July 5, 2019

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

Re: Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments [Docket No. FDA–2019–N–1482] 84 Fed. Reg. 12969 (April 3, 2019)

Dear Sir/Madam:

The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on the above-referenced FDA Request for Comments on *Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds*.

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. We also develop reference standards for analytical testing.

With respect to the legal and regulatory status of cannabis and cannabis-derived compounds, USP defers to FDA and appropriate government authorities and respects these determinations. As authorities consider various factors and implications, USP welcomes the opportunity to share data and information generated from our current and ongoing scientific work with respect to cannabis and cannabis-derived compounds.

From our interactions with various stakeholders throughout the last several years, we have learned of the critical and growing need for scientific articulation for quality attributes for cannabis and related products to help protect patients and consumers from harm. As more products become available and sourced more broadly, and states continue to adopt initiatives allowing the use of cannabis, potential exposure to, and associated risk of harm from contaminated, substandard, or super-potent products is increasing. We appreciate FDA's commitment to address the marketing and regulation of cannabis and cannabis-derived products while continuing to protect the public's safety.

Regardless of product category, one of the primary purposes of a public standard is to help

[1] USP is an independent, scientific, nonprofit public health organization devoted to improving health through the development of public standards. USP's mission is to improve global health through 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. 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*). 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.

regulators protect public health by providing scientifically validated tests to ensure the identity, constituent composition, and strength of a product. Public standards help monitor product quality so that adulterants/contaminants can be identified and controlled so that they are absent or below the level of concern. Public standards are essential to help prevent harm to patients and consumers: they facilitate the manufacture of products that are pure and not adulterated, and help limit exposure to toxic substances, pathogenic microorganisms, harmful additives and in this instance, synthetic cannabinoid analogs. A robust standard in this area should therefore include limits for contaminants such as pesticide residues, microbial load, aflatoxin levels, and elemental contaminants, based on reliable scientific information.

I. Components of quality standards for cannabis and cannabis-derived compounds

Our comments seek to address the question posed in the Federal Register Notice, "Are there particular standards or processes needed to ensure manufacturing quality and consistency of products containing cannabis or cannabis-derived compounds, including standards applied to evaluate product quality?"

Standards help to ensure manufacturing quality and consistency. As related to botanical derived products such as cannabis and cannabis-derived compounds, quality standards should include appropriate analytical procedures and acceptance criteria to define identity, strength, purity, constituents, and limits for contaminants.

- **Identity:** The use of orthogonal analytical procedures and acceptance criteria can help identify the different cultivars of cannabis. Examples such as secondary metabolite profiles, DNA based methods (as presented in recent USP workshops), microscopic and chromatographic tests can be useful for the identification and discrimination of hemp[2] from other cannabis varieties that contain more than 0.3% delta-9 tetrahydrocannabinol (THC). Identity of cannabis and cannabis-derived products should be linked with clear nomenclature, including reference to plant part, product, and/or herbal preparation. USP developed a guideline to appropriately name botanical articles, which aligns with FDA requirements for dietary supplement naming.[3]

- **Strength and composition:** Because the effects of the article depend on its chemical composition, essential variables that impact the constituent composition should be included in the definitions. Some examples include age of the plant, ideal climate, harvest seasons and postharvest process conditions (drying process, extraction solvents, extraction ratios, etc.). Validated HPLC-based and GC-based chromatographic methods for quantitation of the cannabinoids have been developed to

[2] 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.

[3] 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.

determine the strength and composition of the article.[4]

- **Contaminant identification and limits:** The limits for contaminants, 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.[5,6] Furthermore, because pesticide drift may occur, causing unintentional pesticide contamination during harvesting or processing of botanicals, toxicologically-based limits could be useful for specifications.

II. Specifications for cannabis and cannabis-derived compounds

Three years ago, USP and other stakeholders began discussions about the quality of cannabis. These discussions occurred as a result of stakeholder concern about the potential for harm with respect to cannabis regulated by the states for medical use. Over time, the discussions have expanded.

- **Cannabis inflorescence:** In 2016, USP convened a dialog with interested stakeholders to evaluate what tools would valuable in support of protecting patients' health regarding the use of cannabis for medical purposes.[7] 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.

  The Expert Panel has made significant progress defining suitable specifications for cannabis inflorescence, which covers multiple chemotypes of Cannabis sativa flower

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[4] Mudge EM, Murch SJ, Brown PN. Leaner and greener analysis of cannabinoids. *Anal Bioanal Chem.* 2017;409(12):3153-3163; Ibrahim EA, Gul W, Gul SW, et al. Determination of Acid and Neutral Cannabinoids in Extracts of Different Strains of Cannabis sativa Using GC-FID. *Planta medica.* 2018;84(4):250-259; AOAC Official Method 2018.11. Quantitation of Cannabinoids in Cannabis Dried Plant Materials, Concentrates, and Oils Liquid Chromatography–Diode Array Detection Technique with Optional Mass Spectrometric Detection.

[5] These General Chapters include <467> Residual Solvents, <1111> Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use, and <2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements.

[6] 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.

[7] 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].

[8] 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).

material with varying levels of THC and cannabidiol (CBD) related compounds. 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 THC and CBD. The proposed quantitative liquid and gas chromatographic methods enable quantitation of the major constituents, including the CBDs and THCs. Scientifically based limits for pesticide residues, elemental contaminants, aflatoxins, and microbial load have also been identified.

- **Hemp:** Recently, FDA listed three hemp derived materials as generally recognized as safe (GRAS) for use in food.[8]

  Specifications and methods for hemp should accurately identify plant constituents such as fats and oils, and set maximum levels of cannabinoids, including CBD and THC. Because the GRAS ingredients from hemp seeds or seed oil are not naturally expected to contain significant levels of cannabinoids, these specifications should be sufficiently sensitive in identifying products that contain CBD in amounts higher than expected (such as from spiking or contamination).

  Unprocessed cannabis contains both delta-9-tetrahydrocannabinolic acid (THCA) and THC. Under exposure to heat, THCA (which is the predominant form) is decarboxylated to the psychoactive chemical THC. Therefore, methods used to characterize the amount of THC in cannabis products should account for both THCA and THC to accurately represent the total biologically relevant THC content.

  USP is working on developing analytical methods to detect the synthetic cannabinoid analogs. Studies have reported serious health effects associated with the use of synthetic cannabinoids,[9] highlighting the need to develop and validate screening procedures to detect these synthetic compounds.

III. USP plans to disseminate scientific information on key quality specifications for cannabis

USP does not intend to publish a compendial standard for cannabis inflorescence at this time.[10] However, because significant progress has been made to define suitable quality specifications

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[9] See, for example, Horth RZ, Crouch B, Horowitz BZ, Prebish A, Slawson M, McNair J, Elsholz C, Gilley S, Robertson J, Risk I, Hill M, Fletcher L, Hou W, Peterson D, Adams K, Vitek D, Nakashima A, Dunn A. Notes from the Field: Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol - Utah, 2017-2018. MMWR Morb Mortal Wkly Rep. 2018 May 25;67(20):587-588.

[10] USP will adhere to existing compendial processes and admissions criteria with respect to cannabis and cannabis-derived compounds. With respect to dietary supplements, USP does not admit monographs for development where FDA has issued a specific opinion or taken enforcement action to indicate that there is no legal basis to market that substance in the U.S. Should the legal status of specific products containing cannabis or cannabis-derived compounds change, compendial standards could help ensure adherence to specifications for products containing these compounds.

for this plant material, we plan to publish our work in a scientific paper to make it available to interested stakeholders.

We believe it is critical for all stakeholders to work together to comprehensively assess the field of cannabis, hemp and CBD in terms of quality, and we pledge to join with others in this effort. We look forward to collaborating with the Agency and concerned parties to continue the work around providing context around development and appropriate use of standards—for example, developing specifications (including validated analytical methods and acceptance criteria), and methodologies to help mitigate public health risks associated with contaminated, substandard, or super-potent cannabis inflorescence products.

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We look forward to continuing the dialog and exploration of science-based standards that can help prevent harm and protect public health and welcome the opportunity to meet with FDA to discuss how USP can continue to help ensure product quality to advance our common goals of protecting and promoting public health.

Thank you again for the opportunity to comment. For more information, please contact Gabriel Giancaspro, Ph.D., Vice President, Science—Dietary Supplements and Herbal Medicines, at (301) 816-8343 or gig@usp.org.

Sincerely,

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