



A State of Revision

USP's Guideline for the Submission of Requests for Revision

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USP's new guideline will assist the industry to help set the monograph standards by which the industry must abide. This column suggests how to apply the guideline to gain the maximum benefit.

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Users of the *United States Pharmacopeia–National Formulary (USP–NF)* may have an understandable tendency to think of it as a reference book—indeed, its size (>3000 pages in the 2004 edition) and tenure (continuous publication since 1820) recommend it for this purpose. Yet the truth is that *USP–NF* has been under continuous revision by its users since its inception at the first pharmacopeial convention in the nation's capital. Users in industry, government, and academia can submit requests for revision of the public standards in the compendia and, in fact, are the very source of the monographs that are published in *USP–NF*. Contrary to widely held public perceptions, USP does not unilaterally establish drug standards without public input.

In an effort to make the monograph creation and revision process more efficient, USP's Prescription–Non-Prescription Stakeholders Forum created a number of project teams in 2000, several of which were directed to provide recommendations about the content and presentation of drug substance monographs. The Non-Complex Actives Drug Substance, Complex Actives, and Excipient Project Teams contributed to the creation of a guideline to aid parties who were interested in submitting requests for revisions to *USP–NF*. After multiple iterations and as a result of noteworthy collaborative efforts involving USP's core staff and members of USP's Council of Experts, USP recently released its "USP Guideline for Submitting Requests for Revision to the *USP–NF*."

This 75-page document (not counting a number of addenda) provides helpful information about submitting new monographs and revising existing monographs for noncomplex substances and products, biological and biotechnology substances and products, excipients, and vaccines. The guideline describes the information needed for USP's Council of Experts and its Expert Committees to evaluate a request for revision, including specification documentation requirements, guidance about the contents of a monograph, and current USP ap-

proaches concerning monograph layout, ICH terminology, and article-specific standard concepts. The guideline is available in PDF format on the USP Web site at www.usp.org. The entire document is available as a complimentary download (724 KB), or users can download only those sections of immediate interest and applicability. The guideline also will be available in print form.

Highlights of the guideline

Organization. After a glossary, the guideline is divided into four chapters: noncomplex drug substances and products; biological/biotechnological drug substances and products; excipients; and vaccines. The addenda at present include 33 pages of templates for drafting monographs for drug substances, tablets and capsules, and excipients. These templates show the general format of monographs and are powerful, but not exhaustive, tools to assist monograph writers.

Procedures. When a *USP–NF* monograph does not exist, sponsors may request a revision, or USP staff may ask sponsors to provide a proposed revision in the compendia so as to include a monograph. In either case, the provision of information is voluntary. At times, issues of timing and intellectual property arise regarding a monograph. Given that the provision of information is voluntary, there should be no timing issue for a sponsor. USP follows US law regarding the protection of intellectual property. Requests for revision containing confidential information are handled according to USP's document-disclosure policy (for more details, see the current *USP–NF*).

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

- send a sponsor the draft monograph based on the request for revision at the same time the draft is sent to the Expert Committee(s)
- provide a sponsor with summary comments from the responsible Expert Committee(s)

- when acceptable to the Expert Committee, invite a sponsor to participate in committee deliberations about the request for revision
- with sponsor and Expert Committee approval, invite an FDA reviewer to attend committee deliberations about the request for revision.

To recapitulate, a major objective of the guideline is to assist a sponsor in developing the information needed to support a monograph and to clarify the associated benefits. USP recognizes the intellectual property rights involved in the production of a drug product and the confidential nature of any materials submitted to USP. The guideline also spells out the specific benefits that USP is offering to a sponsor in exchange for the sponsor's efforts to create a monograph. Sponsors of a monograph usually include pioneer and multisource manufacturers, but USP can obtain monographs in many other ways as well.

When a *USP-NF* monograph already exists or when a proposal for a new monograph has appeared in *Pharmaceutical Forum*, the request for revision should include the rationale, a description of the proposed change, and supporting data, as needed. The rationale can be editorial, scientific, or economic. Data should be included to demonstrate that the submitted procedure is equivalent to or better than the official procedure. If the data cannot clearly show equivalency, the submitter should request that the procedure be reviewed as an additional procedure.

The sponsor should indicate when a request is not applicable to other marketed ingredients and products (e.g., an impurity profile that is associated with a specific route of synthesis or a performance test that is associated with a specific formulation). These additional tests may be added to the monograph when the need is demonstrated. USP's Expert Committees will not revise monographs to exclude legally marketed ingredients and products in the absence of a significant public health reason. 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. Descriptions of

proposed changes and the data needed to support such changes are presented in specific chapters of this guideline.

Standards. The guideline specifies the conditions necessary to cause a change to an official standard and suggests that additional tests and procedures may be added to a monograph when need is demonstrated. The implications of this statement will have a profound effect on the future development of monographs. On the basis of this statement, monographs can now have various impurity procedures, with associated labeling requirements, for each synthetic route. This approach also may be applied to assay procedures. The inclusion of these additional tests and procedures will be allowed only with the concurrence of the Expert Committee; therefore sufficient rationale should be included in a request for revision.

Summary

The "USP Guideline for Submitting Requests for Revision to the *USP-NF*" is a concise but powerful tool that will be of significant use to industry, government, and academic practitioners. In addition, pharmaceutical industry scientists who are unfamiliar with the purview and mechanisms of USP can profit from careful study of the guideline because it clearly outlines some of the key activities of USP and its constituent activities. Indeed, because the standards set by the constant revision of the *USP-NF* are enforced by regulatory agencies in several nations, it benefits the industry as a matter of good regulatory science to become more closely involved in developing and modernizing the monographs by which the industry operates. **PT**