U.S. Pharmacopeial Convention

October 16, 2015

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Also submitted electronically to http:/www.regulations.gov

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

Subject: Comments of USP on Botanical Drug Development Draft Guidance for Industry, Docket Number FDA-2000-D-0103

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to provide comments to Food and Drug Administration (FDA) on Botanical Drug Development Draft Guidance for Industry.

USP is an independent, science-based, non-profit organization that throughout nearly 200-year history has worked to help ensure patients receive high-quality, safe and effective medicines. USP achieves this through our legally recognized role in setting public standards for the purity, quality, strength, packaging and labeling of drugs, including botanical drugs.

USP supports FDA's efforts to provide draft guidance on botanical drug development. In support of this effort, USP is submitting specific comments. USP highlights two of the comments that are elaborated below in more detail. First, USP has a statutory role in the naming of drug substances including botanical drugs. Second, if available, compendial methods and acceptance criteria should be referenced in the draft guidance to help ensure the quality of botanical drugs.

USP submits the following specific comments:

Line 47. USP seeks clarification on what constitutes a "plant material" in the draft guidance. It is not clear if the term is limited to plant parts, plant products like oils, resins, latexes, gums, or what degree of processing of the plant that is acceptable for the term. This clarification could be incorporated in a form of a glossary along with other term definitions pertaining to this guideline. USP suggests adoption of the following definitions in the draft guidance:

"Plant materials": include the whole plant or a specific part of the plant (e.g., leaf, fruiting body, root, stem bark, etc.).

"Plant products": substances produced naturally by a plant or plant part that do not require extensive processing to be obtained, such as gums, latex, resins, etc.

"Plant processed forms": include plant powders, dry extracts, dry juices, liquid articles and fractions but do not include isolated pure compounds.

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Line 64. Add " of plant material" following the word "fermentation". If fermentation is not limited to microorganisms grown on botanical raw materials, the guideline may be understood to be applicable to all fermentation products, even those derived from synthetic fermentation broths.

Line 109-113. Change "Considering the complexity of botanical drugs, there are challenges to this approach. Interested parties (e.g.: a botanical drug manufacturer)..." to "Interested parties (e.g.: a botanical drug manufacturer) should contact USP for guidance about submission of compendial monograph proposals, and the Division of Non Prescription Drug Products..." It is not clear why FDA is indicating in Lines 109-110 that "there are challenges in that approach." FDA should recommend that the requester contact USP for guidance if a proposal for a USP-NF monograph is required by 21 CFR 330.10(a)(2). USP Expert Committees have the necessary expertise and are capable of handling the complexities related to botanical drugs and compendial monograph development.

Line 129. Suggest adding the following note with regard to agricultural practice and collection: Although GAP should be followed, and controls on GAPs should be reported, it should not be understood that a unique set of GAP controls is a necessary condition to achieve consistency in batch-to-batch production. Variations on GAPs could be possible and consistency could be achieved by controlling and adjusting the processing of the material after harvesting (drying conditions, extraction conditions, standardization) as controlled by the Quality Control tests.

Line 132. Throughout the draft guidance (for example, Lines 174, 218 and 242): Change the term "chemical constituents" to "otherwise characteristic constituents" or just "constituents". Although the constituents of a plant material may have a well-defined chemical structure, this may not be always the case, and the word "chemical" may have a synthetic connotation not intended as part of this guideline.

Line 136. Delete the words "mechanism of". Mechanism of action is often unknown or very complex, involving the effect of different constituents on several bio-pathways in complex animal models. Enzymatic interactions, metabolism, absorption effects may further opaque the true mechanism of action. USP's suggestion is to keep only the intended final ***action*** on the bioassays, even when the mechanism is not fully understood.

Line 189. Delete "chemistry, manufacturing, and controls (CMC) or " We believe that dietary supplements legally in the market are required to be in compliance with the current GMPs for dietary supplements, which require manufacturers to set specifications for identity, purity, and strength. Therefore, chemistry, manufacturing and controls are already in use and the mere fact that the botanical has been in the market as a dietary supplement should not be a reason to require less CMC when a drug application is initiated with FDA. Moreover, we believe that if a compendial monograph for a botanical dietary supplement has been established, the minimum specifications for chemical controls set a forth in the compendia should be taken into account. Therefore we also recommend including the following sentence after the period in Line 191: "If a compendial monograph for a botanical dietary supplement has been

established, the minimum specifications for chemical controls set a forth in the compendial monograph should be taken into account."

Line 213. Add the following before the colon: "including minimum information to establish the traceability of the quality from phase to phase. At a minimum, information that relates to the quality of the botanical throughout the different phases of study should be consistent for the product in order to validate the findings in the IND phase as applicable to subsequent phases."

Line 225. Change "botanist who described" to "botanist or botanists currently recognized as the authority for" Many botanists have described the species over the years and sometimes more than one author is associated with a particular Latin binomial.

Lines 243-244. Change "(e.g.: those...") to "as present in the plant material, especially those that can be used as a characteristic profile for identification and quality control purposes" and delete parenthesis. .

Line 299. Delete "organoleptic." Organoleptic examination is a very subjective and weak test for authentication and should not be recommended for safety reasons.

Line 300. After examination." add the following sentence: "DNA methods may be suitable at this stage, as indicated in the USP general chapter <563> *Identification of Articles of Botanical Origin*."

Line 382. Add: "If available, compendial methods and acceptance criteria should be used to ensure minimum quality of the material." We believe that the use of public official compendial standards would help ensure a minimum level of quality.

Line 422. Standardized methods for detecting viruses capable of causing food-borne, or in this case, botanical drug-borne diseases, are not widely available, other than ISO/TS 15216-1:2013 and ISO/TS 15216-2:2013 for Hepatitis A and Norovirus. FDA may want to reference these tests in the guidance.

Line 426. USP recommends that FDA reference ICH Q1A(R2) Stability Testing in the draft guidance.

Lines 464-472. Delete entire sentences. Replace with: "In some cases may be permissible to standardize levels of active constituents in a botanical drug product to achieve batch-to-batch consistency in the therapeutic effect. In general, this approach would only be appropriate in situations in which the active constituents in the drug substance are known and there is a substantial natural variation in the concentrations of these active constituents in the botanical raw material (e.g., due to changes in growing conditions over time that cannot be controlled). In such cases, Standardization to a consistent level of constituents may be achieved by mixing different batches of plant materials with different strengths or content of certain constituents, provided that the different batches all meet the criteria for identity or by the addition of excipients" USP recommends that the practice of adding active constituents or other markers be avoided as the addition of these substances is regarded as a form of adulteration, even in cases where the active constituents are known. The practice of standardization through mixing different batches o addition of

excipients is also adopted in the European Pharmacopeia (see European Pharmacopeia Information Chapter 5.23. Monographs on Herbal Drug Extracts).

Line 617. After "substances." Insert the following sentence: "If available, compendial methods to determine this variability should be used. Variability should include measurements of dosage form performance, such as dissolution testing, disintegration, content uniformity, etc., that help to ensure batch to batch consistency as related to potential issues of inconsistent bioavailability."

Line 668. After "below." insert the following sentence: "If available, use of compendial methods and acceptance criteria should be encouraged for the parameters listed below."

Line 941. After "study." insert the following sentence: "If available, compendial methods and acceptance criteria are encouraged to ensure minimum standards of quality."

Line 948. Comment: Information on geographical location should be provided but should not constitute basis for identity of the material. A species grown in a location different from the one submitted in an NDA could meet all identity, strength, and purity specifications and also have an indistinguishable safety and efficacy profile, once adequate post harvesting treatment has been performed.

Line 953. Add: "DNA methods may be also useful at earlier phases. The USP General Chapter <563> *Identification of Articles of Botanical Origin*" may be used as guidance.

Line 980. If available, compendial identification tests and acceptance criteria should be used.

Line 1015. Change "linearity" to "strength-response correlation." Linearity of response in bioassays is rarely accomplished. Typically sigmoid curves or log responses are evident.

Line 1028. Insert after "class.": "If available, compendial specifications are should be used."

Line 1032. Insert after "constituent," the following: ",and the total amount of multiple constituents in the same class." In addition to individual components, the total content of a class of compounds may be relevant."

Lines 1064-1073. We believe the information in the Naming Consideration section of the draft guidance including footnote 39 is not accurate. USP has long-standing recognition in U.S. law in establishing the names of drugs, including botanical drugs, pursuant to Section 502(e)(3) of the Federal Food, Drug and Cosmetic Act ("the Act") and 21 CFR § 299.4. Under the Act, if an article is compliant with the current *USP-NF* monograph (e.g., meets the identity, purity, or strength specifications of the monograph) then it must use the established name in the *USP-NF* and adhere to the compendial quality standards. The USAN Council's ability to designate an established name of a

drug is primarily undertaken only when the article is not recognized in the *USP-NF* and has not been given a nonproprietary name by the appropriate USP Expert Committee. There is no legal basis either under the Act or 21 CFR § 299.4 for the USAN Council to supersede USP's authority to designate an established name for a botanical drug when the drug is compliant with a current *USP-NF* monograph with regard to identity, purity, and strength.

In practice, the naming system is a very collaborative effort. USP along with the American Medical Association, the American Pharmacists Association are organizations that comprise the USAN Council. FDA is also a participant in the USAN Council naming system. The USAN Council process starts early in the drug development process (prior to FDA approval) when manufacturers seek an approved name for a drug substance.[1] The USAN Council chooses each U.S. Adopted Name with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official USP-NF.[2] Decisions reached by the USAN Council are unanimous and the results have been continually published by USP since 1963 in the *USP Dictionary of USAN and International Drug Names*.[3] As USP develops a monograph for an approved product and creates an official title, it will generally align with the USAN Council's nonproprietary name for the drug substance as USP is active in establishing this name as part of the USAN Council and shares a similar scientific approach.

Line 1127. Insert after "health.": "Compendial quality control methods for performance (dissolution, disintegration, etc.) should be applied to monitor batch to batch consistency that may impact on the ability of the dosage form to release the content for absorption or local action, thus impacting also on the bioavailability of the constituents from the botanical ingredient.

Thank you for your consideration of these comments. If I can be of further assistance, please feel free to contact me at (301) 816–8343 or gig@usp.org.

Sincerely,

Gabriel Giancaspro, Ph.D.
Vice President , Dietary Supplements and Herbal Medicines

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[1] *See, Preface, Role of Nonproprietary Names-Federal Law and USP, USP Dictionary of USAN and International Drug Names* (2015).
http://www.uspusan.com/usan/pub/index1.html for information on USAN Council naming procedures.

[2] *See, Preface, USAN Program, USP Dictionary of USAN and International Drug Names* (2015).
http://www.uspusan.com/usan/pub/index1.html

[3] The USAN Council also works with the World Health Organization (WHO) to coordinate and harmonize to the extent feasible, with WHO's International Nonproprietary Names (INN).