires the active participation of Sponsors and can be resource-intensive. To assist Sponsors, USP will: (1) send a Sponsor the draft monograph based on their Request for Revision prior to publication in the *Pharmacopeial Forum (PF)* (2) where acceptable to the Expert Committee, invite a Sponsor to participate in the relevant Expert Committee’s

deliberations on the Request for Revision; and (3) with Sponsor and Expert Committee approval, invite an FDA reviewer to attend Expert Committee deliberations of the Request for Revision.

**Procedures for Submitting Requests for Revision Relating to an Existing or Previously Proposed *USP-NF* Monograph** A Sponsor may submit a Request for Revision to revise an official or previously proposed (in development) *USP-NF* monograph. Revisions may be directed at an entire monograph or specific monograph tests, procedures, and/or acceptance criteria. USP also welcomes revisions directed to changes in General Chapters. The Request for Revision should include the rationale, description of the proposed change, and supporting data, where needed. The rationale can be editorial, science-based, or economic-based. Because revisions to monographs in *USP-NF* can be resource intensive, Sponsors should request revisions to existing procedures only when the change represents a significant improvement. Description of the proposed change and data needed to support a change are described in specific sections of this guideline.

**Accelerated Revisions** Certain situations may require that a Request for Revision be completed and become official more quickly than through USP's standard revision process. In such cases, the Request for Revision may be processed using one of USP's accelerated revision processes, in accordance with the USP Guideline on the Use of Accelerated Processes for Revisions to the *USP-NF* available on the USP Web site at <http://www.usp.org/USPNF/submitMonograph/acceleratedProcessGuideline.html>.

**Flexible Monographs** At times, an ingredient and/or a drug product, including dietary supplement ingredients and products and biologicals and biotechnological ingredients and products, exhibit different attributes that have been determined by the FDA not to impact their safety and/or efficacy, i.e., their identity as official ingredients and products. Examples include different polymorphic forms,<sup>2</sup> impurities, hydrates, and dissolution cases. In these instances, USP will allow different tests, procedures, and/or acceptance criteria reflecting these different attributes within a single monograph, with suitable validation, under its flexible monograph approach.<sup>3</sup>

The flexible monograph approach may be used in conjunction with USP's Pending Monograph approach, described below, to allow a proposed revision to a monograph incorporating the new tests, procedures or acceptance criteria to be published on USP's Web site even if the Sponsor of the Request for Revision does not have FDA

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<sup>2</sup> Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate. For further information, see the FDA's Guidance for Industry on ANDAs: Pharmaceutical Solid Polymorphism—Chemistry, Manufacturing, and Controls Information. Rockville, MD; 2004.

<sup>3</sup> For additional information on the adoption of the flexible monograph approach by USP's Council of Experts Executive Committee, see Policies and Announcements. *Pharm Forum*. 2005;31(3):690–691.

approval at the time but is seeking such approval. Sponsors of Requests for Revision are encouraged to utilize the flexible monograph approach where applicable, together with the Pending Monograph approach. For specific questions, please contact the appropriate USP Scientific Liaison.

**Pending Monographs** Under the Pending Monograph approach, a new monograph may be developed and published on USP's Web site even if the article has not yet received FDA approval, as long as the Sponsor is seeking or intends to seek such approval. Pending Monographs are considered authorized, rather than official text, but are intended to be moved into the *USP-NF* and become official upon FDA approval of the article. Any RS developed as a component of a Pending Monograph may be made available for distribution at any time following Web site publication of the draft or final Pending Monograph. Further information regarding the Pending Monographs approach can be found in the Pending Monographs Guideline posted on USP's Web site at <http://www.usp.org/standards/pending/guidelines.html>.

**Relation of Standards to FDA-Approved Specifications** Although sponsors are understood to be voluntarily proposing the specifications and other aspects of what are essentially private standards, USP's mission is to establish public standards that help assure the identity and quality of medicines across manufacturers. Consistent with and in furtherance of this mission, USP is committed to doing all it reasonably can to assure that *USP-NF* standards and related methods are developed through an objective, independent, science-based process, and that the resulting official compendial standards not have the effect of favoring any manufacturer over others or putting any FDA-approved product out of compliance. Accordingly, in submitting a Request for Revision consistent with the Submission Guidelines, ***Sponsors warrant and certify that the proposed test, methods and specifications are consistent with, and no more stringent than, those contained in Sponsor applications or supplements submitted to and approved by FDA. Sponsors further warrant and certify that any proposed specifications that are more stringent than those approved by FDA in an initial application or prior supplement have been clearly identified and appropriately explained in the information provided to USP.*** In addition, if any specifications submitted by Sponsor deviate from ICH limits, Sponsor shall provide the justification for such deviation. If the deviation is not based on safety or other public health concerns, USP reserves the right to revert to ICH limits.

**Reference Materials** USP Reference Standards are a key monograph component (*see General Notices*, §5.80). It is USP policy that any reference materials likely to be required for use with a *USP* or *NF* standard (approved by an Expert Committee as suitable for use as comparison standards in *USP* or *NF* tests and assays) either accompany a Sponsor's submission, or be part of an overall monograph development commitment. ***By submitting a Request for Revision, a Sponsor undertakes to provide all appropriate information and background materials, including suitable reference materials, and furthermore by any such submission such a Sponsor acknowledges and agrees that if for any reason such reference materials are not timely provided, or prove inadequate for compendial use, that USP is authorized to source such materials***

*elsewhere, and to use any such materials and resulting RS as a component in USP monographs and as a part of USP's public compendial standards.*

**Intellectual Property.** At times, issues of timing and intellectual property arise regarding a monograph. Under USP's Intellectual Property Policy, available on USP's Web site, USP respects intellectual property rights and uses its best efforts to adhere to all applicable laws regarding protection of intellectual property. USP is not, however, responsible for the protection or enforcement of intellectual property rights in the U.S. and elsewhere, and because USP's standards are intended to be public standards available for the use and benefit of all parties, ***USP requests that Sponsors disclose in their Requests for Revision whether any portion of the methods or procedures submitted is subject to patent or other Sponsor-held intellectual property rights. In cases where patented methods, procedures or materials required for compendial tests and assays (such as RS or photomicrographs) are proposed, USP may seek assistance from the Sponsor in obtaining clearance or license for use by any persons seeking to use or apply a USP public standard incorporating such method, procedure or material, and may consider other approaches including the solicitation of other Requests for Revision that use alternative methods or procedures. USP reserves the right to indicate in a resulting monograph or general chapter whether methods or procedures are subject to such intellectual property rights.***

**Confidentiality Policy; Sponsor Identification.** USP's Confidentiality Policy, available on USP's Web site, makes it the responsibility of all USP employees, as well as USP's expert volunteers, to "protect confidential information whether generated by USP or by third parties," including "other information which USP or a third party may deem confidential." Furthermore, under USP's Document Disclosure Policy, also available on USP's Web site, while it is USP's policy to disclose information and records, any such disclosure must be "consistent with . . . the need to protect the confidentiality of trade secrets and deliberations and to pursue its standards-setting activities without disruption." USP of course will also not disclose any document containing trade secrets or confidential commercial secrets, "if such documents have been specifically designated as such when submitted to USP . . ." Accordingly, in furtherance of both the Confidentiality and Document Disclosure policies, ***Sponsors should indicate in their Request for Revision whether any of the submitted documents or other information should be treated as confidential. Any submitted documents not clearly marked confidential will be subject to disclosure under the Document Disclosure Policy.*** As a general policy, USP undertakes to keep Sponsor and reference material donor names confidential, but USP reserves the right to disclose the identity of a Sponsor or donor at its discretion if circumstances warrant.