

December 2, 2016

Steve Cornish
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Re: ISO Proposal for a New Field of Technical Activity – Medicinal Plants

Dear Mr. Cornish:

The United States Pharmacopeial Convention, Inc. (USP) appreciates this opportunity to submit comments on the ISO proposal for a new field of technical activity – Medicinal Plants. From the information provided by ANSI, the draft Scope Statement for the proposed ISO technical activity and the proposed program of work are reproduced below:

Draft Scope Statement for the proposed ISO technical activity:

- Standardization in the field of medicinal plants as well as medicinal plants propagation materials, in particular terminology, sampling, test methods and analysis, product specifications, safety and quality requirements for packaging, storage and transportation. Medicinal plants substances with regard to safety and quality such as content of active material, values for physical, chemical specifications and microbial contaminants, chemical residues and heavy metals etc., must be based on recognized international standards or deliverables and should be laid down in written form.
- Excluded: Excluded are products covered by ISO/TC 54 Essential oils, ISO/TC 245 Traditional Chinese Medicine and ISO/TC 215 Health Informatics.

The proposed program of work is:

1. To establish basic standards such as “Terminology of Medicinal Plants”;
 2. To establish requirements for Medicinal plants (in areas such as hygiene, safety, technical requirements, transportation and storage, packaging, characterization and specification, and quality control);
- Priority will be placed on establishing terminology, classification, cost and productivity standards that will resonate with the market place and provide immediate value to consumers

The following pages: (1) summarize USP’s role in promoting the safety and quality of botanical drugs, dietary supplements, and herbal medicines through the development of public standards; and (2) provide comments specifically on the ISO proposal.

I. The Role of USP as a Standard-Setting Organization in Assuring the Safety and Quality of Botanical Drugs, Dietary Supplements and Herbal Medicines

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 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 botanical drugs, dietary supplements, and herbal medicines in the United States and across the globe. USP standards are used in about 140 countries worldwide, and are often referenced as the basis for the specifications set in contractual agreements between buyers and sellers in international trade.

Since the passage of the Federal Food and Drugs Act of 1906, USP’s drug standards have been incorporated into federal law.¹ Today, the drug adulteration and misbranding provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) require compliance with standards in the *United States Pharmacopeia* and *National Formulary*.² These publications are named as “official compendia” in the law; the previously-separate volumes now exist as a single publication, the *United States Pharmacopeia-National Formulary (USP-NF)*.³

In the dietary supplement sector, 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 supplements represented significant developments in the industry. Under DSHEA, USP standards are binding for manufacturers who label their

¹ Federal Food and Drugs Act of 1906, 34 Stat. 768 §§ 6-7 (1906), repealed by the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 329(a).

² FDCA §§ 501(b), 502(g); 21 U.S.C. §§ 351(b), 352(g).

³ FDCA § 201(j); 21 U.S.C. § 321(j).

supplements as compliant with USP specifications.⁴ Additionally, because USP’s science-based specifications aim to help assure 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.⁵

With respect to botanical drugs, dietary supplements, and herbal medicines, USP works to develop validated, peer-reviewed public standards – called “monographs” – for ingredients and finished products that include tests, procedures, and acceptance criteria to ensure the quality, purity, identity, and strength of such products. To develop monographs, USP works with volunteer experts from a wide cross-section of stakeholders – including the industry, academics, and regulators. Monographs are developed after an open and transparent public consultation process in which volunteer experts – termed “Expert Committees” – consider and evaluate feedback from manufacturers, regulators, suppliers, and any other interested parties. The goal of this transparent and open process is to ensure that science and public health drive the ultimate outcome. Monographs, associated analytical methods, and guidelines for their use are published and updated on a regular basis in the *USP-NF* (which contains standards for drug substances, excipients, medical devices, and dietary supplements)⁶ and in the *Food Chemicals Codex (FCC)* (which contains standards for food ingredients).⁷

To further assist the dietary supplement industry, USP also publishes the *Dietary Supplements Compendium (DSC)*, a comprehensive resource for dietary supplement manufacturers and ingredient suppliers that compiles monographs, legal and regulatory

⁴ FDCA § 403(s)(2)(D). 21 U.S.C. § 343(s)(2)(D).

⁵ 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.

⁶ See <http://www.usp.org/usp-nf>.

⁷ See <http://www.usp.org/store/products/food-chemicals-codex-fcc>.

excerpts, FDA guidance documents, and reference tools relevant to the dietary supplement supply chain.⁸

To assist stakeholders engaged in the production of herbal ingredients for use in herbal medicines, USP publishes the *Herbal Medicines Compendium (HMC)*. The *HMC* is a freely available, online resource that provides standards for herbal ingredients intended for use in herbal medicines worldwide.⁹ Standards are expressed primarily in monographs. *HMC* standards may be adopted or adapted into a national pharmacopoeia or other related compendium. Herbal ingredients eligible for *HMC* standards include those that have been approved by a national authority for use in herbal medicines or are included in a national pharmacopoeia. When coupled with sound registration processes and manufactured according to suitable good manufacturing practices, standards in the *HMC* can become an important part of the safety net that helps ensure access to high-quality herbal medicines.

To complement the production of documentary standards, USP also develops and supplies the industry with Reference Standards for drug and dietary supplement ingredients and finished products. Reference Standards are highly characterized substances intended for use in conducting quality control tests and analytical procedures associated with specifications in established monographs.

II. USP Comments on ISO Proposal

Based on our history and experience, USP provides the following comments regarding the ISO proposal:

a. The Term “Medicinal Plants” Requires Precise Definition to Inform the Scope of the Proposal.

As currently drafted, the ISO proposal does not clearly define the term, “Medicinal Plant.” As you know, botanical preparations are widely used in traditional medical practices around world and are regulated differently according to the national laws.¹⁰ In the United States, botanical products that are represented to cure, mitigate or prevent disease are regulated as

⁸ See <http://www.usp.org/store/products/dietary-supplements-compendium>.

⁹ See <http://hmc.usp.org/>.

¹⁰ WHO. National policy on traditional medicine and regulation of herbal medicines. May 2005. <http://apps.who.int/medicinedocs/pdf/s7916e/s7916e.pdf>

drugs. FDA enforces a rigorous pre-market approval process for such products, requiring demonstration of both safety and efficacy. Dietary supplements are not subject to the same pre-market approval process, but such products may bear only “structure-function” claims, i.e., claims that describe the role of a nutrient or dietary ingredient intended to affect the normal structure or function of the human body. Such claims are distinct from “medicinal” claims, which would render a product subject to regulation as a drug.

To the extent that ISO’s activity is intended to capture products with “medicinal” claims in the United States, such standards will be of limited utility for products that already are subject to stringent safety and efficacy standards, as well as FDA pre-market review. To the extent that ISO’s activity is intended to capture botanically-derived dietary supplement products, it is not appropriate under the U.S. regulatory framework to refer to such products as “Medicinal Plants.”

Because of the distinct and complex regulatory frameworks that may apply to botanically-derived ingredients that are positioned as drugs versus dietary supplements in jurisdictions around the world, we strongly encourage ISO to define the term “Medicinal Plants” with precision, as this will significantly affect the Scope of the technical activity envisioned.

b. ISO Should Seek to Avoid Redundancy in Performing the Technical Activity.

As you are aware, standards and monographs for botanicals that are widely used in various traditional systems are available from several international organizations. For example, *USP-NF*, *HMC*, American Herbal Pharmacopeia, British Pharmacopoeia, European Pharmacopoeia, Indian Pharmacopoeia, *Ayurvedic* Pharmacopoeia of India, and Chinese Pharmacopoeia all have monographs for botanical drugs, dietary supplements, and traditional medicine. The ISO proposal does not clearly indicate that the group plans to conduct an assessment of existing, well-established resources relevant to “Medicinal Plants.” To promote effective use of resources and to eliminate redundancy, we suggest that such an assessment be performed prior to commencing the technical activity.

c. The Technical Activity Should be Premised on Scientific Rigor.

If the ISO proposal is to be adopted, serious consideration must be given to the need to ensure scientific validity of the proposed analytical methods. Assuming for the moment that “Medicinal Plants” is defined to refer to botanical supplements, the dietary supplement GMP

regulations in the United States define *Quality* to mean that “the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants.”¹¹ These regulations also stipulate that the analytical methods be scientifically valid and the methods be established as appropriate for their intended use.¹² Relevant analytical attributes such as specificity, precision, accuracy, robustness, limit of quantitation, linearity, and range should be established for the methods that may be proposed from the activity. Additional information on the validation of analytical methods is provided in USP General Chapter <1225> *Validation of Compendial Procedures*, and the International Conference on Harmonization (ICH) document, *Validation of Analytical Procedures*.

As currently drafted, the proposal does not make clear how the technical activity will be designed to ensure that scientific rigor drives the development of standards. Without this key element present, the utility of the resulting standards may be significantly limited in the global regulatory environment.

We thank ANSI for the opportunity to comment on the ISO proposal. We hope that the above comments are helpful to you. Please feel free to contact Gabriel Giancaspro, Ph.D., Vice President, Science—Dietary Supplements, and Herbal Medicines, at gig@usp.org or (301) 816-8343 with any inquiries related to these comments.

Sincerely,



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¹¹ 21 C.F.R. § 111.3.

¹² 21 C.F.R. § 111.75(h)(1).