



U.S. Pharmacopeia
The Standard of QualitySM

December 2, 2011

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on "Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues"; Docket No. FDA-2011D-0376

Dear Sir or Madam,

The United States Pharmacopeial Convention ("USP") submits our comments to the Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient Notifications and Related Issues ("Guidance") as referenced above, published by the Food and Drug Administration ("FDA") on July 5, 2011. USP believes that compendial standards could be used in conjunction with the draft guidance to facilitate the notification process and help manufacturers and regulators provide safe and quality dietary supplements to consumers. More generally, USP believes that publicly available specifications with independently characterized and tested reference materials are key to assuring the quality and safety of all foods, including dietary supplements. Without establishing quality relative to safety, there is no way to assure consistency of a food and/or food ingredient over time in the marketplace.

USP Background

USP is a scientific nonprofit organization that sets standards for the quality, purity, identity, and strength of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. USP publishes two compendia relating to dietary supplements. The first is the *United States Pharmacopeia* and *National Formulary* (collectively, "*USP-NF*"), which is recognized under federal law. The second is the *Dietary Supplements Compendium* ("*DSC*"), a comprehensive resource for the dietary supplement industry. Of relevance to the proposed Guidance, these compendia contain monographs for dietary ingredients and dietary supplements that include specifications as tests, procedures and acceptance criteria to ensure their quality, purity, identity, and strength. The monographs contained in the compendia are developed and validated by industry and academic experts, evaluated by USP's Dietary Supplement Expert Committee (DSEC), and disseminated for public review and comment. The DSEC responds to public comments and approves the monograph for publication in the *USP-NF* and *DSC*. Prior to undertaking the development of a monograph for a dietary ingredient, the DSEC performs a literature-based safety review to determine that the ingredient does not present safety issues for purposes of admission into the *USP-NF* and this review is also made public. The DSEC and the subcommittees and Expert Panels that support them, are composed of independent experts drawn from industry, academia, government and other areas with much expertise in the area of dietary supplements, and include FDA CFSAN liaisons. USP also supplies the industry with reference standards to evaluate dietary ingredients and dietary supplements using the specifications in *USP-NF* or *DSC* monographs. USP's dietary supplement standards are used throughout the world to help ensure the quality of dietary supplements and other botanical ingredients.

The food misbranding provision of the Federal Food, Drug and Cosmetic Act ("FDCA"), Section 403(s), recognizes two of USP's official compendia, the *USP* and *NF*, as being federally enforceable under certain circumstances to the extent that a particular supplement is covered by the specifications in either compendium.¹ Specifically, manufacturers who label their dietary supplements as being compliant with *USP* specifications and fail to so comply

¹ See definition of the term "official compendium," FDCA § 201(j); 21 U.S.C. § 321 (j).

Headquarters

12601 Twinbrook Parkway
Rockville, Maryland 20852
+1-301-881-0666

Europe/Middle East/Africa

Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP-India Private Limited

ICI Knowledge Park
Genome Valley
Labs 7-10, Phase III
Turkapally, Shameerpet
Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-2348-0088

USP-China

Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
Shanghai, 201203, China
+86-21-51370600

USP-Brazil

W Torre Technology Park
Avenida Ceci 1600, Barueri
São Paulo/SP - Brasil
+55 11 3245-6400

may be deemed to be misbranded.² USP's position on the value of compendial standards to the dietary supplement industry and regulators has been elaborated in earlier publications.³

Comments

USP commends FDA for issuing this draft Guidance and believes that this is an important step to help ensure the safety and quality of dietary supplement ingredients. Our comments below reflect USP's extensive experience in developing monographs containing quality specifications for dietary ingredients and dietary supplements through a diligent process that includes a threshold safety review of each ingredient for the purpose of determining whether to admit the monograph into the compendium. We recognize that USP's threshold safety analysis is not intended to assess the intrinsic safety of a dietary ingredient.⁴ However, USP's experience has shown that compendial quality standards for dietary ingredients and dietary supplements can provide a helpful resource to both industry and FDA in overall efforts to demonstrate and assess the quality and safety of these articles.

Comments on question IV.B. Exemptions from NDI notification requirements and reliance on compendial standards:

The draft Guidance recognizes some conditions under which notification is not required for an NDI. An exemption from the notification requirement applies to an NDI that has been present in the food supply and is not chemically altered from its conventional food form and is intended to be consumed under the same conditions of use. The Guidance also recognizes that changes in manufacturing processes for a grandfathered dietary ingredient or an NDI that was the subject of a prior notification will require a new notification only if the chemical properties of the ingredient are altered. We commend the FDA for providing these exemptions as they reduce the regulatory burden, and help eliminate potentially redundant notifications by dietary supplement manufacturers. We believe that compendial standards can reduce the regulatory burden in these cases providing assurance that the ingredients that are manufactured via different processes meet the same (equivalent or better) specifications for quality, purity, identity, and strength. Compendial quality standards also address the concerns that different manufacturing processes might introduce different impurity profiles, by setting appropriate limits for impurities through USP's flexible monograph approach⁵. Accordingly, we suggest that an additional exemption to notification requirements be considered for NDIs that claim to comply with compendial standards in a *USP-NF* or *DSC* monograph (The *DSC* includes, at the time of publication, monographs that are identical copies of selected *USP-NF* compendial standards that are collected separately to be useful to the dietary supplement industry). As noted above, the development of *USP* monographs for dietary supplements includes a threshold safety review of the dietary ingredient in question (for the limited purpose of determining whether to admit it into the compendium) and comprehensive quality specifications pertaining to the quality, purity, identity, and strength of the ingredient.⁶ Recognition of compliance with USP's compendial standards as an exception to the NDI notification requirement would further ease the administrative burden associated with notifications while still being protective of consumers. It would also help the FDA and dietary supplement manufacturers establish consistent quality specifications that will deliver to consumers the quality product they expect.

Comment on question IV.B.4. Use of solvents for extraction of botanical constituents

The Guidance states that use of solvents other than water or aqueous ethanol to make a botanical extract will chemically alter a food - usually by extracting different types of constituents than are extracted using water or aqueous ethanol - thereby requiring submission of an NDI notification. We do not believe that selective extraction should be considered chemical modification. For example, extraction with hot water

² FDCA § 403(s); 21 U.S.C. § 343(s).

³ Schiff PL Jr., Srinivasan VS, Giancaspro GI, et al. The development of USP botanical dietary supplement monographs, 1995-2005. *J Nat Prod.* 2006; 69(3):464-72. See also, Miller RK, Celestino C, Giancaspro GI, Williams RL, FDA's dietary supplement CGMPs: standards without standardization. *Food Drug Law J.* 2008;63(4):929-42.

⁴ USP Admission Criteria and Safety Classification for Dietary Supplements Guideline. <http://www.usp.org/pdf/EN/USPNF/2009-10-21AdmissionDSGuidelineFinal1.0.pdf> (Accessed 21 November, 2011).

⁵ Flexible monograph approach allows different tests, procedures, and/or acceptance criteria within a single monograph, with suitable validation, reflecting the different attributes that do not impact the safety and/or benefits of an ingredient. *Pharm Forum.* 2005;31(3):690-691.

⁶ *Id.*

may induce more chemical reactions by hydrolysis than an extraction with an aprotic solvent, such as hexane or supercritical CO₂. *USP-NF* monographs for botanical extracts also include limits for residual solvents via General Chapter <467> Residual Solvents. Considering the case-by-case evaluation by DSEC of the likely chemical modification from the use of solvents for extraction, we suggest making an exception to the NDI notification requirement for botanical extracts created with solvents other than water or aqueous ethanol that comply with the specifications in *USP-NF* monographs.

Comment on question IV.C.2. Reliance on compendial standards to avoid the need for multiple submissions for the same dietary ingredient:

The Guidance states that each manufacturer of an NDI for which notification is required needs to submit such notification to the Agency, even if another manufacturer or distributor has already successfully submitted a notification for the same ingredient. FDA's rationale for this position is that the composition and labeling of the dietary supplement may differ among manufacturers, and the manufacturing processes and specifications needed to establish the identity of an NDI are usually trade secrets that are not available in the NDI docket. However, these specifications may be available through USP as public standards.

While respecting FDA's concerns, USP considers this requirement redundant and burdensome where two manufacturers essentially are manufacturing the same dietary ingredient, labeling them similarly in terms of usage, and meeting the same compendial specifications. USP has vast experience providing public specifications through its flexible monograph approach for generic prescription drugs that are manufactured by different methods, and yet meet common compendial acceptance criteria for quality, purity, identity, and strength. Accordingly, if compendial monograph specifications are available for a dietary ingredient which already has been the subject of a successful notification, a manufacturer meeting those specifications should not be required to submit an additional NDI notification. Adoption of compendial standards in this fashion would reduce the burden for the industry (in preparing the NDI notification) and for the regulators (in reviewing the notification) thus saving time, resources and effort. Even if the FDA is unwilling to provide a blanket exception to the notification process for NDIs meeting compendial standards, as suggested above, it should at least consider making an exemption to the notification requirement for manufacturers producing the same NDI that has been the subject of a prior notification, as long as these additional manufacturers are meeting the compendial standards of a USP monograph.

Comment on question VI.A.5. Importance of quality specifications to provide safe dietary supplements, and recognition of the role of compendial standards:

In the section "What to include in a NDI notification," the Guidance recognizes that quality and safety are intertwined. USP agrees that quality and safety are closely related, and that safety is potentially compromised when quality is compromised. Compendial standards (and associated reference materials) are efficient and effective resources to establish the quality, purity, identity and strength of dietary ingredients and dietary supplements across manufacturers. USP is encouraged that the draft Guidance recognizes the usefulness of *USP-NF* standards for dietary ingredient and dietary supplement quality, and supports the recognition in the draft Guidance of USP's General Chapters <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests, <791> pH and <231> Heavy Metals in Table 1. We encourage the agency to incorporate in the Guidance other quality specifications contained in *USP-NF* general chapters, such as General Chapters <561> Articles of Botanical Origin, <563> Identification of Articles of Botanical Origin, <565> Botanical Extracts, <2021> Microbial Enumeration Tests – Nutritional and Dietary Supplements, and <467> Residual Solvents.

We also note, however, that USP monographs for dietary supplements include standards pertaining to all of the following specifications that are highlighted in VI.A.5 of the draft Guidance:

1. An identity specification for each component;
2. Component specifications necessary to ensure that specifications for the quality, purity, identity, and strength of dietary supplements manufactured using the components are met; and
3. Limits on the types of contamination that may adulterate or lead to adulteration of the finished product.

Thus, even if the agency declines to exempt from NDI notification ingredients that meet the specifications of an *USP* monograph, the agency should recognize in the Guidance that compliance with a compendial monograph will satisfy the requirements for specifications in a notification set forth in VI.A.4 and 5.

Thank you for the opportunity to submit these comments. We submit our comments in the hope that they will help ease FDA's regulatory burden by reducing the need to review every NDI submission, assist industry by avoiding the submission of expensive and time-consuming redundant NDI notifications, and promote consumer access to safe and quality dietary supplements. Please let us know if we can be of any further assistance.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Williams", with a stylized flourish at the end.

Roger L. Williams, M.D.
Chief Executive Officer