U S Pharmacopeia
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August 11, 2003

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Number 96N-0417, Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements

Dear Sir or Madam:

This letter provides the comments of the United States Pharmacopeia (USP) to the proposed rule "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements," which appeared in the March 13, 2003 Federal Register.[1]

USP Background

USP is a not-for-profit organization that promotes public health by the establishment of state-of-the-art standards to ensure the quality of medicines and other health care technologies. In pursuit of our mission, USP establishes and disseminates validated, peer reviewed monographs for dietary supplements ingredients and products. These monographs include tests, procedures and acceptance criteria to ensure the identity, strength, purity and quality of an article. The procedures contained in the monographs are developed and validated by industry experts, evaluated by USP's Expert Committees, and sent out for public review prior to dissemination as part of official monographs. USP also supplies the industry with reference standards to evaluate dietary supplement products using these monographs.

USP publishes its monographs in the *United States Pharmacopeia-National Formulary* (*USP-NF*), a publication of standards for drugs, dietary supplements, devices, and biologics. The Federal Food, Drug, & Cosmetic Act (FDCA) defines the *USP-NF* as official compendia.[2] In addition, the FDCA recognizes the official compendia in the misbranding provisions for food. Specifically, the law states that a dietary supplement is misbranded if:

(D) the supplement—

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[1] 68 Fed. Reg. 12158 (March 13, 2003).

[2] 21 U.S.C. § 321(j). Official compendium is defined as "the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them."

(i) is covered by the specifications of an official compendium;
(ii) is represented as conforming to the specifications of an official compendium; and
(iii) fails to so conform . . . [3]

USP also operates the Dietary Supplement Verification Program (DSVP), a rigorous, voluntary certification program to help ensure the quality of dietary supplements. DSVP has been embraced by several companies seeking to undergo a thorough approach that will help to ensure the identity, strength, and quality of a dietary supplement. DSVP currently follows *USP-NF* General Chapter 2750 *Manufacturing Practices for Dietary Supplements* which includes the following components: written procedures, expiration dating, and adherence to *USP-NF* monographs. DSVP coordinates use of General Chapter 2750 with the Food and Drug Administration's (FDA) March 13th proposed rule.

Comments

USP commends FDA's efforts in issuing this proposed rule and believes that this is an important step to ensuring the safety and quality of dietary supplements. USP is encouraged that the proposed rule recognizes the usefulness of *USP-NF* General Chapter 2750 and supports the recognition in the proposed rule of USP's microbial limits for dietary ingredients and supplements and its reference standards.[4]

Our comments below reflect USP's extensive experience in developing monographs for dietary supplements and its experience with DSVP. This experience has shown that efforts by USP, the industry, and the agency to establish requirements for dietary supplement ingredients and products lead to improved quality. For example, we believe USP's efforts, through the compendia and DSVP, to establish dissolution or disintegration testing, pesticide testing, and expiration dating have contributed to better dietary supplement product quality.

Scientifically valid procedures[5]

USP establishes scientifically valid procedures in its compendia, *USP-NF,* and we encourage the agency to designate compendial procedures as "scientifically valid." USP recommends that the agency do this by adding a regulatory definition of "scientifically valid" that includes compendial procedures. A definition is important to proposed 21 C.F.R. §111.35(h), which states that a company must use an appropriate test to determine whether specifications are met and that an appropriate test is one that is a scientifically valid method. In the proposed rule, FDA did not define but instead characterized its own and AOAC procedures as scientifically valid but failed to mention compendial procedures.[6] This overlooks USP's well-established process of publishing

[3] Id. § 343(s)(2)(D).
[4] 68 Fed. Reg. 12159, 12200 and 12250.
[5] USP recommends that the agency revise its proposed regulation to use the term "procedure," which has replaced the term "method" in the global regulatory environment. USP has used the term "procedure" throughout these comments.
[6] 68 Fed. Reg. 12198.

scientifically valid procedures, which includes review by an Expert Committee, public review, publication in the compendia, and an opportunity for continuous revision.

Moreover, the failure to acknowledge compendial procedures as scientifically valid would be inconsistent with the law. Federal law regarding dietary supplements specifically recognizes the specifications of an official compendium, but not of other organizations.[7] While adherence to compendial specifications is voluntary under the law, once an article represents that it conforms to the official compendial specifications, the official compendial procedures must be used to determine non-compliance.

USP has a wealth of analytical procedures for dietary supplements. USP has established validated and peer reviewed procedures in monographs for over 200 dietary supplement ingredients and products, including approximately 70 botanicals. Currently, approximately 30 additional monographs for botanicals are proposed in the *Pharmacopeial Forum,* USP's publication for public review of proposed monographs and chapters. For those dietary supplements and dietary ingredients not found in the *USP-NF*, USP encourages the submission of monographs, including tests and procedures, for evaluation by USP Expert Committees and inclusion in *USP-NF*.

USP emphasizes that a scientifically valid procedure, in and of itself, is not sufficient as a public standard. USP's monographs include several components, including definition, description, packaging, storage, and labeling statements. In addition, a USP dietary supplement monograph contains the specification for the article, which includes tests, procedures, and acceptance criteria. Furthermore, USP's dietary supplement botanical preparation monographs frequently include general, standardized approaches to the preparation of the article. This is an especially critical component, given that multiple different procedures create different analytes and associated requirements for different analytical procedures.

Reference Materials

USP supports proposed regulation 21 C.F.R. § 111.60 requiring criteria for selecting reference materials within laboratory operations. The use of reference materials is an integral part of assuring the identity, purity, quality, strength and composition of a dietary supplement and/or dietary ingredient. USP also supports the proposed rule's recommendation for the use of compendial standards.[8] As publisher of the nation's official compendia, USP provides official USP Reference Standards for use when testing articles according to compendial procedures. Official USP Reference Standards are validated in a collaborative arrangement generally by not less than three laboratories, one of which is an FDA laboratory. Data for these candidate reference standards are then reviewed by USP's Reference Standard Committee, which is a special committee of USP's Council of Experts. Via this process, USP has prepared over 90 official USP Reference Standards for dietary supplement ingredients, including approximately 20 for botanical dietary supplements.

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[7] 21 U.S.C. § 343(s)(2)(D). Specifications are the tests, procedures, and acceptance criteria used to characterize an article.

[8] 68 Fed. Reg. 12208.

Dissolution and Disintegration

USP also recommends that the proposed rule contain dissolution or disintegration requirements for dietary supplements. FDA contends that such requirements are premature and therefore are not included in the proposed rule. USP disagrees; such requirements are important tools to establish the quality of dietary supplements. [9] USP had identified this as an issue at its 1990 meeting of its Convention membership and revised compendial monographs to require either dissolution or disintegration testing. In addition, USP's DSVP requires this testing for dietary supplements in the program.

FDA has in fact adopted by regulation USP dissolution requirements for certain dietary supplements, such as folic acid and calcium.[10] USP believes that the agency similarly should require dissolution and disintegration testing whenever scientifically available and that appearance in an official compendium of a disintegration or dissolution test shall be prima facie evidence of such availability. At the least, dissolution and disintegration requirements should be adopted for vitamins and minerals and those dietary supplements with well-characterized active ingredients. In addition, USP recommends that the agency, like USP, adopt disintegration testing for botanicals products. The failure to require this testing could result in dietary supplements that are not bioavailable and may have negative health implications. Consumers have a right to expect that the dietary supplement product purchased will deliver to the body the item stated on the label.

Expiration Dating

With respect to expiration dating of dietary supplements, USP recommends that the agency —like USP—require expiration dating. Without this, manufacturers cannot possibly assure the appropriate potency or strength of the dietary supplement for the product's "shelf life." This is inconsistent with FDA's own regulation requiring 100% potency for the duration of a dietary supplement's shelf life.[11] Theoretically, a product would be required to retain 100% potency even if sold years or decades after its manufacture. Furthermore, without an expiration date and records to establish this dating, any investigation of a subpotent product is likely to be compromised. USP believes that the agency should set in place expiration date requirements, including test procedures to determine it.

Testing

Proposed regulations § 21 C.F.R. § 111.35(g)(2)(i) and (ii) require that when no scientific procedure is available, testing must be completed on each lot of components, dietary ingredients, or dietary supplements. Such testing must be performed "in-process in accordance with the master manufacturing record . . . ." USP suggests that the agency consider modifying the amount of testing based on the use of a

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[9] Id at 12163.
[10] 21 C.F.R. §§101.79(c)(2)(ii)(B) and 101.72(c)(2)(ii)(C).
[11] Id. § 101.36

certificate of analysis. While a certificate of analysis may not be completely relied upon to forego testing of a received ingredient, the amount of testing may take into account the past quality history of the supplier and the type of ingredient (*e.g.* vitamin, mineral, botanical). This is consistent with 21 C.F.R. § 211.84(d) for drug components.

Similarly, for proposed regulation 21 C.F.R. § 111.35(g)(1) involving finished batches of dietary ingredients or dietary supplements, USP encourages the agency to adopt a statistical approach to process validation instead of testing each lot. This would provide a scientifically valid way to assure quality of the product without the burden of testing each batch.

Labeling

The proposed rule discusses that manufacturers should not place an unqualified statement on the label stating the product is "produced in compliance with dietary supplement current good manufacturing practice requirements."[12] According to the proposed rule, such statement may mislead consumers into believing that the dietary supplement is superior or is safe and effective. USP believes that the rule should be modified to exclude statements such as the dietary supplement "is produced using good laboratory practices" or "is produced using good practices" or "is produced in compliance with USP good manufacturing practices." These or similar statements currently appear on dietary supplement labels and may also be misleading.

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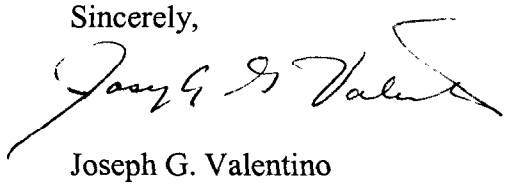
We trust that the agency finds these comments useful. If you have any further questions, please do not hesitate to contact me.

Sincerely,



Joseph G. Valentino
Senior Vice President, Secretary, and
General Counsel

[12] 68 Fed. Reg. 12164.