

VIA ELECTRONIC SUBMISSION

December 4, 2017

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

**Re: Development of a List of Pre-Dietary Supplement Health and Education Act Dietary Ingredients; Public Meeting; Request for Comments; Docket No. FDA-2017-N-4625
82 Fed. Reg. 42098 (Sept. 6, 2017)**

The United States Pharmacopeial Convention, Inc. (USP) welcomes this opportunity to submit comments on FDA's planned development of a list of pre-Dietary Supplement Health and Education Act ingredients (pre-DSHEA list). An authoritative list of pre-DSHEA ingredients, as proposed by FDA, which provides clarity with respect to the regulatory status of dietary ingredients used or intended for use in dietary supplements, could prove helpful to industry and other stakeholders.

In comments previously submitted to FDA, we described our role as a standards-setting organization in advancing the quality of dietary supplements.¹ USP develops public quality standards through an open, collaborative process with public participation and input from stakeholders including representatives from academia, industry, and government. Particularly relevant to the current topic, USP has a longstanding program of developing identity specifications for dietary ingredients used in dietary supplements.

USP representatives attended FDA's October 3, 2017 public meeting on the development of a pre-DSHEA list, and were pleased to provide brief comments on both meeting topics, namely: (1) the standard of evidence necessary to determine that an ingredient was marketed before October 15, 1994; and (2) issues related to the process that should be used to develop the list. We appreciate your consideration as we reiterate and expand upon our thinking and put forth suggestions for new ways to enhance and expand USP's partnership with FDA. In particular, we describe new ways in which we believe we can be leveraged as a resource to FDA, the industry, and the public in the development of a pre-DSHEA list.

¹ See Attachment A (USP Comments to FDA Re: Draft Guidance for Industry – Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Docket No. FDA-2011-D-0376; 81 Fed.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), submitted December 12, 2016).

We respectfully suggest the following:

- Adopting a flexible, judicious, and defensible approach to the types of documentation that will provide sufficient confidence regarding the marketing status of a particular ingredient.
- The potential utility of public standards in establishing both: (1) the identity of dietary ingredients marketed prior to October 15, 1994; and (2) where such identity is conserved despite post-DSHEA manufacturing process changes.

We elaborate on these points below.

I. Standard of Evidence to Determine Pre-DSHEA Marketing Status

In FDA's "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry" (August 2016) (Revised Draft Guidance), the Agency contemplates two main factors for placing an ingredient on an authoritative pre-DSHEA list: "(1) adequate documentation of marketing for use as or in a dietary supplement in the U.S. before October 15, 1994; and (2) a precise description of the identity of the ingredient marketed. Records offered to support an item's inclusion on the list should specify the date of marketing in the U.S. and clearly identify the ingredient marketed on that date. Documentation of an ingredient's identity should be sufficiently precise to uniquely identify the ingredient."²

With respect to the first factor, the Revised Draft Guidance specifies the following types of documentation to establish that an ingredient is not a new dietary ingredient (NDI): "written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. Examples include sales records, bills of lading, sales contracts, manufacturing records, commercial invoices, magazine advertisements, mail order catalogs, or sales brochures."³ As expressed at the October 3 public meeting, dietary supplement and dietary ingredient manufacturers may face significant challenges in locating the specific types of documentation cited in the Revised Draft Guidance as appropriate evidence for determining pre-DSHEA marketing status. We respectfully recommend FDA adopt a flexible, judicious, and defensible approach that will provide sufficient confidence regarding the marketing status of a particular ingredient, even where that may mean considering alternative forms of documentation, or combinations of sources that, taken together, supply the requisite information about a dietary ingredient's pre-DSHEA marketing status. We also suggest FDA consider the potential utility of product descriptions in scientific literature that pre-dates October 15, 1994. In cases where published study methods reference a specific ingredient that was commercially available to the principal

² Revised Draft Guidance, at IV.A.11 (p. 20).

³ *Id.* at IV.A.9 (pp. 17-18).

investigators/study authors, this should qualify as “adequate documentation” of pre-1994 marketing history.

Regarding the second factor, we agree that a pre-DSHEA list must contain a clear and sufficiently detailed description of the identity of the ingredients included therein. To this end, public standards can prove central to FDA and the industry with respect to establishing both the name and the identity of specific ingredients over time and should include the following:

- A clear, consistent, and scientifically based nonproprietary name for the ingredient;
- 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.

USP has expertise in nomenclature and the development of public quality standards that may prove helpful in the creation of a pre-DSHEA list. The long established approach to linking the official title in the *USP* on the label of a medicine to publicly available quality standards has created a single, consistent, and reliable system proven to benefit public health. USP also has a nomenclature guideline specific for dietary supplements that is consistent with FDA label requirements, and is a fundamental link between the named ingredient and its identity.⁴ An official title and monograph specifications connect the name of the article to a fixed standard of identity and quality. USP’s open, transparent process for creating official titles and public identity standards can help eliminate doubt or confusion regarding which ingredients are included in a pre-DSHEA list.

Relatedly, public standards can help provide clarity on whether changes in manufacturing processes have any impact on the identity of a dietary ingredient that would warrant exclusion from a pre-DSHEA list. For example, because USP monographs include detailed criteria relating to ingredient identification, these could be used as a tool in establishing that dietary ingredients that meet monograph specifications may share the same identity, regardless of manufacturing method. Compensial standards can assist in reducing the regulatory burden by eliminating potentially redundant notifications to FDA by dietary supplement manufacturers in case of the ingredients that are manufactured via different processes but meet the same specifications for quality, purity, identity, and strength. Compensial quality standards also address the

⁴ Guideline for Assigning Titles to *USP* Dietary Supplement Monographs, available at: <http://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-assigning-titles-to-usp-dietary-supplement-monograph.pdf>.

concerns that different manufacturing processes might introduce different impurity profiles, by setting appropriate limits for impurities through USP's flexible monograph approach. Thus, where a pre-DSHEA dietary ingredient is manufactured using a "new" method – i.e., a method different from those used to produce the same ingredient prior to October 15, 1994 – conformance to a public standard may provide evidence that the change in the manufacturing method does not "alter the identity of the ingredient" in a manner that converts it to an NDI. We urge FDA to consider clarifying that ingredients retain their pre-DSHEA status if they continue to conform to established identity specifications that characterized the pre-DSHEA product, even if the production process has changed since October 15, 1994.

II. Process for Developing Pre-DSHEA List

At the October 3 public meeting, many concepts were put forth for FDA to consider for the development of a process to create a pre-DSHEA list, and considerations included topics such as transparency, expertise, certainty, feasibility, and accountability. Furthermore, ideas were presented regarding the possible convening and composition of an expert panel that might vote on ingredients for inclusion, a public comment period during which interested parties could review and comment on panel decisions, and a process that would allow for submitters to protect confidential information provided to support ingredient evaluation. In our public standards setting role, these are issues that USP embraces and administers on a regular basis in the development and publication of compendial standards.

As detailed in our prior comments on the Revised Draft Guidance, USP has significant experience with administering an open, collaborative process to set public quality standards, which include an evaluation of literature from multiple sources to determine the admissibility of dietary ingredients to the compendia.⁵ Many of the same principles and outcomes of our work in the development and publication of our standards could prove useful in the creation of a pre-DSHEA list. Some examples include:

- We recruit and administer the operations of hundreds of independent scientific volunteer experts, organized into Expert Committees and Expert Panels to develop and revise public quality standards.
- We implement strict policies regarding confidentiality and conflict of interest management.
- We have a robust public comment process for publishing proposed *USP-NF* standards in our *Pharmacopeial Forum (PF)*, typically providing a 90-day window during which any interested

⁵ See Guideline for the Admission of Dietary Supplement Ingredients to the *USP-NF* Monograph Development Process (Admission Guideline), available at: <https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-the-admission-of-dietary-supplement-ingredients.pdf>.

parties may provide input for consideration by scientific experts prior to finalization of the standards.

- We revise our public standards as appropriate to keep them up-to-date with the available science and knowledge.

To the extent that FDA would find it beneficial to have USP share more information about our processes – and perhaps to discuss how information USP has developed for certain dietary ingredients in the *USP-NF* could be leveraged in developing a pre-DSHEA list – USP stands ready to participate in such dialogue.

It was reiterated at the October 3 public meeting that parties who may wish to submit information to support an ingredient's inclusion in a pre-DSHEA list likely will seek to preserve the confidentiality of certain documents. As an independent standards-setting organization, USP has established policies and procedures to protect third party confidentiality while facilitating the development and finalization of public standards. Additional details regarding our confidentiality and document disclosure policies are shared as an Attachment to these comments.⁶ FDA and others may find these policies informative in the development and implementation of a system that balances the creation of a public list against the protection of private information.

III. Safety Considerations

USP understands and agrees that the determination of the pre-DSHEA status of a dietary ingredient is a factual inquiry that does not itself implicate safety considerations. Further, the development of a pre-DSHEA list would not alter the existing responsibility of manufacturers and distributors to ensure the safety of the pre-DSHEA dietary ingredients and dietary supplements that they market.⁷ To support the industry in this regard, FDA may wish to consider the development of supporting guidance documents on how safety assessments for dietary ingredients in supplements should be conducted, similar to the guidance the Agency recently has developed to aid in the performance of GRAS evaluations for food ingredients and the use of GRAS panels. We anticipate that FDA will continue a dialogue with industry and other stakeholders to determine the appropriate coverage and positioning of a pre-DSHEA list, as well as any supporting guidance documents that may need to be developed.

Participants at the October 3 public meeting raised questions regarding the potential implications that a pre-DSHEA list might have in terms of

⁶ Attachment B, USP Commitment to Confidentiality.

⁷ 21 USC 342(f)(1)(A) (describing the “significant or unreasonable risk of illness or injury” standard as rendering a dietary ingredient or dietary supplement adulterated); 21 USC 331(a)-(c) (prohibiting the introduction, delivery for introduction, adulteration, or receipt in interstate commerce, of adulterated products).

suggesting or establishing the safety of the listed ingredients. As noted above, before admitting any dietary ingredient available for sale in the U.S. into the *USP-NF*, a subcommittee of independent experts performs a case by case ingredient evaluation. To facilitate this independent review, USP researches and evaluates diverse sources of information that will enable the experts to determine admission into the compendia based on whether the ingredient is associated with a potential serious risk to health from its use in dietary supplements.⁸ History of use information, publically available safety and toxicology studies, and adverse event report data are considered by the expert committee in a weight of evidence evaluation of the data. USP only admits into the *USP-NF* dietary ingredients “for which the available evidence does not indicate a serious risk to health or other public health concern that precludes development of a *USP-NF* monograph and that could be approved for inclusion in the compendia with or without a cautionary label statement.”⁹ USP’s admission evaluation based on the determination of a serious risk to health purposefully differs from an assessment of the “significant or unreasonable risk” and is designed to meet the intended objective for USP, to determine admissibility into the compendium. In the course of this admission evaluation, USP develops ingredient-specific dossiers that we are willing to share with stakeholders.¹⁰

We thank FDA for the opportunity to submit comments on the Agency’s proposed future development of a pre-DSHEA list. We hope that these comments serve as a helpful resource to FDA and to the industry. USP and its compendial resources can have a role in this area, and we welcome the chance to work with stakeholders to advance dietary supplement quality and consumer safety.

We look forward to meeting with FDA representatives responsible for dietary supplements to fully explore and expand upon our shared goals, and to discuss areas where USP might offer resources and capabilities to

⁸ The USP definition of serious risk to health is taken from FDA’s definition of a serious adverse event. “Serious risk to health means that the use of the Ingredients could: (A) result in: (i) death; (ii) a life-threatening experience; (iii) inpatient hospitalization; (iv) a persistent or significant disability or incapacity; or (v) a congenital anomaly or birth defect; or (B) require, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).” USP Admission Guideline, at 2.

⁹ USP Admission Guideline, at 2.

¹⁰ The USP *Dietary Supplements Compendium (DSC)* is a comprehensive resource for dietary supplement manufacturers and ingredient suppliers, including around 500 monographs for botanical and non-botanical dietary ingredients and dietary supplements. The *DSC* also includes summary admission evaluations for some commonly used dietary ingredients. See <http://www.usp.org/products/dietary-supplements-compedium>.

work collaboratively with FDA, the industry, and the general public on the development of a pre-DSHEA list.

For more information, please contact Elizabeth Miller, Pharm.D., Vice President, U.S. Public Policy and Regulatory Affairs, at ehm@usp.org; (240) 221-2064.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J. Venema', written over a light blue horizontal line.

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VIA ELECTRONIC SUBMISSION

December 12, 2016

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**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.

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>.

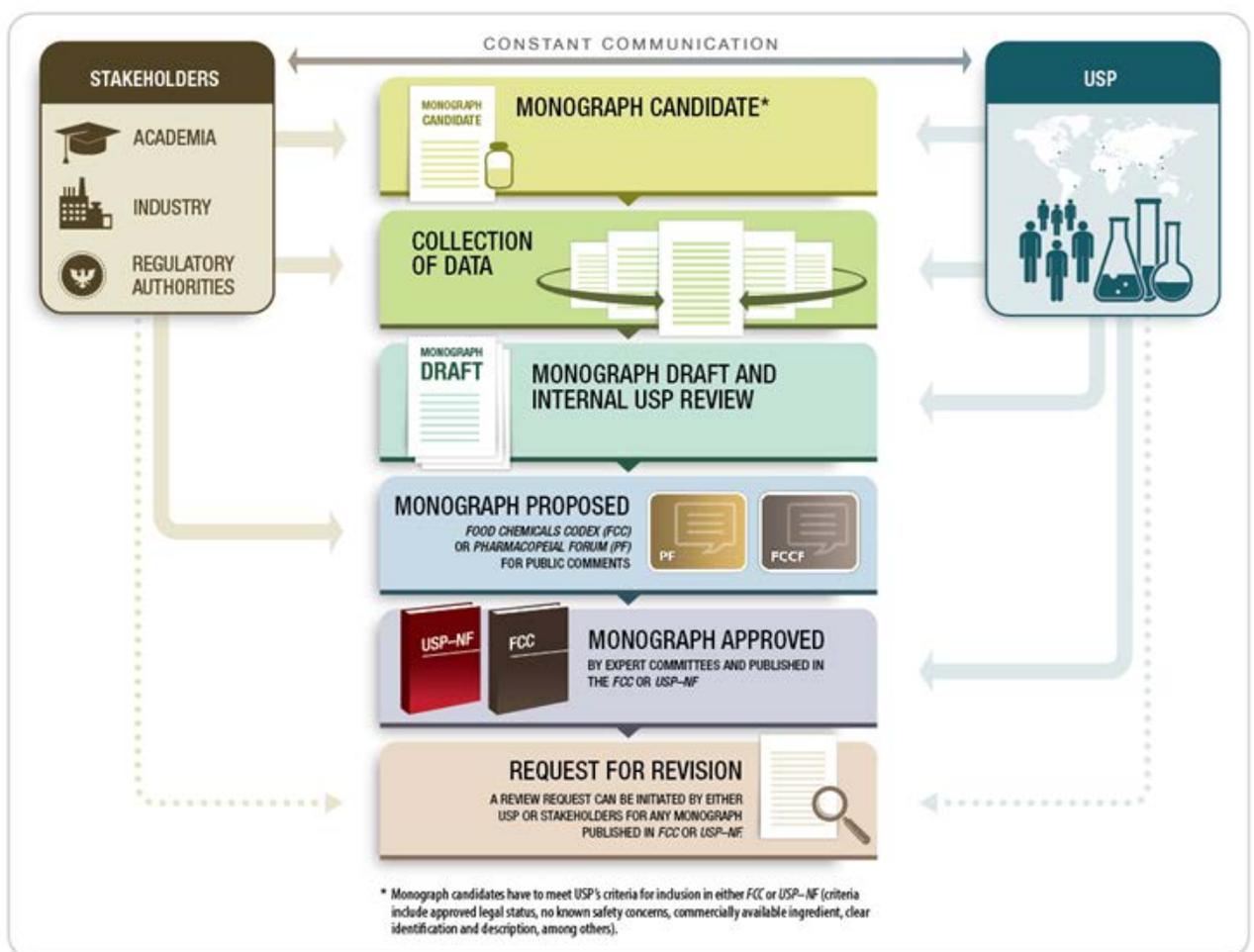
⁴ See <http://www.usp.org/store/products/food-chemicals-codex-fcc>.

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

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.

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 CO₂. 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 CO₂ – 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.

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.

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).

USP Commitment to Confidentiality

USP understands that third parties that seek to collaborate or partner with us possess data that they consider to be proprietary and confidential. As an independent, standards-setting organization with nearly 200 years of working with volunteer experts and various stakeholders, USP has significant experience with the receipt and protection of confidential information.

To address the concerns typically covered in confidentiality agreements, USP has established policies and procedures that provide the highest safeguards to confidential information submitted by third parties. These policies and associated handling procedures represent best practices employed by USP to protect third party confidentiality while facilitating development and finalization of a public standard. Due to these safeguards, USP does not generally enter into confidentiality agreements with individual companies.

USP's overarching organizational policies are found in our [Code of Ethics](#), which applies to our staff and volunteers. These policies reflect our strong commitment to confidentiality and are implemented through specific rules and procedures as described below.

Confidentiality Policy

Our Confidentiality Policy ([USP Code of Ethics, pages 12-13](#)) requires the following individuals to maintain the confidentiality of all information designated as such by a third party:

- USP Board members ([Rules of Business Practice for the 2015-2020 USP Board of Trustees, sec. 2.03](#))
- Volunteer experts, namely:
 - Expert Committee members ([Rules and Procedures of the 2015-2020 Council of Experts, sec. 2.06\(a\) and \(b\)](#))
 - Expert Panel members, where confidentiality is required ([Rules and Procedures of the 2015-2020 Council of Experts, sec. 2.06\(b\), 5.05\(b\)](#))
- Government liaisons¹ ([Rules and Procedures of the 2015-2020 Council of Experts, sec. 6.02](#))
- USP staff (Employee Handbook)

USP Board members, volunteer experts, and government liaisons must sign confidentiality agreements reflecting these obligations and requiring them to safeguard any and all information deemed confidential.

Classification and Handling of Confidential Information

Third party information is presumed confidential unless otherwise indicated by USP staff. USP is a secured facility, and staff use best practices in the secure storage of confidential information on our network. Further, confidential information is clearly marked as such in the limited cases in which such information is shared (e.g., in materials shared with USP expert volunteers). Volunteer experts are required to receive and send any confidential electronic communications from a private email address, not shared with or accessible to their employer

¹ Government liaisons are representatives from the U.S. Food and Drug Administration (FDA) or other federal or state governmental agencies in the U.S., or from government agencies in other countries. They participate in USP's standards-setting process, but do not vote on USP standards.

or any other third party ([Rules and Procedures of the 2015-2020 Council of Experts, sec. 2.06\(a\)](#)).

Document Disclosure Policy

USP protects third party confidential information to the fullest extent permitted by law. USP staff begin every expert meeting by reminding our volunteer experts and government liaisons of their confidentiality obligations. Under our Document Disclosure Policy ([Document Disclosure Policy; Code of Ethics, pages 7-8](#)), we do not release confidential information to requesting parties.

USP's confidentiality policy and procedures do not apply when a third party's information is required to be disclosed by law, regulation, rule, act or order of any governmental authority or agency, such as identifying country of origin on USP reference materials ([USP Guideline for Submitting Requests for Revision to USP-NF General Information for All Submissions, Part C](#)). Nevertheless, we are committed to pursuing reasonable efforts to protect third party confidential information even when faced with a compelled disclosure request.

Intellectual Property Policy

There are many types of data protected by third party intellectual property rights that USP does not need to access for the purpose of developing a public standard. For instance, we rarely need access to information about patented manufacturing technologies or product formulations. Before submitting sensitive information to USP, we recommend working with a USP staff contact to narrow down the data set such that you will not need to disclose any more confidential information than is absolutely necessary to meet the goals of your collaboration or partnership with USP.

Under our Intellectual Property Policy ([USP Guideline for Submitting Requests for Revision to USP-NF General Information for All Submissions, Part C; Code of Ethics, pages 19-20](#)), USP respects intellectual property rights and uses its best efforts to adhere to all applicable laws regarding protection of intellectual property. However, USP is not responsible for the protection or enforcement of intellectual property rights in the U.S. and elsewhere. Additionally, because USP's standards are intended to be public standards available for the use and benefit of all parties, USP requests that third parties disclose whether any portion of the data shared with us is subject to patent or other sponsor-held intellectual property rights.

In cases where patented methods, procedures or materials required for compendial tests and assays are proposed, USP may seek assistance from the sponsor in obtaining clearance or license for use by any persons seeking to use or apply a USP public standard incorporating such method, procedure or material, and may consider other approaches to avoid publishing a public standard that includes material protected by third party intellectual property rights. USP reserves the right to indicate in a resulting public standard whether methods or procedures are subject to third party intellectual property rights.