Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance assists applicants and drug master file (MF) holders in the initiation of either revisions to an existing monograph(s) or development of a new monograph(s) under the United States Pharmacopeial Convention Pending Monograph Process (USP-PMP) during FDA's evaluation of a drug master file or drug product application.[2] This guidance describes the process that allows for the revision of compendial standards that are harmonized with the approved quality and labeling requirements for a drug product application.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Under sections 501 and 502 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug with a name recognized in an official compendium must comply with compendial identity standards or be deemed adulterated, misbranded, or both.[3] To avoid being deemed adulterated,

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Veterinary Medicine at the Food and Drug Administration.

[2] In this guidance, the term *application* may refer to a new drug application (NDA), an abbreviated new drug application (ANDA), a new animal drug application (NADA), or an abbreviated new animal drug application (ANADA), as well as supplements to all these applications. For investigational new animal drugs, an applicant's proposed revision to an existing monograph or development of a new monograph may also be reviewed under the investigational new animal drug file. The abbreviation *MF* may refer to drug master files or veterinary master files.

[3] See sections 501(b) and 502(e)(3)(B) and (g) of the FD&C Act; also 21 CFR 299.5.

such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs from compendial standards.[4] The term *official compendium* means the official United States Pharmacopeia (USP), official Homeopathic Pharmacopeia of the United States, official National Formulary (NF), or any supplement to any of these.[5]

The official USP-NF compendium is published by the United States Pharmacopeial Convention (USP), a private, non-governmental organization. USP revises (or develops) compendial standards from draft standards and supporting data that it receives from the pharmaceutical industry and/or the public, and reflects those standards in the USP-NF through, among other things, individual drug product and drug substance monographs.

It is the responsibility of both the applicant and MF holder to ensure that a drug product or drug substance complies with applicable standards in the USP-NF. When official USP-NF monograph(s) are available for the drug substance and/or drug product named in the application, FDA compares the quality standards found within the official USP-NF monograph with the quality attributes found in the application as part of the evaluation process. If the submitted information is not in compliance with official compendial standards, applicants and/or MF holders provide justification to FDA and should work with USP to revise the monograph. (Approval of the proposed changes is contingent upon FDA science and risk-based assessments.) Though the USP-NF is legally recognized in the FD&C Act, and USP works closely with FDA, FDA typically cannot share the application-specific information contained in submitted regulatory filings with USP because this information is considered proprietary and confidential.[6] An applicant or an MF holder therefore should provide any information needed to revise or develop an official monograph directly to USP.

Applicants and MF holders can petition USP to revise standards in official monographs.[7] However, the USP standards development processes do not accept proposals requesting changes to compendial standards (or proposing a new monograph) from applicants with drug products that are not currently approved by FDA.[8] Historically, if during the evaluation of an application it was clear that the proposed specifications would not comply with the current monograph, approval of the application (and patient access to the drug) was delayed in some cases pending the applicant making revisions to enable the product to meet the monograph. The USP-PMP was developed to address these issues.

[4] See section 501(b) of the FD&C Act and 21 CFR 299.5(c).
[5] See section 201(j) of the FD&C Act.
[6] See 21 CFR 314.430.
[7] Note: FDA cannot provide the information needed to revise USP-NF monographs to USP. Information contained in regulatory filings submitted to FDA is considered proprietary and confidential. The applicant or the applicant's referenced MF holder must provide such information to USP. (See the previous paragraph.)
[8] Similarly, MF holders must be referenced by a currently approved drug product to propose changes to compendial standards.

III. THE USP PENDING MONOGRAPH PROCESS[9]

The USP-PMP enables revisions to and/or development of official monographs to begin before FDA's approval process is complete. The purpose of the USP-PMP is to ensure availability of a revised official USP-NF monograph that is consistent with FDA-approved specifications immediately following FDA approval of the application. This results in an official USP-NF monograph much faster than would be possible if monograph development or revision started only after final FDA approval of the drug product.

The following is excerpted from the USP Pending Monograph Guideline:[10]

> The USP Pending Monograph process allows for development of monographs or monograph revisions for articles awaiting approval by FDA, and permits publication of these proposals in Pharmacopeial Forum (PF) for notice and comment where required in accordance with USP's typical Request for Revision processes. Following publication in PF, these proposals remain in an unofficial status until FDA approval of the market application held by the donor. The Pending Monograph process is available where USP does not yet have a monograph for a drug, or where there is an existing monograph with requirements that are not met by a potential product under review by FDA, and allows the new or revised monograph to become official more rapidly than would be possible if development began only after final FDA approval. In cases where there is an existing monograph, it is common for the application holder to propose reconciliation between their product and the existing monograph requirement by donating analytical methodology and reference standard bulk material as necessary to revise the monograph. The USP Pending Monograph process allows for development of these proposals in a number of different ways, depending on the type of change that is needed and the amount of time available before the anticipated approval. In any case, these proposals remain in an unofficial status until FDA approval of the market application held by the donor.

[9] For further details on the USP-PMP, applicants should reference the USP Pending Monograph Guideline, which describes USP's roles and responsibilities in the process. USP's guideline covers the portion of the process that is between the applicant and USP; it does not include FDA application assessment activities. To initiate a USP-PMP proposal, applicants should refer to the guideline (found at http://www.usp.org) and directly contact USP as indicated.

[10] Ibid.

IV. INITIATING THE USP-PMP

Under the USP-PMP, applicants who have successfully filed an application with FDA may propose revisions to an existing monograph (or development of a new monograph) while the application is being assessed by FDA.[11,12] Applicants who submit an application for a drug product (or who reference an MF for a drug substance) that does not meet or differs from the applicable official compendial standards should contact USP directly to initiate a USP-PMP proposal. Applicants who do not initiate the USP-PMP may risk delay in the approval of any application that is not in alignment with the official USP-NF monograph(s). Alternatively, applicants of drug products that do not meet (or differ from) the official compendial standards may elect to have all differences, and the extent of each such difference, plainly stated on its label, thus indicating that the product does not meet applicable compendial standards.[13] Therefore, we strongly recommend that applicants initiate a USP-PMP proposal if submitting applications as described above. In either situation — initiating the USP-PMP or labeling the product with the difference(s) — FDA will conduct thorough application evaluations using current established practices to determine the acceptability of the quality standards proposed in the application.

V. RECOMMENDATIONS FOR APPLICANTS

To avoid potential delays, USP-PMP proposals should be initiated very early in the application evaluation process. We recommend that those who intend to initiate the USP-PMP begin working on a proposal concurrent with an application's submission to FDA. The applicant's intention to initiate the USP-PMP should be stated in the cover letter of the application and should also be prominently displayed in all applicable section(s) (i.e., the drug substance specification section (section 3.2.S.4.1) and/or the drug product specification section (3.2.P.5.1), as applicable). Applicants and MF holders should follow USP's guidelines for USP-PMP proposals and submit the appropriate information directly to USP.

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[11] MF holders may also initiate the USP-PMP for revisions of an existing monograph (or development of a new monograph) while the application they support (i.e., the application in which the MF is referenced) is under assessment by FDA. MF holders should coordinate USP-PMP initiation with the applicant.

[12] Applications submitted to FDA undergo an initial filing assessment. NDAs are filed once FDA makes a threshold determination that the NDA is sufficiently complete to permit a substantive review. (See 21 CFR 314.101(a).) ANDAs are received once FDA makes a threshold determination that the ANDA is substantially complete. (See 21 CFR 314.101(b)(1).) Once the filing assessment is complete, applicants receive communication either acknowledging submission of the application or indicating a refusal to file the NDA or refusal to receive the ANDA. For more information, see the following: guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* (December 2016); draft guidance for industry *Good ANDA Submission Practices* (January 2018); and draft guidance for industry *Refuse to File: NDA and BLA Submissions to CDER* (December 2017). When final, these guidances will represent FDA's current thinking on these topics. For animal drug applications, see 21 CFR 514.110 – Reasons for refusing to file applications, and CVM *g*uidance for industry #119 *How the Center for Veterinary Medicine Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug*. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[13] See section 501(b) of the FD&C Act and 21 CFR 299.5(c).

Once a USP-PMP is initiated, the applicant should keep USP apprised of the application's status and work with USP to make any necessary changes to the proposal. For example, if during FDA's evaluation the applicant is notified that the application's specifications must be modified before it can be approved (and therefore the application's final specifications will differ from what was proposed in the USP-PMP proposal), the applicant (or the referenced MF holder, as applicable) should contact USP to update the proposal. This ensures that the compendial standards in the proposal reflect the standards in the application at the time of approval. Per the USP-PMP guideline, pending monographs will not advance to an official status until after an application has been approved by FDA and FDA has confirmed the compendial specifications in the USP-PMP proposal. As such, applicants should inform USP of final FDA approval. Once notified, USP will begin the confirmation process with FDA.

Participation in the USP-PMP does not confer FDA acceptability of the compendial standards proposed for the product, nor preclude full application evaluation by FDA; all applications will be subject to complete evaluation using current established practices.

APPENDIX
QUESTIONS AND ANSWERS

1. My product is not expected to meet the USP-NF monograph, but I will not use the "USP" designation in the established name. Does this exempt my product from complying with the USP-NF monograph (and thus negate the need for a USP-PMP proposal)?

No. As described in current regulations referenced in the guidance, a drug with a name recognized in an official compendium is subject to the monograph standards found within. The applicable standards apply to such drugs whether or not the added designation "USP" is used. If your product cannot meet the official monograph, you should initiate the USP-PMP regardless of whether you intend to use "USP" with the established name. (Note: Use of the "USP" designation with the established name is optional for any drug with a name recognized in the USP.)

2. My application has been accepted for filing (for an NDA) or received (for an ANDA), but there's no USP monograph for this drug substance/product. Should I initiate the USP-PMP?

The USP-PMP was developed as a practical way to expedite the monograph revision and development process based on the new applicants' specifications provided in applications submitted to FDA. Although creation of a public standard can be beneficial to all stakeholders, FDA typically does not require monograph development when no monograph exists.

3. I'm an MF holder. There's no monograph for my drug substance, but my client has submitted an application to FDA. Can I use the USP-PMP to develop a monograph for my drug substance?

Yes. MF holders cross-referenced by an application currently under evaluation by FDA can contact USP to initiate a USP-PMP. We recommend that USP-PMP proposals be initiated as early as possible. However, you should coordinate with the applicant to ensure that the USP-PMP proposal is consistent with the drug substance information in the application submitted to FDA. It is the applicant's responsibility to update the application with specifications consistent with the USP-PMP. Only the specifications found in the approved application can be confirmed to USP.

4. My application's referenced MF has initiated a USP-PMP. What should I do?

In this situation, applicants should work with the MF holder to ensure that the USP-PMP proposal is consistent with the drug substance information in the application submitted to FDA. Only the specifications found in the approved drug product application can be confirmed by FDA to USP.

5. I've initiated a USP-PMP proposal. What happens when FDA recommends that I revise my specifications (e.g., test, test method, acceptance criteria) during the assessment cycle?

Applicants should contact USP and update their proposals to ensure that the application's final approved specifications are consistent with their USP-PMP proposal. FDA can only confirm whether the specifications presented in the proposal match the specifications in the application at the time of approval; FDA cannot divulge specific inconsistencies. If the USP-PMP proposal is not consistent with the application's final approved specifications, the draft monograph will not move forward and the applicant will be required to revise the product labeling to plainly state all differences from the official USP-NF monograph.

6. FDA recommended that I initiate the USP-PMP. Is this required for approval?

Initiation of the USP-PMP is not required for approval; however, applicants who do not initiate the USP-PMP when recommended may risk delay in the approval of any application that is not in alignment with the relevant official USP-NF monograph(s). Alternatively, applicants of drug products that do not meet (or differ from) the official compendial standards may elect to have all differences and the extent of each such difference plainly stated on its label, in accordance with current regulations.

7. My application has been tentatively approved. Will my USP-PMP proposal advance to official status?

Final approval (and FDA confirmation of the approved specifications) is required by USP before a USP-PMP proposal can be incorporated into the official USP-NF. FDA will not confirm tentatively approved specifications.

8. If I choose to label my product with all respects it differs from the official USP-NF monograph, what sort of statement is necessary?

Industry cooperation is essential to ensure that modern compendial standards are available to the public. However, for applicants who instead choose to label their products in accordance with current regulations, we recommend that they work with the applicable division to develop appropriate labeling statements for their products.

9. I initiated a USP-PMP proposal. In my ANDA, the proposed labeling included statements to show all respects in which the drug differs from the current USP-NF monograph. When should I update my labeling with the USP-NF test number?

We recommend that you update your labeling and document this in the next annual report. An applicant may also submit an amendment containing revised labeling during review of the ANDA or in response to a request by FDA (e.g., in response to deficiencies identified in an

Information Request, a Discipline Review letter, or Complete Response letter). Please note that as outlined in the guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), amendments to ANDAs may impact GDUFA goal dates.[14]

10. A product that does not meet the current USP-NF monograph may risk approval delays if a USP-PMP is not initiated. My product is not expected to meet the USP-NF monograph. When should I prepare my USP-PMP proposal? When should I contact USP?

We recommend that you initiate USP-PMP proposals as early as allowed by the USP Pending Monograph guidelines. It may be beneficial to prepare the proposal and initiate contact with USP concurrent with the submission to FDA. The USP-PMP proposal is between the applicant/holder and USP; therefore, it may be helpful to either review the most current version of USP's Pending Monograph Guideline for any changes to the initiation criteria or contact USP directly to determine the best approach.

11. We have submitted our MF to FDA with analytical methods for the drug substance that are not compliant with the official USP-NF monograph. We have demonstrated, through method equivalency studies, that our in-house methods are either equivalent or superior to the USP methods. Do we need to initiate the USP-PMP process to have our methods added to the drug substance USP-NF monograph?

No. It is not necessary to initiate the USP-PMP for analytical method equivalency. Though a compendial article must conform to the official monograph specifications/acceptance criteria, the analytical procedures used to show conformance may differ from official USP methods if the alternative methods are fully validated, suitable for use, and provide comparable results to the official USP method, as determined by FDA. In the event of a dispute, the compendial method is considered legally conclusive. As such, the drug must be able to meet the compendial standards if tested as described in the applicable official monograph(s).

[14] The Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II, FDA Reauthorization Act of 2017 (Public Law 115-52 Title III)) was signed into law on August 18, 2017, to facilitate timely access to quality, affordable generic medicines. Under the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter) that accompanied the legislation, FDA agreed to certain review goals and procedures for amendments under assessment as of or received on or after the GDUFA II effective date (i.e., October 1, 2017). See the referenced guidance for further information.