

## VIA ELECTRONIC SUBMISSION

September 1, 2021

The Honorable Charles Schumer  
Majority Leader  
322 Hart Senate Office Building  
Washington, DC 20510

The Honorable Cory Booker  
717 Hart Senate Office Building  
Washington, DC 20510

The Honorable Ron Wyden  
221 Dirksen Senate Office Building  
Washington, DC 20510

**Re: USP Comments in Response to the Cannabis Administration and Opportunity Act Discussion Draft**

Dear Senators Schumer, Wyden, and Booker,

On behalf of the United States Pharmacopeia (USP), we greatly appreciate the opportunity to provide feedback on the Cannabis Administration and Opportunity Act (CAOA) Discussion Draft.

USP is an independent, scientific, non-profit public health organization founded in 1820 to help ensure the quality and consistency of medicines relied upon by Americans. 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.<sup>1</sup> An area 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. USP's science-based public quality standards are recognized in U.S. law as official standards for medicines, dietary supplements, and food ingredients. These quality standards are also utilized in more than 140 countries around the world.

As noted in the CAO A Discussion Draft materials, in recent years, there has been an increase in the number of cannabis and cannabis-derived compounds on the U.S. market. As such, there is a critical and growing need for standardizing the quality attributes for cannabis and related products to help protect patients and consumers from harm. To that end, we applaud the inclusion of cannabis product standards (proposed section 1106 of the Federal Food, Drug, and Cosmetic Act (FFDCA)) in the CAO A Discussion Draft. Our comments focus on the importance of standards for cannabis and cannabis-derived

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<sup>1</sup> Our standards are developed by Expert Committees and Expert Panels and are published in the *United States Pharmacopeia-National Formulary (USP-NF)* and the *Food Chemicals Codex (FCC)*. We also develop physical reference standards for analytical testing. 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, including 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*.

products, provide suggestions to clarify the definitions of such products, and include recommendations to help ensure product quality.

## **I. Adherence to Public Quality Standards for Cannabis Will Help Protect Patient Safety**

Products containing cannabis and cannabis-derived substances, including cannabidiol (CBD), that are legally marketed in the United States should adhere to science-based, transparent public quality standards. Adherence to quality standards is critical due to the increased number and use of cannabis products in the U.S. market, quality-related issues present in these products, and the variability inherent in cannabis and cannabis-related products as botanical compounds.

Public standards for ingredients and products are essential to help ensure public trust in quality and to help prevent harm to the public.<sup>2</sup> They facilitate the consistent manufacturing of products and help limit exposure to toxic substances, pathogenic microorganisms, and harmful additives. Public quality standards also provide valuable information to manufacturers to support the early development of new and existing products and address common quality issues, which is especially important for manufacturers with little or no experience with producing certain products and that may be unfamiliar with the approaches on how to ensure quality. Further, standards and associated analytical methods provide tools to create efficiency in product development and consistency across manufacturers and to the regulatory review process. Outlined in the Attachment are attributes and considerations to help ensure the quality of cannabis products.

### **A. The Explosive Growth of Cannabis Products Creates Expanded Patient Safety Risks**

The number of cannabis products in the U.S. market has dramatically increased over the past several years. Total sales of cannabis in states where it is currently legal under state law are projected to grow at an annual growth rate (CAGR) of 14% over the next six years, reaching nearly \$30 billion by 2025. Annual sales of cannabis for medical use are projected to grow at a 17% CAGR through 2025, reaching approximately \$13.1

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<sup>2</sup> For example, to help address alcohol-based hand sanitizers that were contaminated with methanol, USP revised its alcohol monographs to include an identification test for methanol, which would require manufacturers to detect and quantify any methanol present for each lot of alcohol. See Revision Bulletin, Alcohol, at [https://www.uspnf.com/sites/default/files/usp\\_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf](https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf) (Aug. 17, 2020); Revision Bulletin, Isopropyl Alcohol, at [https://www.uspnf.com/sites/default/files/usp\\_pdf/EN/USPNF/revisions/isopropyl-alcohol-rb-notice-20210730.pdf](https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/isopropyl-alcohol-rb-notice-20210730.pdf) (July 30, 2021); Revision Bulletin, Azeotropic Isopropyl Alcohol, at [https://www.uspnf.com/sites/default/files/usp\\_pdf/EN/USPNF/revisions/azeotropic-isopropyl-alcohol-rb-notice-20210730.pdf](https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/azeotropic-isopropyl-alcohol-rb-notice-20210730.pdf) (July 30, 2021). A similar approach was used to address public health crises in several other cases, including glycerin products that tested positive for diethylene glycol (DEG), (see <https://www.usp.org/frequently-asked-questions/glycerin>) and heparin products that contained adulterated active pharmaceutical ingredients from China (see <https://www.usp.org/frequently-asked-questions/heparin/heparin-monograph-revision>).

billion.<sup>3</sup> Further, approximately 38.4 million adults consume cannabis at least once annually.<sup>4</sup> With the large number of cannabis products sold and consumed by the public follows a substantial increase in the potential for risk to public health, making concerns about the safety and quality of these products urgent. Public quality standards can help mitigate these risks.

## B. Quality-Related Challenges

Considerable variation in cannabinoid content among different specimens of the same strain of the cannabis plant presents a challenge to maintaining consistent quality across products.<sup>5</sup> The U.S. Food and Drug Administration (FDA) has consistently communicated concerns and questions regarding the science, safety, and quality of CBD and other cannabis-derived compounds, including for example, adverse reactions that may be associated with CBD products and risks that may be associated with the long-term use of CBD products.<sup>6, 7</sup>

A 2020 FDA report to Congress identified product quality concerns in mislabeled and adulterated products labeled to contain CBD.<sup>8</sup> FDA stated in the report that in its sampling of CBD products, more than half were mislabeled and contained 20 percent more CBD versus labeled claims.<sup>9</sup> Additionally, nearly half of those sampled contained tetrahydrocannabinol (THC), the psychoactive component of marijuana. Other publications and reports have also highlighted concerns about mislabeled CBD

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<sup>3</sup> BusinessWire, “U.S. Cannabis Industry Market Projections Up 20% to \$30 Billion by 2025,” <https://www.businesswire.com/news/home/20190917005284/en/U.S.-Cannabis-Industry-Market-Projections-Up-20-to-30-Billion-by-2025> (Sept. 17, 2019), citing New Frontier Data’s “The U.S. Cannabis Report 2019 Industry Outlook.”

<sup>4</sup> *Id.*

<sup>5</sup> See Jikomes, N., Zoorob, M., “The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products,” *Sci Rep* 8, 4519 (2018). <https://doi.org/10.1038/s41598-018-22755-2>

<sup>6</sup> See FDA webpage, “Better Data for a Better Understanding of the Use and Safety Profile of Cannabidiol (CBD) Products,” at <https://www.fda.gov/news-events/fda-voices/better-data-better-understanding-use-and-safety-profile-cannabidiol-cbd-products>.

<sup>7</sup> See FDA webpage, “What You Need to Know (And What We’re Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD,” at <https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis>.

<sup>8</sup> Report to the U.S. House Committee on Appropriations and the U.S. Senate Committee on Appropriations, Sampling Study of the Current Cannabidiol Marketplace to Determine the Extent That Products are Mislabeled or Adulterated, Report in Response to Further Consolidated Appropriations Act, 2020, U.S. Food and Drug Administration, at <https://files.constantcontact.com/0ac3ac29601/07fb4b7e-2a70-4190-ba6b-9bb8f9f2264c.pdf>.

<sup>9</sup> *Id.*

products and serious adverse effects or drug interactions associated with CBD.<sup>10</sup> Furthermore, products labeled as containing CBD have also been the subject of FDA warning letters,<sup>11</sup> which include unapproved new drug, misbranding, and/or adulteration violations.<sup>12</sup> In particular, warning letters state that certain products containing CBD are unapproved drugs, and some include violations related to current good manufacturing practice (CGMP) requirements. Public quality standards on cannabis and cannabis-derived products could provide information on the quality attributes and materials, and testing in terms of identity, composition, and purity that could help manufacturers with CGMP and other requirements and prevent patient harm resulting from exposure to substandard, contaminated, or adulterated cannabis products.

### C. Variability of Cannabis Products

Botanical quality is impacted by several variables, including plant genetics, cultivation, collection, and post-harvest conditions. Ensuring the quality and consistency of plant-derived substances is critical to ensure the right plant parts, growth conditions, and to control other factors that impact composition, such as extraction and processing methods. FDA's guidance on "Botanical Drug Development"<sup>13</sup> and draft guidance on "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research"<sup>14</sup> recognize the complexity of botanical articles and emphasize the need for appropriate quality specifications. Adherence to public quality standards that include scientifically valid analytical procedures and acceptance criteria to define identity, strength, purity, and limits for contaminants can help ensure public trust that cannabis and cannabis-derived products are what they purport to be.

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<sup>10</sup> Bonn-Miller, et al., "Labeling Accuracy of Cannabidiol Extracts Sold Online," *JAMA*, 2017;318(17):1708-1709, at <https://jamanetwork.com/journals/jama/fullarticle/2661569> (Nov. 7, 2017); Stone, Emma, "CBD Buyer Beware: Leafreport Decided to Uncover Which CBD Brands are Testing, and Which are Not," at <https://www.leafreport.com/education/cbd-buyer-beware-leafreport-decided-to-uncover-which-cbd-brands-are-testing-and-which-are-not-10643> (May 13, 2021); Citti, et al., "Analysis of impurities of cannabidiol from hemp. Isolation, characterization and synthesis of cannabidibutol, the novel cannabidiol butyl analog," *J. Pharm. Biomed. Anal.* 2019 Oct 25;175:112752, at <https://pubmed.ncbi.nlm.nih.gov/31330283/> (July 12, 2019); Pirrung, Michael, "Synthetic Access to Cannabidiol and Analogs as Active Pharmaceutical Ingredients," *J. Med. Chem.* 2020 Nov 12;63(21):12131-12136, at <https://pubmed.ncbi.nlm.nih.gov/32531156/> (July 13, 2020).

<sup>11</sup> FDA Warning Letters and Test Results for Cannabidiol-Related Products, at <https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products>.

<sup>12</sup> In particular, the products may be unapproved new drugs sold in violation of sections 505(a) and 301(d) of the FD&C Act, misbranded drugs under section 502(f)(1) of the FD&C Act, and/or adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act.

<sup>13</sup> FDA Guidance, "Botanical Drug Development," <https://www.fda.gov/media/93113/download> (Dec. 2016).

<sup>14</sup> FDA Draft Guidance, "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research," <https://www.fda.gov/media/140319/download> (July 2020).

For example, CBD, which is one of the major cannabinoids from the plant *Cannabis sativa* L., 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 subsequent purification processes. Appropriate analytical methods can help to ensure the detection, resolution and control of impurities and contaminants from natural or synthetic processes and help determine the origin of CBD (e.g., is it derived from hemp).<sup>15</sup>

## **II. CBD as a Dietary Supplement Ingredient**

Proposed section 505 of the CAOA Discussion Draft would create a legal pathway for the use of CBD derived from hemp in dietary supplements. This section would amend the definition of “dietary supplement” in the FFDCFA such that products containing CBD derived from hemp could meet the definition of a dietary supplement.<sup>16</sup> The quality of CBD could vary widely depending on the extraction and purification processes, resulting in potential contamination with other cannabinoids or terpenes. Consistent with the CGMP expectations for dietary supplements (21 CFR part 111), quality specifications for CBD should be established to define its identity, purity, and limits on contaminants. As an ingredient, the quality of CBD should be controlled at not less than 98% purity, with limits on contaminants based on available toxicological data, and should include additional tests to ensure nature-identical isomeric form. Further, the quality specifications should differentiate CBD derived from hemp (or “hemp-derived CBD”) from synthetically-derived CBD.

## **III. Responses to Specific Questions in CAOA Discussion Draft**

### **A. Appropriate Way to Measure Potency of Cannabis and Cannabis Products**

The USP Cannabis Expert Panel recently published information on quality considerations for cannabis inflorescence for medical use, which provides scientifically valid methods, information on physical reference standards, and acceptance criteria to establish the content of cannabinoids and terpenes.<sup>17</sup> Specifically, high-performance

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<sup>15</sup> The State of New York proposed rulemaking that define CBD as naturally occurring phytocannabinoid CBD found in hemp but does not include synthetic CBD. See “Addition of Part 1005 to Title 10 NYCARR (Cannabinoid Hemp),” at [https://regs.health.ny.gov/sites/default/files/proposed-regulations/Cannabinoid%20Hemp\\_0.pdf](https://regs.health.ny.gov/sites/default/files/proposed-regulations/Cannabinoid%20Hemp_0.pdf).

<sup>16</sup> We note that there is no revision to the corresponding prohibited act provision in section 301(II) of the FFDCFA to make it permissible for foods, including dietary supplements, to contain CBD derived from hemp.

<sup>17</sup> 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>.

liquid chromatograph (HPLC) and gas chromatography (GC) methods help ensure the content of cannabinoids (a measure of potency) and batch-to-batch consistency. These recommendations are aligned with the principles in the FDA guidance on “Botanical Drug Development.”<sup>18</sup> The Expert Panel also recommended suitable specifications for cannabis inflorescence covering multiple chemotypes of the cannabis flower with varying levels of THC, CBD, and related cannabinoid compounds.

### **B. Interaction Between the Definitions of “Cannabis,” “Cannabis Product,” and “Hemp”**

The terms “cannabis” and “cannabis product” should be clearly defined and should specify (if appropriate) the source of the article. The term “hemp-derived CBD” should also be used to differentiate from synthetic-derived CBD. Such definitions will help to identify the substance to which the name applies, and the name that may be used by healthcare professionals, patients, or consumers. Suitable definitions are critical for highly variable botanicals such as cannabis. Based on extensive analysis of data, the USP Cannabis Expert Panel recently suggested differentiation of cannabis into three chemotypes – THC-dominant, CBD-dominant and THC/CBD intermediate type.<sup>19</sup> Quality specifications associated with particular names could help in establishing the identity of the articles and in differentiating articles that are named differently.

In addition, we recommend that definitions for “cannabis,” “cannabis product,” and “hemp-derived CBD” clearly articulate the appropriate regulatory paradigm for each product. For example, because the revised definition of “dietary supplement” in proposed section 502 of the CAOA Discussion Draft excludes “cannabis products,” which are defined not to include hemp under the proposed section 201(ss) of the FFDCa, dietary supplements containing permissible hemp ingredients (including CBD derived from hemp) would not be subject to any of the provisions of proposed Chapter XI of the FFDCa, including any standards that are developed for cannabis products under proposed section 1106 of the FFDCa. Regarding hemp, because it is not included in the definition of “cannabis,” the requirements under proposed Chapter XI will also not apply to conventional food products containing hemp ingredients.

USP is concerned that these proposed definitional changes will create varying quality requirements for ingredients derived from cannabis, depending on whether or not the products are subject to the requirements for “cannabis products” defined under proposed section 201(ss) of the FFDCa. Thus, we recommend that the CAOA Discussion Draft language clarify the applicability of standards under proposed section 1106 to cannabis ingredients.

### **C. Interaction Between the Definitions of “Cannabis,” “Cannabis Product,” and FFDCa Drugs Containing Cannabis**

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<sup>18</sup> FDA Guidance, *supra* note 13.

<sup>19</sup> See Sarma ND, et al., *supra* note 17.

We note that under the CAO A Discussion Draft, it appears that if a “cannabis product” meets the definition of a “drug” under section 201(g)(1) of the FFDC A, including an unapproved new drug, it would not be considered a “cannabis product” subject to any cannabis standards established under proposed section 1106 of the CAO A Discussion Draft. USP is concerned that this definitional language could cause confusion about the appropriateness of enforcing standards established under proposed section 1106 for unapproved products meeting the definition of a “drug” (e.g., products containing cannabis and bearing disease claims).

In addition, we recommend that the CAO A Discussion Draft clarify FDA’s enforcement authority such that FDA has appropriate enforcement mechanisms to ensure that for cannabis ingredients, regardless of whether they are included in products defined as drugs, foods, dietary supplements, or cosmetics, are regulated to meet appropriate quality standards. The CAO A Discussion Draft does not include all of the same enforcement mechanisms that are available for food, drug, and cosmetic products, for products regulated exclusively under proposed Chapter XI.

Regarding the development of drugs containing cannabis and cannabis products, we refer to FDA’s recently issued draft guidance.<sup>20</sup> Legally marketed drug products have to undergo FDA’s approval process to determine if the drug is safe and effective for a particular indicated use. The draft guidance includes reference to certain USP general chapters as considerations for drug development using cannabis or cannabis-derived compounds. USP provided comments in response to this draft guidance discussing resources for information on quality considerations for cannabis used for clinical research.<sup>21</sup>

#### **D. Appropriate Classification and Regulation of Synthetically-Derived THC and CBD**

Cannabinoids, such as THC or CBD, can be isolated from the cannabis plant, or derived through synthetic processes. There are currently FDA-approved drug products that contain dronabinol, a synthetically derived delta-9 THC, as the active pharmaceutical ingredient.<sup>22</sup>

Substances that are chemically indistinguishable will exhibit the same biological properties, irrespective of whether the source is natural or synthetic. Use of public quality standards can help to control the quality of synthetically-derived or cannabis-

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<sup>20</sup> FDA draft guidance on “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research,” at <https://www.fda.gov/media/140319/download> (July 2020).

<sup>21</sup> USP comments in response to 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>.

<sup>22</sup> Marinol (dronabinol) was approved in 1985, Syndros (dronabinol) was approved in 2016, in addition to multiple generic drug products.

derived constituents, including setting appropriate limits for impurities. USP standards may help demonstrate if the quality of two ingredients that are obtained using different processes are similar.

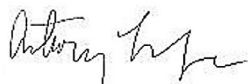
#### IV. Conclusion

USP remains dedicated to improving global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines, foods, and dietary supplements. Irrespective of any regulatory pathway for products containing cannabis and cannabis-derived substances, including CBD, USP supports the adherence to science-based, public quality standards for products that are legally marketed in the United States. This is particularly important due to the variability in cannabis and cannabis-related products, quality issues related to these products, and the significant increase in the number of cannabis products that exist in the U.S. marketplace.

As such, legislative language highlighting the need for standards for cannabis products, such as in proposed section 1106 of the FFDCA in the CAO Discussion Draft, is essential to help protect public health. Based on our 200-year contribution to botanical standards, USP is in a unique position to contribute scientifically valid analytical methods and data-based acceptance criteria, supported by appropriate reference standards, to define identity, composition/assay and toxicologically based limits on contaminants.

Thank you for the opportunity to discuss the importance of quality in products containing cannabis and how public standards can help ensure the quality of cannabis and cannabis-derived compounds. For more information, please contact Joseph M. Hill, Director, U.S. Government Affairs (202) 239-4137 or [joe.hill@usp.org](mailto:joe.hill@usp.org).

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# Attachment

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

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 cannabis and cannabis-derived compounds, we recommend that they consider certain USP guidelines and standards (e.g., general chapters and reference standards). We have elaborated on these considerations in our comments to FDA and the United States Department of Agriculture (USDA).<sup>23</sup>

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,<sup>24</sup> 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*

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<sup>23</sup> 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,” submitted Sept. 17, 2020, at <https://www.regulations.gov/document?D=FDA-2020-D-1079-0029>.

<sup>24</sup> 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.

*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, 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.<sup>25</sup>

## **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 (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.<sup>26</sup> 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*;

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<sup>25</sup> 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>.

<sup>26</sup> 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),<sup>27</sup> 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

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<sup>27</sup> 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).

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.

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.<sup>28</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>29</sup>

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.<sup>30</sup> USP has also developed thoroughly characterized unique cannabinoid reference standards, which are qualified for applications such as identification tests, system

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<sup>28</sup> See Sarma ND, et al., *supra* note 17.

<sup>29</sup> FDA Guidance, *supra* note 13.

<sup>30</sup> See Sarma ND, et al., *supra* note 17.

suitability tests, or chromatographic peak markers, and for quantitative measurements.<sup>31</sup>

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 the 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 (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.<sup>32</sup>

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.<sup>33</sup> Because the

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<sup>31</sup> For more information, see <https://www.usp.org/dietary-supplements-herbal-medicines/cannabis>.

<sup>32</sup> 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>.

<sup>33</sup> 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).

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*. 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.<sup>34</sup> 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 contaminants for CBD, with suitable methods to analyze related compounds or impurities derived from hemp or from synthetic processes.

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<sup>34</sup> 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>.