

## VIA ELECTRONIC SUBMISSION

September 17, 2020

Food and Drug Administration  
Division of Dockets Management  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2020-D-1079 for "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research" Draft Guidance for Industry**

Dear Sir/Madam,

The United States Pharmacopeia (USP)<sup>1</sup> appreciates the opportunity to comment on FDA's draft guidance *Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research*.<sup>2</sup> 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 the analytical testing of products.<sup>3</sup>

### Public Quality Standards

USP supports the recommendations in the draft guidance that stress the importance of quality in conducting clinical research related to the development of drugs containing cannabis and cannabis-derived compounds. Interest in cannabis and cannabis-derived products is active and growing, and USP is concerned about the safety and quality of

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<sup>1</sup> 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.

<sup>2</sup> We incorporate by reference our comments submitted to FDA's docket on "Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds," (Docket No. FDA-2019-N-1482), dated July 5, 2019, at <https://www.regulations.gov/document?D=FDA-2019-N-1482-3122>. We noted in our comments that quality standards for botanical-derived products, such as cannabis and cannabis-derived compounds, should include appropriate analytical procedures and acceptance criteria to define identity, strength, purity, constituents, and limits for contaminants.

<sup>3</sup> 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*.

cannabis products. We applaud the Agency for developing this draft guidance, which we believe can help stimulate robust clinical and laboratory studies. In that context, public quality standards can also help support sound and reproducible scientific and clinical research that can help fill scientific knowledge gaps in this area. Public quality standards serve an important role in supporting the early development of drug products, including for clinical research involving cannabis and cannabis-derived compounds. Public standards help ensure the identity, quality, purity, potency or strength of drugs and control impurities including contaminants, such that they are absent or below the level of concern. USP agrees that robust standards in this area should include methods and limits for contaminants, such as pesticide residues, microbial load, aflatoxin levels, and elemental contaminants, based on reliable scientific information. Quality considerations regarding the use of cannabis and cannabis-derived compounds for medical purposes have been and are currently being discussed by USP's Cannabis Expert Panel.<sup>4,5</sup>

## Resources for Information on Quality Considerations

We support the draft guidance's references to the *USP-NF* chapters on tests, equipment, and analytical methods for drug quality aspects, such as identification, excipients, impurities, and microbiological controls for sterile, as well as nonsterile products. Specifically, we support the references to the USP general chapters on articles of botanical origin,<sup>6</sup> microbiological examination of nonsterile products,<sup>7</sup> and elemental impurities limits<sup>8</sup> for drug development using cannabis and cannabis-derived compounds. USP also supports the draft guidance recommendations regarding container closure system selection, stating that applicants should provide adequate characterization and safety assessment of extractable and leachable compounds and should be consistent with USP general chapters on assessing extractables and drug product leachables.<sup>9</sup>

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<sup>4</sup> The Cannabis Expert Panel originally convened in 2016 and included representation from academia and industry, and government representatives from the United States (including FDA, National Institutes of Health, and state representatives) and Canada, to develop science-based specifications for cannabis inflorescence.

<sup>5</sup> 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), at [https://www.uspnf.com/sites/default/files/usp\\_pdf/EN/USPNF/usp-nf-notice/usp\\_stim\\_article\\_medical\\_cannabis.pdf](https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notice/usp_stim_article_medical_cannabis.pdf) (Jan.-Feb. 2016).

<sup>6</sup> USP General Chapter <561> *Articles of Botanical Origin*, particularly regarding tests for residual pesticides, including any pesticides routinely used in the countries of origin of botanical raw materials; USP General Chapter <563> *Identification of Articles of Botanical Origin*.

<sup>7</sup> USP General Chapters <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*.

<sup>8</sup> USP General Chapter <232> *Elemental Impurities—Limits*.

<sup>9</sup> USP General Chapters <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* and <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*.

We note that the USP Cannabis Expert Panel recently published cannabis-specific information on quality specifications, which can also be a helpful resource for information on quality considerations for cannabis used for clinical research.<sup>10</sup> 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 (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*.<sup>11</sup>

The Expert Panel also recommended suitable specifications for cannabis inflorescence covering multiple chemotypes of *Cannabis sativa* flower material with varying levels of delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD)-related compounds.<sup>12</sup> 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 CBD and THC.

## Validated Analytical Methods

The draft guidance states that for phase 2 and 3 investigational drug studies and for new drug application submissions, laboratories must use validated analytical methods. USP supports the draft guidance's reference to the ICH guidance for industry *Q2 (R1) Validation of Analytical Procedures: Text and Methodology* for recommendations regarding method validations. We note that the USP Cannabis Expert Panel publication includes methods that meet the ICH Q2 (R1) guidance.<sup>13</sup> We further suggest consideration of including of a reference to USP compendial procedures in the guidance to establish the suitability of analytical methods. Specifically, USP General Chapter <1225> *Validation of Compendial Procedures*, which is aligned with ICH Q2 (R1), with appropriately characterized reference standards, can be used to develop validated test methods that accurately determine the content of THC. USP General Chapter <1225> provides principles for validation of analytical procedures. Further, the chapter describes the data elements for validation of an analytical

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<sup>10</sup> 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. *J Natural Products* 83 (4), 1334-1351, 2020, at <https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b01200>.

<sup>11</sup> FDA Guidance, *Botanical Drug Development*, at <https://www.fda.gov/media/93113/download>.

<sup>12</sup> See *supra*, at 10.

<sup>13</sup> See *id.*

method for a quantitative limit test, including establishing the accuracy, precision, specificity, quantitation limit, and linearity.<sup>14</sup>

## Calculation of Percent Delta-9 THC

Our comments submitted to USDA's docket on "Establishment of a Domestic Hemp Production Program" explain USP's perspective regarding the calculation of delta-9 THC content.<sup>15</sup> USP's publication on quality attributes for cannabis inflorescence provides science-based chromatographic methods and reference standards to help ensure resolution (separation) of THC from its carboxylated form and from other cannabinoids.<sup>16</sup> In particular, we would like to emphasize the procedures for sampling and testing cannabis varieties grown and harvested to ensure hemp does not exceed the acceptable delta-9 THC level.

We support the draft guidance reference to the USP General Notices and Requirements section 7.20, *Rounding Rules*, for use when calculating and reporting the level of delta-9 THC to FDA. According to the USP General Notices 7.20, *Rounding Rules*, the observed or calculated values shall be rounded off to the number of decimal places that is in agreement with the limit expression. When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than five, it is eliminated, and the preceding digit is unchanged. If this digit is equal to or greater than five, it is eliminated, and the preceding digit is increased by one. In case of limiting the THC concentration to NMT 0.3%, the hemp lots with reportable values NMT 0.34% pass the acceptance criteria according to the rounding rules.

## Nomenclature

USP believes that more guidance is needed on adequate descriptions and appropriate nomenclature to describe cannabis and cannabis-derived compounds used in clinical trials. 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). Information

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<sup>14</sup> For additional information on validated analytical methods for the three cannabis chemotypes to accurately identify plant constituents, and set specifications for cannabinoids, including CBD and THC, see *id.* Specifications also should be sufficiently sensitive in identifying products that contain cannabinoids in amounts higher than expected (such as from spiking or contamination). 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 cannabinoid analogs, highlighting the need to develop and validate screening procedures to detect these synthetic compounds. 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.

<sup>15</sup> USP comments to USDA dated December 19, 2019: Docket No. AMS-SC-19-0042; SC19-990-2 IR; 84 FR 58522 (Oct. 31, 2019); 7 CFR part 990; Establishment of a Domestic Hemp Production Program; Interim final rule with request for comments, at <https://www.regulations.gov/document?D=AMS-SC-19-0042-1518>.

<sup>16</sup> See *supra*, at 10.

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. In alignment with FDA's draft guidance on dietary supplements,<sup>17</sup> USP developed a nomenclature guideline for the naming of botanical dietary supplement products.<sup>18</sup>

In addition, USP's 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.<sup>19</sup> The use of orthogonal analytical procedures and acceptance criteria can help identify the different cultivars of cannabis. Other recommendations provided in this publication include morphological/microscopic and chromatographic tests for the identification of the chemotypes. Similarly, hemp should be differentiated from other cannabis varieties that contain more than 0.3% THC. This resource may be helpful in providing additional information to inform this guidance.

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USP thanks FDA for the opportunity to provide comments in response to this draft guidance. In particular, we note the importance of public quality standards for the use of cannabis and cannabis-derived compounds in clinical research for drug products. We look forward to continuing the dialog and exploration of science-based standards that can help prevent harm and protect public health. We 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.

For more information, please contact Marissa Chaet Brykman, Esq., Director, U.S. Regulatory Policy, at [marissa.brykman@usp.org](mailto:marissa.brykman@usp.org); (301) 692-3660.

Sincerely,



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<sup>17</sup> FDA Draft Guidance, *Dietary Supplement: New Dietary Ingredient Notifications and Related Issues*, at <https://www.fda.gov/media/99538/download>.

<sup>18</sup> 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>.

<sup>19</sup> See *supra*, at 10.