

VIA ELECTRONIC SUBMISSION

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FOR SUBMISSION TO “GENERAL COMMENT” SECTION

The United States Pharmacopeia (USP) appreciates the opportunity to provide comments for this consultation. USP is an independent, scientific, nonprofit public health organization devoted to improving global public health through the development of public standards and related programs that help ensure the quality, safety, and benefit of medicines, dietary supplements, and foods. 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 in the *Food Chemicals Codex (FCC)*. USP develops public quality standards for medicines, food ingredients, and dietary supplements through an open, transparent process, with participation from academia, healthcare, industry, and government. One of USP’s areas of expertise and focus is the development of standards for articles of botanical origin, including analytical procedures and acceptance criteria to help ensure their identity, purity, and strength.

With respect to the legal and regulatory status of cannabis and cannabis-containing products, USP defers to the applicable government authorities. 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 cannabis-containing products to help protect patients and consumers from harm.

In light of the known quality issues with cannabis and the active ongoing clinical research in this field, healthcare professionals, the research community, and the public will benefit from increased quality control of cannabis. Information on the quality attributes of materials in terms of identity, composition, and purity, and the scientific resources to test for these, can help prevent patient harm resulting from exposure to substandard, contaminated, or adulterated cannabis products. In addition, cannabis and its constituents prepared according to consistent quality standards can increase the reproducibility and applicability of preclinical and clinical data.

The USP Cannabis Expert Panel published information on cannabis inflorescence quality specifications for medical purposes. (See Sarma ND, *et al.*, “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> (hereinafter referred to as “USP publication”). 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.

I. Essential Quality Attributes for Cannabis and Cannabis-Containing Products

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. Additional considerations include controls for process-related degradants in cannabis-containing products, such as extracts which undergo solvent extractions and undergo multiple stages of purification.

As regulatory bodies are developing product quality specifications for cannabis and cannabis-containing products, we recommend that they consider certain USP guidelines and standards (e.g., documentary standards and reference standards). Documentary and reference standards help to assess the quality, strength, identity, and purity of chemical medicines, biologics, food chemicals and ingredients, and dietary supplements, among other items. Documentary standards are published the *USP-NF* or *FCC*, and the reference standards are highly characterized ingredients, developed in alignment with the specifications outlined in the *USP-NF* or *FCC*, to verify that the product and its ingredients can pass tests to ensure adherence to quality specifications.

For botanically-derived products, such as those including cannabis and cannabis-containing products, 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

Identity is an important attribute for defining cannabis and cannabis-containing products. 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 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 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 delta-9 tetrahydrocannabinol (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.

B. Nomenclature

Identity of cannabis and cannabis-containing products should be linked with clear nomenclature, including reference to plant part, product, and/or herbal preparation and processing. USP believes that more guidance is needed on adequate descriptions and appropriate nomenclature to describe cannabis and cannabis-containing products, including hemp and its extracts. This is due to the extensive and varied approaches to the naming of cannabis varieties (“strains”) and its derived products (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. 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 U.S. FDA’s draft guidance, “Dietary Supplement: New Dietary Ingredient Notifications and Related Issues” (See <https://www.fda.gov/media/99538/download> (Aug. 2016)).

C. Composition

Because the effects of the cannabis article depend on its chemical composition, fit-for-purpose validated analytical methods are needed to quantitatively measure the constituents. While delta-9 THC and cannabidiol (CBD) are the well-known and most-studied cannabinoids, their chromatographic separation from other cannabinoids, which could be psychoactive, 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.).

D. 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. (See Ma C, Oketch-Rabah H, 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). 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*;
- USP Chapter <2021> *Microbiological Enumeration Tests-Nutritional and Dietary 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.

E. 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), “Validation of Analytical Procedures: Text and Methodology,” with appropriately characterized reference standards could be used to develop validated test methods that accurately determine the content of delta-9 THC, as well as other components of interest. 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.

F. Sampling Considerations

A robust sampling plan 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.

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. Packaging, Labeling, and Other Recommendations

A. Packaging and Storage

Regarding packaging and storage considerations, cannabis inflorescence should be stored in a cool and dry place in well-closed containers and protected from light and moisture. Water activity during storage should be maintained at 0.60 ± 0.05 . USP General Chapter <659> *Packaging and Storage Requirements* defines cool conditions at any temperature between 8 and 15°C (46°F and 59°F), and a dry place to be a place that does not exceed 40% average relative humidity at 20°C (68°F) or the equivalent water vapor pressure at other temperatures. (See USP Publication).

B. Labeling

Appropriate labeling information helps patients and healthcare practitioners assess whether a product is suitable for particular needs. In addition to ensuring compliance with the applicable state or country requirements for labeling, standardized definitions for the ingredients in cannabis products help describe an article appropriately. USP nomenclature guidelines may be useful in this regard. (See USP Herbal Medicines Compendium, Guideline for Assigning Titles to USP Herbal Medicines Compendium Monographs, Version 1.0, at https://hmc.usp.org/sites/default/files/documents/Nomenclature_guideline/HMC%20Nomenclature%20Guidelines%20v.%201.0.pdf).

Considering the wide variety of cannabis chemotypes, product labeling should specify the nature of the article and whether the plant chemotype is THC-dominant (commonly referred to as Type I), THC/CBD-intermediate (commonly referred to as Type II), or CBD-dominant (commonly referred to as Type III). The label should state the name of the article as *Cannabis* Inflorescence and the scientific Latin binomial. The label should state in mg/g the amount of the “total THC,” taking into account the potential of tetrahydrocannabinolic acid (THCA) to convert to THC, the amount of the “total CBD,” taking into account the potential for cannabidiolic acid (CBDA) to convert to CBD, and any other cannabinoids above 10 mg/g. Since there is a need to investigate the pharmacological interplay between cannabinoids and terpenes, as well as the effects of some of these terpenes on certain clinical conditions, the label should also indicate the dominant or co-dominant terpene(s) as determined by appropriate testing methodologies. In cases where the product conforms to limits for inhaled use found in USP General Chapter <1111> *Microbiological Examination of Nonsterile Products*:

Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use, and in order to aid at-risk populations—those with a pre-existing lung disease, infectious diseases, or immunocompromised function, which may further increase the risk of harm—to choose lower-risk products, the label should identify the product as having a reduced microbial load. When the material is subjected to a microbial reduction process such as irradiation, the method used must be indicated.

Additional requirements for proper packaging and labeling are also necessary to protect the article and to communicate to potential patients, consumers, and healthcare practitioners certain characteristics of the product. These characteristics may include specific ratios between CBD and THC, information about other cannabinoids and terpenes, and any stability/storage information.

C. Water Activity

In the context of the quantitative expression of cannabinoids, the USP Cannabis Expert Panel suggested that the content of cannabinoids should be calculated on a fixed water activity basis. This Panel suggested that the cannabis inflorescence be tested as received at the fixed water activity to reflect the cannabinoid content of the material as received by the consumer. The USP Cannabis Expert Panel recommended that the storage conditions of dried cannabis maintain the water activity (a_w) at 0.60 ± 0.05 to align with the American Society for Testing and Materials (ASTM) specification to maintain water activity, and that laboratories ensure they maintain the water activity of cannabis samples prior to testing so that cannabinoid levels are accurately measured. The recommended water activity level is intended to prevent the material from degradation due to excessive drying (water activity below 0.55) or microbial growth (water activity above 0.65). Reduced water activity will greatly assist in the prevention of microbial proliferation and spoilage.

USP General Chapter <1112> *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* provides information regarding control of water activity for reducing the susceptibility of formulations to microbial contamination. USP General Chapter <922> *Water Activity* outlines the recommended methods to qualify, calibrate, and use water activity meters to accurately measure the water activity of raw materials and products.

USP comments to the United States Department of Agriculture (USDA) in response to the interim final rule on “Establishment of a Domestic Hemp Production Program” highlighted the value of specifications for water activity in the context of expressing analytical measurements on the “dry weight basis.” (See USP comments to USDA in response to 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>.) Since plant material can contain volatile constituents that impact the determination of water by loss on drying, and drying at high temperature may lead to loss of mass due to decarboxylation and other degradation not related to water loss, we suggested that the methods for determining the dry weight basis be clearly defined. The loss on drying of the same material can lead to different results if the material is dried at different temperatures. Loss on drying procedures are typically performed at 105°C for 2 hours or longer until constant consecutive measures are obtained. However, for plant materials with high content of volatiles, pharmacopeial procedures recommend drying over a desiccant (typically phosphorous pentoxide) in a desiccator at low temperatures for several

hours. Specifically, for cannabis, we propose to standardize the definition of “dry weight basis” as a material that has a water activity of not more than 0.65. The wet or fresh plant material should be allowed to dry in a desiccator at not more than 40°C until it reaches the standardized water activity. Analytical determinations on plant materials on the dry weight basis defined in this way should be consistent and accurate, avoiding bias due to the loss of content of volatile constituents and thermal degradation that typically occur at high temperatures.

D. Reportable Value and Measurement Uncertainty

Pertinent to the labeled values of cannabinoids, such as CBD and THC, we would like to highlight a possibility that some test methods might have a larger range of uncertainty that could potentially impact the accuracy of reported results.

The General Notices and Requirements section (General Notices) of the *USP-NF* presents the basic assumptions, definitions, and default conditions for the interpretation and application of the *USP-NF*. General Notices, Section 7, *Test Results*, 7.10 *Interpretation of Requirements* provides guidelines for comparing the analytical results observed in the laboratory (or calculated from experimental measurements) with the stated acceptance criteria to determine whether a lot conforms to the requirements. The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented. Where acceptance criteria are expressed numerically in the *USP-NF* through specification of an upper and/or lower limit, permitted values include the specified values for the acceptance criteria themselves, but no values outside the limit(s). Of relevance for limiting the delta-9 THC concentration in hemp to NMT 0.3%, the acceptance criteria are considered significant to the last digit shown.

According to the General Notices Section 7, *Test Results* 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 needed, 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 5, it is eliminated, and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated, and the preceding digit is increased by 1. 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 General Notices rounding rules.

Thank you again for the opportunity to comment on Health Canada’s proposed regulation amendments for cannabis and cannabis-containing products. We welcome the prospect of meeting with Health Canada to discuss how USP approaches, including documentary and reference standards, can help ensure the quality of cannabis and cannabis-containing products. For more information, please contact Nandakumara Sarma, PhD, RPh, Director, Dietary Supplements and Herbal Medicines, at (301) 816-8354 or DNS@usp.org.

Sincerely yours,

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FOR SUBMISSION TO “REGULATORY DEVELOPMENT—REFERENCE STANDARDS AND TEST KITS” SECTION

The United States Pharmacopeia (USP) appreciates the opportunity to provide comments for this consultation. USP is an independent, scientific, nonprofit public health organization devoted to improving global public health through the development of public standards and related programs that help ensure the quality, safety, and benefit of medicines, dietary supplements, and foods. 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 in the *Food Chemicals Codex (FCC)*. USP develops public quality standards for medicines, food ingredients, and dietary supplements through an open, transparent process, with participation from academia, healthcare, industry, and government. One of USP’s areas of expertise and focus is the development of standards for articles of botanical origin, including analytical procedures and acceptance criteria to help ensure their identity, purity, and strength.

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

With respect to the legal and regulatory status of cannabis and cannabis-containing products, USP defers to the applicable government authorities. 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 cannabis-containing products to help protect patients and consumers from harm.

Reference Standards and Test Kits

Health Canada seeks to authorize analytical testing license holders and government laboratories, beyond the currently licensed processors, to sell reference standards. Based on USP’s extensive experience as the provider of pharmacopeial reference standards, the following comments are provided to inform the public health need for well-characterized reference standards for reliable results when assessing the quality and strength of cannabis products.

The use of reference standards (RS) is necessary for analytical procedures to accurately identify and measure the content of constituents in a material and can help ensure comparability of results and traceability to Système International d’Unités (SI) units. For the purpose of establishing the identity of cannabis and cannabis-containing products, RS may also be used for qualitative applications such as identification tests, system suitability tests, or chromatographic peak markers. Use of well-characterized RS in conjunction with validated analytical methods is critical in order to ensure the accuracy of reported values, and to help ensure batch to batch consistency. Quality of the reference standards will influence the accuracy of measurements and the reliability of labeled values.

As stated above, USP compendial standards include documentary standards, such as a monograph or general chapter, and associated physical RS. These primary RS are established by a robust collaborative testing approach. (See Zeine C, et al., The Value of Pharmacopeial Reference Standards. *Pharmaceutical Technology* 45 (2) 2021, at <https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards>).

Besides thorough characterization of the candidate reference materials using chromatographic and spectroscopic methods, the purity value is assigned to these RS based on the mass balance after subtracting all the impurities determined using chromatographic methods, and other impurities such as residue on ignition, and water.

The U.S. Food and Drug Administration's guidance for industry, "Analytical Procedures and Methods Validation for Drugs and Biologics," states, "Reference standards can often be obtained from USP and may also be available through European Pharmacopoeia, Japanese Pharmacopoeia, World Health Organization, or National Institute of Standards and Technology." The FDA guidance notes that reference materials from other sources should be characterized by procedures including routine and beyond routine release testing as described in ICH Q6B, "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products." Orthogonal methods for reference material characterization may also be needed. Additional testing could include attributes to determine the suitability of the reference material not necessarily captured by the drug substance or product release tests (e.g., more extensive structural identity and orthogonal techniques for potency, purity and impurities). Quality systems are needed for qualification/calibration of a new batch of reference standard material against current RS to prevent drift in the quality attributes. ICH Q7, "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," notes that primary reference standards should be obtained, as appropriate, for the manufacture of active pharmaceutical ingredients. If secondary reference standards are used, the suitability of such should be determined by comparing against the primary reference standard.

USP provides the following thoroughly characterized materials whose use with the analytical methods in the USP publication are validated for their intended use:

- [USP Delta-9-Tetrahydrocannabinol](#) RS 1 mL (1 mg/mL)
- [USP Cannabidiol Solution RS](#) 1 mL (1 mg/mL)
- [USP Cannabidiol RS](#) 30 mg
- [USP Cannabinoid Acids Mixture RS](#) 1 mL
 - 0.25 mg of tetrahydrocannabinolic acid (THCA) [CAS 23978-85-0]
 - 0.25 mg of cannabidiolic acid (CBDA) [CAS 1244- 58-2]
 - 0.050 mg of tetrahydrocannabivarinic acid (THCVA) [CAS 39986-26-0]
 - 0.025 mg of cannabidivarinic acid (CBDVA) [CAS 31932-13-5]
 - 0.025 mg of cannabigerolic acid (CBGA) [CAS 25555-57-1]
- [USP Cannabinoids Mixture RS](#) 1 mL
 - 0.25 mg of tetrahydrocannabinolic acid (THCA) [CAS 23978-85-0]
 - 0.25 mg of cannabidiolic acid (CBDA) [CAS 1244- 58-2]
 - 0.050 mg of tetrahydrocannabivarinic acid (THCVA) [CAS 39986-26-0]
 - 0.025 mg of cannabidivarinic acid (CBDVA) [CAS 31932-13-5]
 - 0.025 mg of cannabigerolic acid (CBGA) [CAS 25555-57-1]

- 0.025 mg of cannabigerol (CBG) [CAS 25654-31- 3]
- 0.025 mg of tetrahydrocannabivarin (THCV) [CAS 31262-37-0]
- 0.025 mg of cannabidivarin (CBDV) [CAS 24274- 48-4]
- [Exo-tetrahydrocannabinol \(1 mL\)](#) (1 mg/mL)

We recommend the use of USP reference standards for cannabis and cannabinoids to validate the development of test kits by analytical testers and government laboratories in Canada. This can help ensure the results from their methods.

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Thank you again for the opportunity to comment on Health Canada’s proposed regulation amendments for cannabis and cannabis-containing products, in particular the section on reference standards and test kits. We welcome the opportunity to meet with Health Canada to discuss how USP approaches, including reference standards, can help ensure the quality of cannabis and cannabis-containing products. For more information, please contact Nandakumara Sarma, PhD, RPh, Director, Dietary Supplements and Herbal Medicines, at (301) 816-8354 or DNS@usp.org.

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