

May 9, 2014

Submitted Electronically
Division of Dockets Management (HFA-305)
United States Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Over-The-Counter Drug Monograph System; Request for Comments, 79 Fed. Reg. 10168 (Feb. 24, 2014); Docket No. FDA-2014-N-0202 ("FR Notice")

The United States Pharmacopeial Convention (USP) appreciates the opportunity to comment to the Food and Drug Administration (FDA) as the Agency assesses the Over-the-Counter Monograph System (OTC System)¹ and considers possible alternatives. We emphasize the following points:

1. USP appreciates FDA's continued recognition of the value of USP standards; USP's historic drug quality mission strengthens the Agency's statutory public health mandate. The required role for USP drug substance monographs in the OTC System is an important safeguard that should not be eroded. (**FR Notice, III.A., p. 10172, Col A, "Strengths and Weaknesses of the Existing OTC Drug Review"**).

USP supports ensuring that drug quality monographs for any active ingredients in Tentative Final Monographs (TFMs) are completed, or on track for completion, and developing an efficient mechanism for finalizing the status of OTC drugs currently marketed under TFM; USP is committed to doing its part in removing barriers to innovation and the introduction of new products in the OTC system.

2. One possible initiative USP is considering that is designed specifically to help bolster FDA and the OTC System is to address the challenge of missing *product* quality standards with a new "group monograph" concept (see page 3 of this letter for more information). The intent would be to better enable the development of compendial quality standards for finished dosage forms (drug products), thereby supporting the *drug substance* monographs that already play an important supporting role in the OTC System. Having compendial standards for drug products, not just their ingredients, could also help support some of the future visions of the Agency related to improved transparency and information about individual products that will be using active ingredients allowed under the OTC System (**FR Notice, I.B.2.c., p. 10170 Col C, "Product Formulation,"; II.C., p. 10171, "Issuing Regulations to Require Product Specific Information..."**).

USP looks forward to receiving continued input on this draft concept from FDA and other stakeholders. FDA can help realize the promise of this and related compendial initiatives by requiring manufacturers that wish to market a new formulation to work with USP on development of a suitable product monograph. USP is convinced this can be accomplished without impeding innovation or slowing the pace of OTC System modernization.

¹ FDA's OTC System monographs, and USP's compendial monographs, serve different purposes and must be distinguished. FDA refers to the various OTC System drug category regulations in the Code of Federal Regulations as "monographs;" see 21 CFR Part 330. Since 1820 USP has also used the term "monographs" in publishing its quality standards developed for individual drug substance or drug products in the *United States Pharmacopeia* and *National Formulary (USP-NF)*.

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I. USP's Role in Law

USP compendial quality standards advance FDA's efforts to provide timely access to safe and effective drugs, both under the adulteration and misbranding provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) and regulations supporting the OTC System (21 CFR Part 330). Under existing law, any drug that is recognized in either *USP* or *NF* is subject to applicable quality standards in the current official version of those compendia. That includes applicable USP quality monographs for drug substances, drug products, ingredients or excipients, which apply whether the drug is marketed OTC or Rx only, and whether a drug is marketed pursuant to a Biologics License Application (BLA), New Drug Application (NDA), or Abbreviated New Drug Application (ANDA), or subject to one of the 21 CFR Part 330 FDA OTC Monographs, or otherwise. See, e.g., FDCA §§201(j), 501(b) and 502(e)(3)(b), and 21 CFR §299.5(a&b). An applicable USP compendial quality monograph can be helpful to both manufacturers and FDA, both in characterizing a drug (ingredient, or product), and helping to assure identity, strength, quality, and purity.

The OTC System regulations provide various additional roles for USP quality standards, but currently only with regard to USP drug substance monographs. For example, the required format for submission of safety and effectiveness data specifies that there either be an official applicable *USP-NF* drug substance (active ingredient) quality monograph, or a proposed standard under development at USP for inclusion into *USP-NF*. 21 CFR §330.10(a)(2) §VII. Time and Extent applications may reference the current *USP-NF* to help satisfy the basic information requirements for a "condition" (an active ingredient, or combination of active ingredients). 21 CFR §330.14(c)(1)(iii). Finally, as a condition of marketing, any active ingredient included in a final OTC Monograph Process monograph "must be recognized in an official *USP-NF* drug monograph that sets forth its standards of identity, strength, quality, and purity." 21 CFR §330.14(h&i).

II. Supporting Regulators and Manufacturers

USP is pleased to support FDA's OTC Monograph Process by providing compendial quality monographs for every active ingredient in the various FDA OTC drug category monographs promulgated in the Code of Federal Regulations. USP is committed to doing its part to assure FDA and those who manufacture or market OTC drugs that the availability of a compendial quality monograph will not impede timely completion of FDA drug category monographs that are not yet final. As already provided in existing regulations, the submission of an FDA monograph may proceed while sponsors are working with USP to develop a compendial standard. USP will prioritize any such work in progress that is needed in order to help FDA bring its Tentative Final Monographs to closure. USP is not aware of any outstanding or unresolved compendial issues that currently prevent any drugs from being marketed under the OTC System, and we are striving to ensure that there are no unintended or avoidable compendial barriers.

One of the apparent shortcomings of the current system in FDA's view is that final formulations are not reviewed by FDA "to ensure product safety, effectiveness, and consistency." **FR Notice, page 10170, col C, "Product Formulation."**

One way to help assure greater Agency awareness and transparency about FDA OTC Monograph System drug products, in furtherance of both consistency and quality, would be for FDA to require that there not only be USP monographs for each active ingredient (drug substance), but also an applicable USP drug product monograph for each new product formulation marketed under the OTC System.

To address any potential concerns about constraining innovation or impeding marketing of new products, FDA could provide the same flexible approach for drug *products* at the time of marketing that is currently allowed for drug *substances* at the time of initial OTC System submissions (that there either be an applicable USP drug product monograph, or that a proposed compendial standard be in development at USP). See 21 CFR §330.10(a)(2) §VII. Only in the event a manufacturer failed to make reasonable efforts to complete the compendial standard development process, would the marketing status of a product be affected; in the meantime, if otherwise acceptable to FDA, marketing of the new drug product could proceed while development of a compendial drug product standard advances to completion. The envisioned outcome is an OTC System in which there are applicable compendial quality standards not only for all active ingredients/drug substances, but as well for all marketed drug products/formulations.

III. Options For Supporting the OTC System; “Group Monograph” Concept

The updating of OTC compendial monographs has at times proved to be a challenge, for many of the same reasons experienced by FDA, including advancements in pharmacological science, and the continued and potentially unlimited evolution of product formulations. USP has continued to work internally and with various stakeholders to develop improved means for modernizing existing monographs, and developing new monographs. The modernization of existing drug *substance* monographs that help support the OTC System is continuing apace. But creating drug *product* monographs, particularly for the ever-changing OTC System, has proved daunting. USP continues to work with FDA and other stakeholders to identify ways to better advance the development of product quality monographs in support of the OTC System. One draft concept involves a “**group monograph**” approach.

The concept of a group monograph, intended uniquely for use with OTC System drug products, would allow key essential quality characteristics to be determined by objective compendial quality standards, including, as appropriate, tests and methods and related reference standards. Anticipated benefits could include a better means to control the quality of products in the marketplace; rapid coverage of new combination products without creating barriers to innovation; incorporating modern technological approaches and orthogonal screening capability; and defining basic but meaningful quality standards for products.

Within a group, all products would be covered, from single-component to combination products. The monograph groups could be defined by their applicability to specific Assay and Impurity (i.e. strength/potency, quality, and purity) and Identification procedures, and each group monograph could define the components that are covered by the monograph and also include a listing of the specific drug products subject to the monograph. The goal would be to cover all drug categories designated in FDA regulations (see 21 CFR Part 330 etc.), but in furtherance of assuring workable tests and methods, particular group monographs would not necessarily mirror each such category, though all OTC System product combinations would be covered by one group monograph or another.

USP envisions that these group monographs could provide basic performance test procedures, impurity procedures for critical process impurities, toxic impurities, or other important impurities. However, in order to ensure universal coverage and for reasons of practicality, it is possible the group monographs would not necessarily be as comprehensive or rigorous as conventional USP monographs. In any event, it

should be underscored that each of the drug substances/active ingredients to be covered and controlled by a group monograph would continue to be supported by a traditional USP monograph.

As with all USP compendial quality standards, should the concept of a "group monograph" advance within a framework established under USP processes, they would be developed by USP's Expert Committees, chaired by experts elected by the USP Convention, and with expert volunteer members elected by the USP Council of Experts. USP standards are established with open and transparent procedures, including opportunity for public notice and comment. USP has a self-supporting process that does not rely on government funding or access to confidential government data, but does provide for close collaboration with FDA through government liaisons participating as non-voting members of USP Expert Committees.

USP has a variety of means and resources at its disposal to develop drug product/finished dosage form monographs in support of the OTC System, whether involving this potential group monograph concept or otherwise. USP has a long history of welcoming voluntary monograph submissions from manufacturers for drug substances and drug products alike. USP particularly invites donor participation in an initiative to provide compendial quality standards for not just OTC system drug substances, but also ultimately all OTC system drug products. USP also has excellent internal laboratory facilities that can contribute to developing new standards, modernizing existing ones, and developing and packaging suitable reference materials (USP Reference Standards).

IV. Conclusion

USP has a longstanding role in drug quality, beginning with publication of the first *Pharmacopoeia of the United States* in 1820. Congress and federal regulatory authorities have made consistent good use of USP standards, and we appreciate FDA's continued recognition of this role. USP is committed to keeping its existing standards scientifically relevant through: modernization; responding in a timely way to changing priorities from FDA and other stakeholders in developing new compendial standards; and ensuring that the development and application of our quality standards never unduly constrain either FDA or manufacturers.

USP is convinced that compendial quality standards can be part of the solution that FDA is seeking for optimizing the OTC System, and that USP can help play a role in support of FDA and other stakeholders without constraining innovation in this important public health space. We are working to find alternative approaches and look forward to a continued conversation with the Agency and all interested parties. We appreciate the expertise available to us as possible concepts are explored.

Should you have additional questions please feel free to contact Ben Firschein, USP's Director of Government Affairs and Policy (baf@usp.org, 301-816-8235), who can put you in touch with appropriate USP staff.

Sincerely,



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