March 30, 2021

Assembly Member Cecilia M. Aguiar-Curry
Room 5144
State Capitol
1303 Tenth Street
Sacramento, CA 95814

Senator Ben Allen
Room 4076
State Capitol
1303 Tenth Street
Sacramento, CA 95814

Re: California Assembly Bill AB-45 and Senate Bill SB-235 "Industrial hemp products"

Dear Assembly Member Aguiar-Curry and Senator Allen,

On behalf of the United States Pharmacopeia (USP), we urge you to consider highlighting the need for quality specifications as part of the regulatory framework for California Assembly Bill AB-45 and Senate Bill SB-235, "Industrial hemp products."

USP is an independent, scientific, nonprofit public health organization devoted to improving global public health through the development of public standards and related programs that help ensure the quality, safety, and benefit of medicines, dietary supplements, and foods.[1] We are governed by the USP Convention, comprising over 450 academic institutions, healthcare practitioner organizations, industry groups and government representatives, including many U.S. Schools of Medicine and Pharmacies from California[2] and the California Medical and Pharmacists Associations.[3]

USP develops public quality standards for medicines, food ingredients, and dietary supplements through an open, transparent process, with participation from academia, healthcare, industry, and government. One of USP's areas of expertise and focus is the development of standards for articles of botanical origin, including analytical procedures and acceptance criteria to help ensure their identity, purity, and strength.

With respect to the national legal and regulatory status of cannabis and cannabis-derived compounds, USP defers to the federal government, including the U.S. Food and Drug Administration (FDA), and other applicable government authorities. At the same time, from our interactions with various stakeholders, including state regulators, throughout the last several years, we have learned of the critical and growing need for scientific articulation of quality attributes for cannabis, hemp, and related products to help protect patients and consumers from harm.

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[1] USP publishes two legally recognized Official Compendia of the United States, combined into a single publication, the *United States Pharmacopeia-National Formulary (USP-NF)*. We also publish a compendium of food ingredient standards, the Food Chemicals Codex (*FCC*).

[2] These Convention members include Keck School of Medicine of University of Southern California, University of California Davis School of Medicine, University of California San Francisco School of Medicine, Touro University California College of Pharmacy, University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Francisco School of Pharmacy, and University of Southern California School of Pharmacy.

[3] For additional information, *see* https://www.usp.org/200-anniversary.

To that end, we urge you to consider within Assembly Bill AB-45 and Senate Bill SB-235, appropriate direction to help ensure that products produced and sold under this pathway meet quality specifications. Outlined in the attachment below are attributes and considerations to help ensure quality in hemp products. In particular, our comments provide information on relevant USP standards and guidelines to establish appropriate nomenclature, identity, tests for cannabinoid content, and limits on contaminants. We believe that USP perspectives regarding quality considerations for hemp complement the testing requirements for contaminant levels in cannabis under Section 26100 of the Business and Professions Code, as referred to in AB-45 and SB-235.

Thank you for the opportunity to present our perspectives on the importance of quality in hemp products and how USP approaches can help ensure the quality of these products. We welcome the opportunity to discuss these issues in more detail at your convenience. Please feel free to contact me at 202-239-4136 or cxh@usp.org.

Sincerely,

Carrie A. Harney, J.D.
Senior Director, U.S. Government and Regulatory Affairs

Attachment

I. Essential Quality Attributes for Hemp

Clearly articulated quality specifications for products help prevent harm to patients and consumers; among other things, they help limit exposure to toxic substances, pathogenic microorganisms, and harmful additives. As regulatory bodies are developing product quality specifications for hemp and hemp-derived compounds, we recommend that they consider certain USP guidelines and standards (e.g., documentary standards and reference standards).[4] We have elaborated on these considerations in our comments to FDA and the United States Department of Agriculture (USDA).[5]

For botanically derived products, such as those including hemp and hemp-derived compounds, quality attributes should include appropriate analytical procedures and acceptance criteria to define identity, strength, purity, constituents, and limits for contaminants, such as pesticide residues, microbial load, aflatoxin levels, and elemental contaminants, based on reliable scientific information.

A. Identity and Nomenclature

The genus *Cannabis* includes several species, subspecies, varieties, and chemotypes. Analysis of large data sets has shown that the prevalent chemotypes of cannabis are genetically evolved to produce predominantly one or more of the cannabinoids. Several varieties of hemp, ranging from fiber-type to those that are bred for cannabinoid content, meet the regulatory definition of hemp,[6] but contain differing levels of cannabinoids and are labeled by several common names. The use of orthogonal analytical procedures and acceptance criteria can help identify and to differentiate the different cultivars of cannabis.

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[4] Documentary and reference standards help to assess the quality, strength, identity, and purity of chemical medicines, biologics, food chemicals and ingredients, and dietary supplements, among other items. Documentary standards are published in the *USP-NF* or *FCC*. Physical reference standards are highly characterized ingredients, developed in alignment with the specifications outlined in the *USP–NF* or *FCC*. They are used in conjunction with these documentary standards to verify that the product and its ingredients can pass tests to ensure adherence to quality specifications.

[5] We incorporate by reference the following USP comments: FDA docket on "Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds," dated July 5, 2019, at https://www.regulations.gov/document?D=FDA-2019-N-1482-3122; USDA interim final rule on "Establishment of a Domestic Hemp Production Program," dated December 19, 2019, at https://www.regulations.gov/document?D=AMS-SC-19-0042-1518; FDA draft guidance on "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research," dated Sept. 17, 2020, at https://www.regulations.gov/document?D=FDA-2020-D-1079-0029.

[6] The Agriculture Improvement Act of 2018, or the "Farm Bill," defined hemp as the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis. *See also,* 7 CFR 990.1, for definitions of hemp and marijuana. Marijuana remains classified as a Schedule I controlled substance regulated by the Drug Enforcement Administration (DEA) under the Controlled Substances Act.

Examples such as secondary metabolite profiles, DNA-based methods, and microscopic and chromatographic tests can be useful for the identification of cannabis and for differentiation of hemp from other cannabis varieties. USP General Chapter[7] <563> *Identification of Articles of Botanical Origin* includes general considerations and recommendations regarding morphological, chromatographic, and genomic methods for establishing botanical identification and could be a useful resource for regulatory agencies.

Identity of hemp and hemp-derived products should be linked with clear nomenclature, including reference to plant part, product, and/or herbal preparation. USP believes that more guidance is needed on adequate descriptions and appropriate nomenclature to describe hemp and hemp-derived compounds, including its extracts. This is due to the extensive and varied approaches to the naming of hemp varieties ("strains") and its derived extracts (e.g., full spectrum, broad spectrum, isolates, and distillates). Information including, but not limited to, plant part, method of extraction, and percentage of critical cannabinoids, should be adequately reflected in the nomenclature used to describe the material.[8]

B. Composition

Because the effects of the hemp article depend on its chemical composition, fit-for-purpose validated analytical methods are needed to quantitatively estimate the constituents. While cannabidiol (CBD) is a well-known and well-studied cannabinoid, its chromatographic separation from other cannabinoids and potentially co-eluting components should be ensured to accurately measure the components. Also, essential variables that impact the constituent composition should be considered in defining the quality specifications. Some variables include age of the plant, ideal climate, harvest seasons, and postharvest process conditions (e.g., drying process, extraction solvents, extraction ratios, etc.).

C. Limits for Contaminants

The limits for contaminants in hemp, including pesticide residues, microbial load, aflatoxin levels, and elemental contaminants, should be based on scientific considerations. Tests and assays contained in USP General Chapters provide analytical methods and acceptance criteria to control contaminants and may be useful for quality assurance.[9] These General Chapters include the following:

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[7] One type of documentary standard is a General Chapter. General Chapters provide broadly applicable information on accepted processes, tests, and methods to support product development and manufacturing. They can be applied to multiple products. Documentary standards can also be product-specific.

[8] USP developed a nomenclature guideline for the naming of botanical dietary supplement products. *See* Guideline for Assigning Titles to *USP* Dietary Supplement Monographs, at https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-assigning-titles-to-usp-dietary-supplement-monograph.pdf. This guideline aligns with FDA's draft guidance, *Dietary Supplement: New Dietary Ingredient Notifications and Related Issues*, at https://www.fda.gov/media/99538/download.

[9] *See* Ma C, Oketch-Rabah H, Kim NC, et al. Quality specifications for articles of botanical origin from the United States Pharmacopeia. *Phytomedicine: international journal of phytotherapy and phytopharmacology.* 2018;45:105-119.

- USP Chapter <232> *Elemental Impurities—Limits*;
- USP Chapter <467> *Residual Solvents*;
- USP Chapter <561> *Articles of Botanical Origin*;
- USP Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*;
- USP Chapter <2021> *Microbiological Enumeration Tests-Nutritional and Supplements*;
- USP Chapter <2022> *Microbiological Procedures for Absence of Specified Microorganisms-Nutritional and Dietary Supplements*; and
- USP Chapter <2023> *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements*.

Furthermore, because pesticide drift may occur, causing unintentional pesticide contamination during harvesting or processing of botanicals, toxicologically-based limits could be useful for specifications.

D. Validated Analytical Testing Methods

The *USP-NF* includes the compendial procedures to establish the suitability of analytical methods. Specifically, USP General Chapter <1225> *Validation of Compendial Procedures*, which is aligned with ICH *Q2 (R1)*,[10] with appropriately characterized reference standards could be used to develop validated test methods that accurately determine the content of delta-9 THC. General Chapter <1225> provides principles for validation of analytical procedures. The chapter describes the data elements required for validation of an analytical method for quantitative limit test, including establishing the accuracy, precision, specificity, quantitation limit, and linearity. USP reference standards, with established suitability for use in analytical methods, can help ensure comparability of results and traceability to Système International d'Unités (SI) units.

E. Sampling Considerations

Robust sampling for hemp is needed for sampling lots for testing to generate analytical data representative of the entire lot. Improper sampling methods could lead to a potentially inaccurate estimation of cannabinoid content (for example, by sampling from only the top two inches of the plant when a lot contains flowers that are also found in the middle or bottom of the plant). It is important to use well-defined systematic collection to ensure representative sampling of the entire lot. We suggest consideration of sampling the square root of the number of plants in a lot, including inflorescences located in the top, middle, and bottom to obtain a gross sample, followed by a quartering procedure to obtain a laboratory sample. Further quartering should be used to obtain the final test sample for analysis.

[10] *See ICH guidance for industry Q2(R1) Validation of Analytical Procedures: Text and Methodology*, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q2-r1-validation-analytical-procedures-text-and-methodology (March 1995).

Once a batch of inflorescence is collected and packaged in containers, representative sampling of a dried hemp batch, sampling from different loci within containers of that batch, is critical to ensure reproducibility of the results and for the appropriate labeling of the lot. Sampling procedures should take this into account and should include a sample homogenization process to increase representativeness of the portion used for a test. Sampling must use proper equipment and documentation following an approved standard operating procedure.

USP General Chapter <561> *Articles of Botanical Origin* describes the sampling procedures applicable to vegetable drugs, including procedures for gross sampling from multiple batches and the test sampling methods, and could be a useful resource for regulatory agencies.

F. Considerations for Quantitation of Delta-9 THC

Recognizing the regulatory requirement to limit the delta-9 THC content in hemp at not more than 0.3 percent on a dry weight basis, the use of an appropriate test method is critical to differentiate between hemp (an agricultural commodity) and marijuana (a Schedule 1 controlled substance). Unprocessed hemp contains both delta-9-tetrahydrocannabinolic acid (THCA) and delta-9 THC. Under exposure to heat, THCA (which is the predominant form) is decarboxylated to the psychoactive chemical delta-9 THC. Therefore, methods used to characterize the amount of delta-9 THC in hemp products should account for both THCA and delta-9 THC to accurately represent the total biologically relevant delta-9 THC content. USP's comments to USDA include our perspectives regarding the calculation of delta-9 THC, including the analytical procedures to determine the "dry weight basis," appropriate tests for quantitative estimation of delta-9 THC based on "postdecarboxylation or other similarly reliable analytical methods," consideration of the analytical methods that ensure resolution (separation) of peaks for delta-9 THC and THCA from other cannabinoids, procedures for sampling, and USP General Notices regarding rounding rules.[11]

Specifications and methods for hemp seed-derived ingredients should include maximum levels of cannabinoids, including CBD and delta-9 THC.[12] Because the GRAS ingredients derived from hemp seeds are not expected to contain significant levels of cannabinoids, these specifications should include sensitive methods that can be used to identify products with CBD present as an impurity.

[11] *See* USP's comments on USDA interim final rule on "Establishment of a Domestic Hemp Production Program," dated December 19, 2019, at https://www.regulations.gov/document?D=AMS-SC-19-0042-1518.

[12] Three hemp seed products (hemp seeds, hemp seed oil, and hemp seed protein) are generally recognized as safe (GRAS). FDA has not objected to the determination that three hemp derived materials are GRAS for use in food. To date, FDA has posted "no-questions" letters regarding the GRAS determination of three hemp seed-derived ingredients for use in human food. These ingredients are the subject of three GRAS Notices submitted to the Agency: hulled hemp seed (GRN765), hemp seed protein powder (GRN771), and hemp seed oil (GRN778).

II. Quality Considerations Specific to CBD

CBD is one the major cannabinoids from the plant *Cannabis sativa* L. CBD can be purified from the plant or chemically produced, with different profiles of impurities or related contaminants depending on the extraction and purification process, or the synthetic precursors and processes. For example, the State of New York proposed rulemaking that define CBD as naturally occurring phytocannabinoid cannabidiol found in hemp but does not include synthetic cannabidiol.[13] Appropriate analytical methods are needed to ensure resolution and control of impurities and contaminants from natural or synthetic processes. Considering the public health needs for assuring quality of CBD products, USP's Cannabis Expert Panel (discussed below) is working on appropriate analytical methods and acceptance criteria for identification, quantitative estimation, and limits on contaminants for CBD, with suitable methods to analyze related compounds or impurities derived from hemp or from synthetic processes.[14]

III. Quality Considerations Specific to Cannabis Inflorescence

We believe that USP perspectives regarding quality considerations for cannabis inflorescence including scientifically valid analytical methods, acceptance criteria, and applicable reference standards also apply to AB-45 and SB-235 and complement the requirements under Section 26100 of the Business and Professions Code.

As a result of stakeholder concern about the potential for harm with respect to cannabis regulated by the states for medical use, in 2016, USP convened a dialog with interested stakeholders to evaluate quality considerations regarding the use of cannabis and cannabis-derived compounds for medical purposes.[15] USP formed an Expert Panel with representation from academia and industry, and government representatives from U.S. states and Canada to develop scientifically-based specifications for cannabis inflorescence.[16]

The Expert Panel published its work defining suitable specifications for cannabis inflorescence, which covers multiple chemotypes of *Cannabis sativa* flower material with

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[13] *See* New York State Proposed Rulemaking, "Addition of Part to Title 10 NYCARR (Cannabinoid Hemp), at https://regs.health.ny.gov/sites/default/files/proposed-regulations/20-21hemp.pdf (Nov. 10, 2020).

[14] We note that under federal law, CBD is only permitted for use for medical purposes if it has been approved by FDA. In 2018, FDA approved the prescription drug product Epidiolex® (cannabidiol) with CBD derived from the cannabis plant as the active pharmaceutical ingredient. Under federal law, CBD is not permitted for use in dietary supplements or food products. However, we understand that various non-prescription CBD products are in the marketplace, and federal and state regulatory authorities are working to define an appropriate framework for those products.

[15] *See* Giancaspro GI KN, Venema J, de Mars S, Devine J, Celestino C, Feaster CE, Firschein BA, Waddell MS, Gardner SM, Jones Jr E. The Advisability and Feasibility of Developing USP Standards for Medical Cannabis, *Stimuli to the Revision Process, Pharmacopeial Forum (PF)* 42(1) [Jan.-Feb. 2016].

[16] For additional information on USP's work relating to the quality of cannabis for medical use, *see* https://www.usp.org/cannabis.

varying levels of delta-9 THC and CBD related compounds.[17] The tests for identity provide unique morphological and microscopic attributes and additional chromatographic fingerprint-based methods that can differentiate the varieties based on the levels of delta-9 THC and CBD. The published quantitative liquid and gas chromatographic methods enable quantitation of the major constituents, including the CBDs and delta-9 THCs. USP has also developed thoroughly characterized unique cannabinoid reference standards, which are qualified for applications such as identification tests, system suitability tests, or chromatographic peak markers, and for quantitative measurements.[18] Scientifically-based limits for pesticide residues, elemental contaminants, aflatoxins, and microbial load have also been identified. USP does not intend to publish a compendial standard in the *USP-NF* or *FCC* for cannabis inflorescence at this time.[19]

[17] *See* Sarma ND, Waye A, ElSohly MA, Brown PN, Elzinga S, Johnson HE, Marles RJ, Melanson JE, Russo E, Deyton L, Hudalla C, Vrdoljak GA, Wurzer JH, Khan IA, Kim N-C, Giancaspro GI., "Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes," *J Natural Products 83* (4), 1334-1351, Apr. 13, 2020, at https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b01200.

[18] For more information, *see* https://www.usp.org/cannabis.

[19] USP will adhere to existing compendial processes and admissions criteria with respect to cannabis and cannabis-derived compounds. With few exceptions, such as articles covered by *Global Health* monographs, the intent is that all articles for which monographs are provided in *USP–NF* are legally marketed in the United States or are contained in legally marketed articles. Should specific products containing cannabis or cannabis-derived compounds obtain legal status in the United States, compendial standards could help ensure adherence to quality specifications for products containing these compounds.