VIA ELECTRONIC SUBMISSION

January 11, 2021

New York State Department of Health
Bureau of Program Counsel, Regulatory Affairs Unit
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Attention: Katherine Ceroalo

Re: State of New York Proposed Rulemaking, "Addition of Part 1005 to Title 10 NYCARR (Cannabinoid Hemp)"

Dear Sir/Madam,

The United States Pharmacopeia (USP) appreciates the opportunity to comment on the State of New York's proposed rulemaking, "Addition of Part 1005 to Title 10 NYCARR (Cannabinoid Hemp)."

USP is an independent, scientific, nonprofit public health organization devoted to improving health through the development of public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. We are governed by the USP Convention, comprising over 450 academic institutions, healthcare practitioner organizations, industry groups and government representatives.[1]

USP develops and publishes its official standards for drugs, excipients, and dietary supplements in the *United States Pharmacopeia-National Formulary (USP-NF)*. We also publish a compendium of food ingredient standards, the *Food Chemicals Codex* (*FCC*). USP develops public quality standards for the identity, strength, and purity of medicines, foods, and dietary supplements through an open, transparent process, with participation from stakeholders including representatives from academia, industry, and government. Our standards are developed by Expert Committees and Expert Panels. We also develop reference standards[2] for analytical testing. 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 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 throughout the last several years, we have learned of the critical and growing need for scientific articulation of quality attributes for cannabis and related products to help protect patients and consumers from harm.

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

[2] USP reference standards are highly characterized chemical specimens—pure materials or mixtures of chemicals that have been tested in multiple laboratories—intended for quality control use in conducting assays and tests in USP's documentary standards for drugs in the *USP–NF*, for dietary supplements in the *USP–NF* and *Dietary Supplements Compendium*, and for foods in the *FCC*.

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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.[3] 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.[4]

The Expert Panel published its work defining suitable specifications for cannabis inflorescence, which covers multiple chemotypes of *Cannabis sativa* flower material with varying levels of delta-9 tetrahydrocannabinol (delta-9 THC) and cannabidiol (CBD) related compounds.[5] The tests, developed 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 proposed quantitative liquid and gas chromatographic methods enable quantitation of the major constituents, including the CBDs and delta-9 THCs. 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.[6]

I. Essential Quality Attributes for Cannabis and Cannabis-Derived Compounds

Public standards are essential to help prevent harm to patients and consumers; they facilitate the manufacture of products that are not adulterated; and they help limit exposure to toxic substances, pathogenic microorganisms, and harmful additives. As regulatory bodies are developing product quality specifications for cannabis and cannabis-derived compounds, we recommend that they consider certain USP guidelines and standards (e.g., general chapters

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[3] *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].

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

[5] *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.

[6] 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.

and reference standards). We have elaborated on these considerations in our comments to FDA and the United States Department of Agriculture (USDA).[7]

For botanically derived products, such as those including cannabis and cannabis-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,[8] 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. 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 that contain more than delta-9 THC. USP General Chapter <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 cannabis and cannabis-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 cannabis and cannabis-derived compounds, including hemp and its extracts. This is due to the extensive and varied approaches to the naming of cannabis 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

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[7] 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.

[8] 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.

cannabinoids, should be adequately reflected in the nomenclature used to describe the material.[9]

B. Composition

Because the effects of the cannabis article depend on its chemical composition, fit-for-purpose validated analytical methods are needed to quantitatively estimate the constituents. While delta-9 THC and CBD are the well-known and most-studied cannabinoids, their 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 cannabis, 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.[10] These General Chapters include the following:

- USP Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*;
- USP Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*;
- 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*;

[9] 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.

[10] *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 <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)*,[11] 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 cannabis and 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.

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.

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[11] *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).

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.

II. Quality Considerations Specific to Cannabis Inflorescence, Hemp, and CBD

A. Cannabis Inflorescence

The USP Cannabis Expert Panel published cannabis-specific information on cannabis inflorescence quality specifications for medical purposes.[12] This publication provides information on scientifically valid methods, reference standards, and acceptance criteria to define identification, chromatographic methods for establishing content of cannabinoids and terpenes, and recommendations regarding limits for contaminants (e.g., pesticide residues, elemental contaminants, microbial contaminants, and mycotoxins) to control the quality of cannabis inflorescence used for medical purposes. Specifically, the chromatographic methods help in the adequate characterization of cannabis through orthogonal high-performance thin-layer chromatograph (HPTLC) and high-performance liquid chromatograph (HPLC) methods, and quantitation of cannabinoids and terpenes, to help ensure batch-to-batch consistency. Risk-based limits for contaminants were based on the assessment of available information from multiple sources. These recommendations are aligned with the principles in the FDA guidance on *Botanical Drug Development*.[13]

In addition, the USP Cannabis Expert Panel publication proposes the classification of cannabis currently available for medical use into three chemotypes based on clinically relevant constituents with methods of identification and recommendations for naming.[14] 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.[15]

The USP Cannabis Expert Panel is currently analyzing information to provide appropriate nomenclature and quality specifications for cannabis extracts that are differently extracted and processed resulting in variable cannabinoid and terpene content. Besides the quality attributes described in Section I above, specifications for limits to residual solvents and process impurities or degradants are uniquely important for extracts.

B. Hemp

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

[12] *See* Sarma ND, et al., *supra* note 5.

[13] FDA Guidance, *Botanical Drug Development*, at https://www.fda.gov/media/93113/download.

[14] *See* Sarma ND, et al., *supra* note 5.

[15] For more information, *see* https://www.usp.org/dietary-supplements-herbal-medicines/cannabis.

(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.[16]

As is the case with cannabis that is not considered hemp, the cannabinoid and terpene content of hemp may vary depending on the nature of the chemotype, the part of the plant, and other factors such as the growth, harvest, and storage conditions. The USP Cannabis Expert Panel is currently analyzing information to provide appropriate nomenclature and quality specifications for hemp and hemp extracts.

Specifications and methods for hemp seed-derived ingredients should include maximum levels of cannabinoids, including CBD and delta-9 THC.[17] 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.

C. CBD

CBD is one the major cannabinoids from the plant *Cannabis sativa* L. CBD can be purified from the plant or chemically produced. In 2018, FDA approved a prescription drug product with CBD derived from the cannabis plant as the active pharmaceutical ingredient.[18] In addition to this approved prescription drug product, various non-prescription CBD products are marketed. Federal and state regulatory authorities are currently working to define an appropriate framework for those products. Considering the public health needs for assuring quality of CBD products, USP's Cannabis Expert Panel is working on appropriate analytical methods and acceptance criteria for identification, quantitative estimation, and limits on

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[16] *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.

[17] 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).

[18] Epidiolex (cannabidiol) oral solution was approved in June 2018 for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. *See* https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms.

contaminants for CBD, with suitable methods to analyze related compounds or impurities derived from hemp or from synthetic processes.

III. Conclusion

The consideration of public quality standards, such as for identity, composition, and limits for contaminants, are crucial for cannabis and cannabis-derived compounds. Additional quality considerations are also important specifically for cannabis inflorescence, hemp, and CBD. We look forward to collaborating with regulatory bodies and other stakeholders to continue the work around providing context for development and the appropriate use of quality standards—for example, developing specifications (including validated analytical methods and acceptance criteria), and other quality considerations and methodologies to help mitigate public health risks associated with products containing contaminated, substandard, or super-potent cannabis or cannabis-derived compounds.

Thank you for the opportunity to discuss the importance of quality in products containing cannabis and how USP approaches can help ensure the quality of cannabis and cannabis-derived compounds. For more information, please contact Nandakumara Sarma, Ph.D., Director, Dietary Supplements and Herbal Medicines at (301) 816-8354 or dns@usp.org.

Sincerely,

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