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VIA ELECTRONIC SUBMISSION

December 12, 2016

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

Re: Draft Guidance for Industry – Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Docket No. FDA-2011-D-0376
81 Fed. Reg. 53486 (August 12, 2016)

The United States Pharmacopeial Convention, Inc. (USP) appreciates this opportunity to submit comments on FDA's revised Draft Guidance on New Dietary Ingredient (NDI) Notifications and Related Issues (Revised Draft Guidance), issued on August 12, 2016. The following pages summarize USP's role in promoting the safety and quality of dietary supplements, through both the development of public standards and the administration of a robust verification program. In this document, we also provide comments on specific sections of the Revised Draft Guidance, highlighting ways in which USP hopes to serve as a resource to FDA, the industry, and the public in improving and maintaining the safety and integrity of the dietary supplement marketplace.

I. The Role of USP as a Standards-Setting Organization in Ensuring the Quality of Dietary Supplements

USP is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements that are manufactured, distributed, and consumed worldwide. USP's standards and programs are informed by global expertise from industry, academia, and regulatory authorities. USP's headquarters are in Rockville, Maryland, and we have facilities in India, China, Brazil, and Ghana, as well as offices in Switzerland, Indonesia, Nigeria, Ethiopia, and the Philippines.

Founded in 1820 with a public health mission, USP has direct experience in facilitating activities and programs that improve the safety and quality of dietary supplements in the United States. Specific to this sector, we discuss the role that USP has played in: (1) the establishment of science-based public quality standards for dietary supplements and dietary ingredients; and (2) the establishment of a verification program that helps manufacturers and distributors ensure and communicate the quality and purity of their products.

A. Development of Public Standards for Dietary Supplements & Dietary Ingredients

The enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA) and FDA's promulgation of good manufacturing practice (GMP) regulations for dietary

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supplements represented significant developments in the industry. Under DSHEA, USP standards are binding for manufacturers who label their supplements as compliant with USP specifications.[1] Additionally, because USP's science-based specifications aim to help ensure product quality and promote transparency, many parties in the dietary supplement industry voluntarily comply with our standards and use USP monographs as the basis for specifications in their contractual agreements. USP holds the view that broader use of science-based public standards – in combination with GMP compliance – can help ensure the quality and consistency of dietary supplements, as is the case for medicines.[2]

USP develops public standards, known as monographs, for dietary ingredients and dietary supplements that include test procedures and acceptance criteria to ascertain the quality, purity, identity, and strength of monographed articles. The monographs, associated analytical methods, and guidelines for their use are published in the *United States Pharmacopeia–National Formulary* (*USP–NF*), which contains standards for drug substances, excipients, medical devices, and dietary supplements,[3] and in the *Food Chemicals Codex* (*FCC*), which contains standards for food ingredients.[4] USP also publishes the *Dietary Supplements Compendium* (*DSC*), a comprehensive resource for dietary supplement manufacturers and ingredient suppliers. The *DSC* is a compilation of monographs, legal and regulatory excerpts, FDA guidance documents, and reference tools relevant to the dietary supplement supply chain.[5]

USP prioritizes the development of dietary supplement monographs based on market prevalence, knowledge of chemical composition, existence of other pharmacopeial standards, interest from a government body, and potential health risks, among other factors. The admission evaluation process for introducing new dietary supplement monographs into the *USP–NF* involves the analysis of safety information from numerous sources, including adverse event reports from FDA MedWatch. This assessment is conducted for the sole purpose of determining whether or not to develop a *USP–NF* compendial monograph and is not designed to be a determination of the intrinsic safety or efficacy of the ingredient or product under review. Nevertheless, the due diligence involved in the review process is designed to exclude ingredients that present serious risks to health.[6] Thus, USP's admission evaluation shares some objectives with the NDI Notification review process.

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[1] 21 U.S.C. § 343(s)(2)(D).

[2] *See, e.g.,* 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; Sarma N, Giancaspro G, Venema J, Dietary supplements quality analysis tools from the United States Pharmacopeia. *Drug Test. Analysis* 2016; 8(3-4):418-23.

[3] See http://www.usp.org/usp-nf.

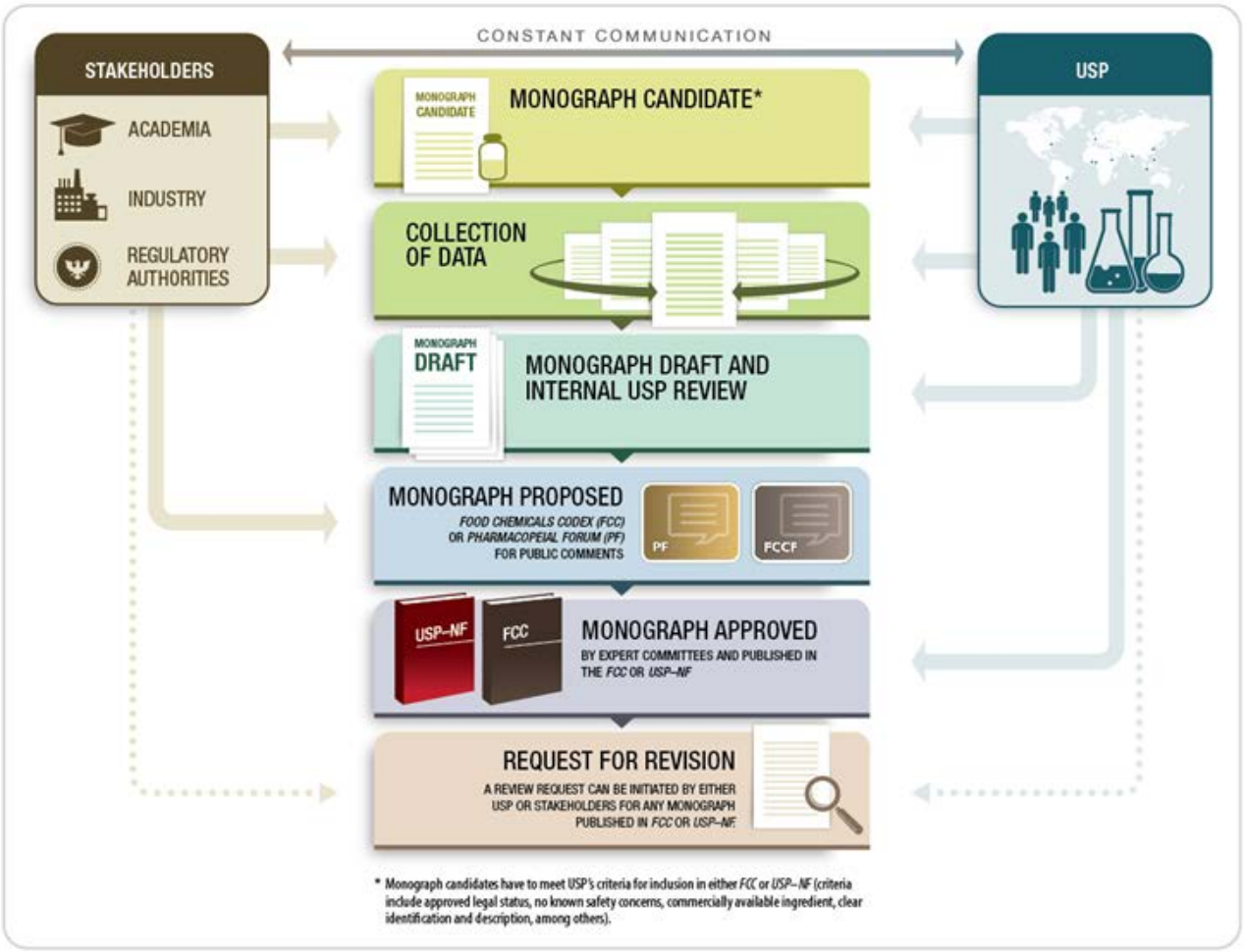
[4] See http://www.usp.org/store/products/food-chemicals-codex-fcc.

[5] See http://www.usp.org/store/products/dietary-supplements-compendium.

[6] For additional detail, see USP Guideline for the Admission of Dietary Supplement Ingredients to the *USP-NF* Monograph Development Process (Effective date 03/30/2016), available at:

To develop public standards, USP works with expert volunteers from a wide cross-section of stakeholders including industry, academia, and regulatory authorities. Monographs are developed after an open and transparent public comment process in which the expert volunteers, assembled into Expert Committees, consider the existing evidence and evaluate comments and feedback from manufacturers, regulators, suppliers, and other interested parties. Ultimately, the goal of this process (shown in Figure 1) is to ensure that the outcome is based on scientific evidence and serves the public health interest.

Figure 1: USP's Monograph Development Process for Dietary Supplements and Dietary Ingredients



In addition to developing monographs, USP leverages its scientific capabilities and its work with expert volunteers to develop broader guidelines that further promote dietary supplement safety. These guidelines are found in USP's General Chapters, which provide

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http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/guideline_for_the_admission_of_dietary_supplement_ingredients_to_the_usp-nf_monograph_development_process_final.pdf.

principles and analytical methods intended to assist the industry and regulators in ensuring the quality and purity of supplements.[7]

To complement the documentary standards, USP also develops and offers Reference Standards for dietary supplements and dietary ingredients. Reference Standards are highly characterized substances intended for use in monograph-prescribed analytical procedures in support of established specifications. USP's current catalog contains more than 300 Reference Standards for dietary supplements, e.g., amino acids, botanicals, vitamins, minerals, purified compounds, complex carbohydrates, and fish oils.

B. Dietary Supplement Verification Program

USP also offers and administers an innovative, voluntary Dietary Supplement Verification Program (DSVP), which complements our efforts to promote dietary supplement quality standards.[8] Launched in 2001, the DSVP is intended to help dietary supplement manufacturers meet FDA's GMP requirements as well as USP's additional supplement manufacturing guidelines. The latter include recommendations of particular interest to retailers, such as recall procedures, expiration dates supported by stability data, and identity testing for all – not just dietary – ingredients (codified in General Chapter <2750> *Manufacturing Practices for Dietary Supplements*).

As part of the DSVP offering, USP conducts a rigorous audit – including an on-site inspection – of a supplement manufacturer's operations. USP scrutinizes documentation and examines quality management, facilities and equipment, materials, production, packaging and labeling, and laboratory control. USP also conducts follow-up surveillance auditing and product testing to ensure continuous adherence to high quality standards. Successful verification enables a manufacturer to include the official USP Verified Mark on the labels and labeling of products that have met all requirements of the verification process. To date, more than 100 dietary supplement formulas have received the USP Verified Mark, representing several major brands and retailers.[9]

II. Comments on FDA's Revised Draft Guidance

We appreciate FDA's issuance of the Revised Draft Guidance. Our comments are intended to highlight specific areas in which USP can offer support and assistance to the Agency and to the industry in the promotion of dietary supplement and dietary ingredient quality. We address these points in turn below.

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[7] *See* Section II.A. of these comments for references to specific General Chapters that may support the dietary supplement industry.
[8] For additional information about the DSVP, see http://www.usp.org/verification-services.
[9] See USP Verified Products Listing, available at: http://www.quality-supplements.org/verified-products/verified-products-listings.

A. Integration of USP Standards into Revised Draft Guidance

USP thanks FDA for recognizing the role that public standards can play in the NDI Notification process. Specifically, FDA cites the following three USP General Chapters in its example of a specification sheet or table for a dietary ingredient:

- <61> *Microbial Examination of Nonsterile Products: Microbial Enumeration Tests*: provides a series of tests designed primarily to determine whether a substance or preparation complies with an established specification for microbiological quality.
- <791> *pH*: provides guidelines for determining the pH of particular substances.
- *USP 30* <231> *Heavy Metals*: provides methods to demonstrate that the content of certain elemental impurities does not exceed the limits specified in individual monographs.[10] Effective January 1, 2018, <231> will be omitted, and all dietary supplements purporting to conform to USP specifications must meet the requirements in <2232> *Elemental Contaminants in Dietary Supplements*.[11] USP continually strives to keep monographs and General Chapters up-to-date, and standards may be omitted, replaced, or modernized over time.

USP's resources encompass significantly more than the three General Chapters highlighted above. Specifically, individual monographs for dietary ingredients include:

- An identity specification for each component;
- Component specifications necessary to ensure that specifications for the quality, purity, strength, and composition of dietary supplements manufactured with those components are met; and
- Limits on contaminants that may adulterate or may lead to adulteration of the finished product.

Also within USP's compendia, the following General Chapters may be particularly useful, as some of them are specific to dietary ingredients or dietary supplements:

- <467> *Residual Solvents*: provides guidelines detailing acceptable amounts of residual solvents in products intended for human consumption.
- <561> *Articles of Botanical Origin*: describes sampling procedures intended to reduce the effect of sampling bias on qualitative and quantitative results when analyzing botanical constituents.
- <563> *Identification of Articles of Botanical Origin*: provides guidelines for establishing the identity of botanical ingredients using orthogonal methods including macroscopic, microscopic, chromatographic, and DNA methods.

[10] See Revised Draft Guidance, at page 58 (Section VI.A.5, Table 2).
[11] Some individual monographs for dietary ingredients will continue to specify limits for elemental contaminants using more up-to-date analytical procedures as described in <233> *Elemental Impurities—Procedures*.

- <565> *Botanical Extracts*: describes principles of extraction for articles of botanical origin.
- <2021> *Microbial Enumeration Tests—Nutritional and Dietary Supplements*: describes tests for estimating the number of viable aerobic microorganisms present in nutritional supplements, from raw materials to finished products.
- **<**2022> *Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements*: provides tests for specific microorganisms, as specified in individual monographs or whose absence from nonsterile nutritional and dietary products is recommended in General Chapter <2023> (described immediately below).
- <2023> *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements*: describes guidelines for establishing Good Manufacturing Practices for microbiological specifications, including microbiological process control, control of the bioburden of raw materials, and control of the manufacturing process.
- <2030> *Supplemental Information for Articles of Botanical Origin*: provides additional information about several aspects of botanical articles, including optimization of pre-harvest conditions for appropriate growth and post-harvest handling to achieve consistent quality with minimum variations in the composition of chemical constituents.
- <2040> *Disintegration and Dissolution of Dietary Supplements*: provides quality-control tools to assess performance characteristics of dietary supplement finished dosage forms.
- <2251> *Screening for Undeclared Drugs and Drug Analogues*: describes analytical methodologies for screening dietary supplements to detect adulteration with synthetically derived pharmaceutical active principles.
- <2750> *Manufacturing Practices for Dietary Supplements*: provides overarching guidance that complements FDA's GMP requirements to address quality control in dietary supplement manufacturing.

Beyond the context of NDI Notifications, USP standards can play a meaningful role in establishing the identity of any dietary ingredient for which a USP monograph exists. In the Revised Draft Guidance, FDA clarifies that an NDI Notification is not required for an NDI that: (1) is a direct food ingredient or approved food additive; (2) has been used in conventional foods; and (3) is to be used as a dietary ingredient without chemical alteration.[12] Because this exemption can result in the marketing of NDIs without notification to FDA – and in some cases, these substances may be fairly novel candidates even in the conventional food supply – USP would like to explore further with the Agency the public health significance that a compendial quality standard may have in these cases to help ensure the identity and purity of such materials. As a specific resource, *FCC* monographs and analytical methods – some of which cover ingredients that are

[12] See Revised Draft Guidance, at page 23 (Section IV.B.2). *See also* 21 U.S.C. § 350b(a)(1).

"generally recognized as safe" (GRAS) or that are approved food additives – may play a role in helping to ensure the safety and quality of dietary ingredients initially marketed as conventional foods.

To the extent that it is helpful, we encourage the Agency, industry, and other stakeholders to consider further and more specific integration of USP standards and similar globally recognized standards into current practice, and we stand ready to assist those who would like to do so.

B. The Role of USP Monographs in Assessing the Significance of Manufacturing Changes

USP appreciates FDA's view that changes in the manufacturing process must be assessed to determine the appropriate regulatory classification of a dietary ingredient. In the Revised Draft Guidance, FDA indicates that certain changes to the manufacturing process for a dietary ingredient marketed in the U.S. prior to October 15, 1994 – i.e., an "old" dietary ingredient – may convert that substance into an NDI.[13] Specifically, FDA states that "[a]ny changes in [the] manufacturing process that alter the identity of the ingredient will convert a previously marketed dietary ingredient into an NDI."[14] An exhaustive assessment of various manufacturing techniques and their potential impact on dietary ingredients is beyond the scope of these comments. However, we wish to highlight the potential utility of compendial specifications in assessing the relevance of manufacturing changes with respect to dietary ingredients for which USP monographs exist.

As indicated above, USP monographs include detailed criteria related to the identity of a particular dietary ingredient, including component specifications and limits on contaminants or impurities. From a scientific standpoint, this means that dietary ingredients that meet USP monograph specifications should be considered substantially equivalent, regardless of manufacturing method. Even where an "old" dietary ingredient is manufactured using a "new" method – i.e., a manufacturing method different from those used to produce the same ingredient prior to October 15, 1994 – USP monograph compliance may provide evidence, where applicable, that the change in the manufacturing method does not "alter the identity of the ingredient" in a manner that converts it to an NDI. This concept also applies to NDIs that are the subject of successful Notifications to FDA. Compliance with an existing USP monograph provides evidence that the dietary ingredient conserves its identity regardless of its method of manufacture or who manufactures it—subsequent NDI Notifications would not be needed.

C. The Role of USP Monographs in Assessing the Impact of Chemical Alteration

We appreciate FDA's desire to provide guidance on which processes result in "chemical alteration" of articles of food present in the food supply. In the Revised Draft Guidance, FDA clarifies its views on the types of processes that the Agency is likely to view as

[13] See *id.* at pages 20-21 (Section IV.A.12).
[14] *Id.* at 21 (underlined emphasis added).

producing chemical alteration of an article of food present in the food supply.[15] FDA also lists the "[u]se of solvents other than water or aqueous ethanol to make an extract or tincture" among its examples of processes that are likely to result in chemical alteration and affect the safety profile of a dietary ingredient.[16] We appreciate the Agency's concern that certain processes may produce chemical alteration capable of affecting the safety of a dietary ingredient. However, the use of solvents other than water or aqueous ethanol to make extracts or tinctures does not necessarily result in chemical alteration. Conversely, water extraction is not always solely a "physical step," as extraction with hot water or steam may induce more hydrolytic reactions than extraction with an aprotic solvent such as hexane or supercritical CO_2. For reasons such as this, it is difficult to set broadly applicable guidelines outlining processes that would always result in chemical alterations of significance to FDA, i.e., alterations that adversely affect the safety profile of a substance when manufactured using an alternative method.

USP's view is that increased reliance on science-based public standards, such as USP compendial specifications, can help alleviate this concern while eliminating the need to scrutinize individual manufacturing processes. USP monographs for dietary ingredients establish the identity of such substances with respect to the criteria relevant to safety and public health, such as quality and purity. Monographs for botanical extracts also require compliance with limits for residual solvents as specified in General Chapter <467> *Residual Solvents*. Thus, to the extent that a dietary ingredient – such as a botanical ingredient extracted with the use of supercritical CO_2 – complies with the applicable monograph, FDA and the industry can have confidence that a modification that may result from a process change does not result in a "chemical alteration" that affects the article's safety profile when compared to its "chemically unaltered" counterpart in the food supply. We encourage FDA to adopt a broader and more flexible interpretation of the concept of "chemical alteration" that will permit the industry, where applicable, to use USP monographs or similar globally acknowledged public standards to conclude that a substance is substantially equivalent to the article present in the food supply, which is the key determination needed to protect public health.

D. The Value of USP Monographs for Synthetic Botanicals

We understand FDA's views regarding the positioning of synthetic botanicals as dietary ingredients. We defer to FDA's interpretation of the relevant legal provisions. From a scientific standpoint, we encourage the Agency to consider the value that USP and similar globally acknowledged public standards can provide in ensuring that nature-derived and synthetic botanicals have common specifications and standards for safety and purity. To the extent that FDA's position may be influenced by concerns that synthetic botanicals may have different safety profiles than botanicals derived from nature, USP and other globally acknowledged compendial standards can play a role in promoting parity across sources. Where a USP monograph exists, it serves as a benchmark for quality and purity that applies generally to the substance, regardless of whether it has been naturally derived or synthesized.

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[15] See *id.* at pages 25-28 (Section IV.B.4-5).
[16] *Id.* at 25.

E. The Role of USP Monographs in Reducing the NDI Notification Burden, Increasing Transparency, and Promoting Public Health

FDA indicates that as part of the NDI Notification process, the Agency will permit the submission of a confidential "master file" containing "manufacturing, specifications, and other identity information needed to completely describe the ingredient."[17] The submitter of the master file could then authorize other firms to reference the contents of the master file in subsequent Notifications. FDA notes its expectations that submitters will consider the contents of NDI master files and ingredient specifications to be trade secrets and thus will only discuss these data with the submitting firm.

We encourage the Agency to recognize that the existence of USP standards and similarly well-known and accepted standards may help alleviate the NDI Notification burden, as downstream submitters can easily reference public standards as the basis for identity criteria. Insofar as a dietary ingredient is described by an applicable USP (or similar globally accepted) monograph, we encourage FDA to view this as an opportunity to reduce regulatory review burden and avoid potentially unnecessary requests of the Agency. As part of USP's ongoing education and outreach efforts toward industry stakeholders, we will encourage the continued submission of candidates for USP monograph development in the dietary supplement sector. In our view, all parties will share the public health benefits and administrative simplicity of relying on readily available, transparent public standards to supply the necessary identity specifications for NDIs.

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We thank FDA for the opportunity to submit comments on the Revised Draft Guidance. We hope that these comments serve as a helpful resource to the Agency and to the industry and that they help clarify the role that USP and its compendial resources can play in promoting the safety and quality of dietary supplements.

We hope to work collaboratively with FDA and with the industry in this area, and we stand ready to provide any additional information that may be helpful to the Agency as you consider additional stakeholder comments and work to finalize the Revised Draft Guidance. Please feel free to contact Gabriel Giancaspro, Ph.D., Vice President, Science—Dietary Supplements and Herbal Medicines, at (301) 816-8343 or gig@usp.org with any inquiries related to these comments or to USP's efforts in the dietary supplement area.

Sincerely yours,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer

[17] *Id.* at pages 28-29 (Section IV.C.1).