USP Cannabis Quality Attributes

There is an active and growing interest in the use of cannabis for medical purposes. As such, there is a critical need for standardizing the quality attributes for cannabis and related products to help protect patients and consumers from harm. Cannabis quality attributes can help mitigate public health risks associated with contaminated, substandard, or adulterated products and support sound and reproducible clinical research.

As cannabis plant material represents a heterogeneous matrix that can contain a complex secondary metabolome with an uneven distribution of constituents, ensuring quality of cannabis and related products requires appropriate sampling procedures and a suite of tests, analytical procedures, and acceptance criteria to define the identity, content of constituents (e.g., cannabinoids), and limits on contaminants. Appropriate tests are needed to connect the nomenclature of cannabis and related products with specifications for the identification and quantitative determination of critical constituents. Limits for contaminants are required to control pesticide residues, microbial levels, mycotoxins, and elemental contaminants based on toxicological considerations.

Considering the inherent variability of cannabis plant materials, the United States Pharmacopeia (USP) Cannabis Expert Panel recently published an article in the *Journal of Natural Products* on differentiation between cannabis chemotypes ("USP JNP article").[1] Cannabis plants in each of these chemotypes may be further subcategorized based on the content of other cannabinoids and/or mono- and sesquiterpene profiles. Science-based analytical methods and acceptance criteria provided by the USP Cannabis Expert Panel are aligned with the existing USP procedures for general tests and assays.

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, including risks related the quality of these products. Cannabis manufacturers may not be aware of how to ensure the quality of their product, for example, quality control, manufacturing processes, and laboratory testing of ingredients to specifications. USP resources, including the USP JNP article, USP General Chapters, HMC monograph and reference standards outlined below can be used to support quality specifications for cannabis and facilitate scientific research on cannabis safety and therapeutic potential. USP public comments to U.S. federal agencies provide further elaboration of USP resources.[2]

USP is committed to supporting manufacturers and regulators in developing appropriate quality specifications for cannabis, cannabis-derived products, and cannabis-related compounds to help address potential harm to the public. With respect to the national legal and regulatory status of cannabis and cannabis-derived products, USP defers to the U.S. Food and Drug Administration (FDA), and other applicable government authorities.

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[1] 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.

[2] USP comments include the following: 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.

USP Resources for Manufacturers, Healthcare Professionals and Regulatory Bodies

Identity and Nomenclature

The genus *Cannabis* includes several species, subspecies, varieties, and chemotypes. USP believes that adequate descriptions and appropriate nomenclature are necessary to describe cannabis and cannabis-derived products, including hemp and its extracts. Based on the secondary metabolite profiles, the Expert Panel suggested adoption of three broad chemotypes of cannabis for labeling: (1) tetrahydrocannabinol (THC)-dominant chemotype; (2) intermediate chemotype with both THC and cannabidiol (CBD); and (3) CBD-dominant chemotype. The following resources can help in establishing the identity of these products with clear nomenclature, including reference to plant part, product, and/or herbal preparation.

- The USP JNP article provides recommended quality specifications for naming and differentiating three major chemotypes of cannabis inflorescence.
- USP nomenclature guidelines for the naming of botanical dietary supplement products was developed to be in alignment with FDA's draft guidance on dietary supplements.
- 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.

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, specifically, delta-9 THC and CBD, which are the most well-known and most-studied cannabinoids.

- HPLC and GC methods are provided in the Supporting Information for the USP JNP article.

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. The USP JNP article provides appropriate tests and assays contained in USP General Chapters and acceptance criteria to control contaminants and may be useful for quality assurance. These General Chapters include the following:

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

- USP General Chapter <232> *Elemental Impurities—Limits*

- USP General Chapter <561> *Articles of Botanical Origin*: Pesticide Residue Analysis; Test for Aflatoxins

- USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*: Microbial limits for products that conform to limits for inhalation use.

Validation of Analytical Testing Methods

Use of scientifically valid analytical methods are necessary to ensure reliable measurements. The *USP-NF* includes the following compendial procedures to establish the suitability of analytical methods:

- USP General Chapter <1225> *Validation of Compendial Procedures*

This chapter is aligned with ICH *Q2 (R1)*,[3] 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.

Reference Standards

The use of reference standards (RS)[4] 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-derived products, RS may also be used for qualitative applications such as identification tests, system suitability tests, or chromatographic peak markers. USP provides the following thoroughly characterized materials whose use with the analytical methods in the USP JNP article are validated for their intended uses:

- 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

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[3] FDA Guidance document: Q2(R1) Validation of Analytical Procedures: Text and Methodology Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q2r1-validation-analytical-procedures-text-and-methodology-guidance-industry

[4] Physical reference standards are highly characterized ingredients, developed in alignment with the specifications outlined in the *United States Pharmacopeia-National Formulary* (*USP–NF*) or *Food Chemicals Codex* (*FCC*). They are used in conjunction with these documentary standards to verify that the product and its ingredients can pass tests to ensure adherence to quality specifications.

- USP Cannabinoids Mixture RS1 mL
- Exo-tetrahydrocannabinol (1 mL) (1 mg/mL)

Sampling Considerations

Robust sampling for lots of cannabis plant materials is needed for testing to generate analytical data representative of the entire lot. Improper sampling methods could lead to a potentially inaccurate estimation of cannabinoid content. The following chapter describes the sampling procedures applicable to botanical drugs, including procedures for gross sampling from multiple batches and the test sampling methods.

- USP General Chapter <561> *Articles of Botanical Origin*

Labeling

Excerpted *USP-NF* Standards

- General Chapter <7> Labeling: A resource that provides definitions and standards for labeling of official articles.

On-Demand Education

- Labeling Requirements for Prescription Drugs, Updates, and Future Direction: A 90-minute on-demand webinar that provides an overview of container labeling issues, standards, and regulations

Packaging

Excerpted *USP-NF* Standards

- Chapter <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems: A framework for the design, justification, and execution of an extractables assessment for packaging and delivery systems
- Chapter <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems: A framework for the design, justification, and implementation of assessments for leachables derived from packaging and delivery systems
- Chapter <671> Containers—Performance Testing: A resource to provide standards for the functional properties of packaging systems
- Chapter <659> Packaging and Storage Requirements: A resource to provide packaging definitions, auxiliary packaging information, and storage condition definitions relevant to storage and distribution

On-Demand Education

- Good Pharmaceutical Packaging: Extractables & Leachables: A 1-day course that addresses the increased regulatory concerns regarding extractables and leachables related to the interaction of drug products with various drug product contact surfaces—including packaging systems and pharmaceutical process equipment

USP Ongoing Work and Priorities

Cannabis for Medical Use and Cannabis-Derived Compounds

USP proposed a cannabis inflorescence monograph for inclusion in the non-official compendium, *Herbal Medicines Compendium* (*HMC*),[5] based on information in the USP JNP article on quality considerations for cannabis inflorescence for medical use. Public comments were received on the "Proposed for Comment" monograph and a revised proposal will be published around May 2024. This international publication provides scientifically valid methods, information on physical reference standards, and acceptance criteria to establish the identity of cannabis chemotypes, content of cannabinoids and terpenes, and limits on contaminants.

USP also provided stakeholders with information on product consistency and quality. For instance, USP proposed an informational general chapter[6] <1568> *Quality Considerations for Cannabis and Cannabis-Derived Products for Clinical Research* for inclusion in the *United States Pharmacopeia-National Formulary* (*USP-NF*). This proposed general chapter provides the specifications for quality attributes that are fundamental to characterizing the materials for clinical research. Published in *PF* 49(3) [May–June 2023] for public comment, the General Chapter <1568> complement the FDA Guidance on cannabis quality for clinical research with specific analytical methods and acceptance criteria.[7] The proposed chapter covers the necessary information regarding appropriate specifications, validated analytical procedures, acceptance criteria, and reference standards to assess the quality of cannabis and cannabis-derived products.

CBD as a Drug Substance

The USP Cannabis Expert Panel developed a CBD drug substance monograph proposal intended for eventual inclusion in the *USP-NF*. The USP Cannabis Expert Panel is evaluating the public comments and USP laboratories are verifying the suitability of methods to separate impurities.

Delta-8 THC and Impurities

Products containing delta-8 THC could lead to adverse public health outcomes. USP published perspectives from the Cannabis Expert Panel about delta-8 THC and other cannabinoids and is

[5] The *Herbal Medicines Compendium* (*HMC*) includes standards for herbal articles used in traditional medicines that have been: (1) approved by a national authority for use as ingredients of herbal medicines or included in a national pharmacopeia; and (2) deemed appropriate for inclusion in the *HMC* by a USP Expert Committee. Including standards in the *HMC* as a USP compendium provides a vehicle to disseminate these standards to stakeholders globally and enables a source of updated information, as the science evolves. Since the *HMC* is not an official compendium as defined in the Federal Food, Drug, and Cosmetic Act, adherence is voluntary for products marketed in the United States. The *Dietary Supplements Compendium* (*DSC*) is another non-official compendium that includes monographs for dietary ingredients and dietary supplements. https://hmc.usp.org/monographs/cannabis-species-inflorescence-1-0

[6] General Chapters in the *USP-NF* that are numbered between <1000> and <1999> are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article.

[7] The FDA guidance, "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research," is at https://www.fda.gov/media/164690/download (January 2023). *See also*, USP comments on the FDA draft guidance, "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research," at https://www.regulations.gov/document/FDA-2020-D-1079-0029.

continuing work on analytical methods to resolve impurities.[8] USP has collaborated with an external laboratory to generate information on the identity of impurities in synthesized Δ^8-THC products and develop analytical methods to separate these impurities using chromatographic methods. Thirteen impurities were isolated and characterized by spectral analyses. The method was then applied to the analysis of 21 commercial Δ^8-THC samples, which showed variable impurity profiles.[9] These activities extend the Cannabis EP's commentary on public health concerns regarding Δ^8-THC and provide validated analytical methods to help regulators, industry, and public health professionals characterize the public health concern from products marketed as Δ^8-THC or CBD in terms of their label accuracy, and the levels of contaminants and impurities.

Hemp Aerial Parts and Extracts

Hemp aerial parts are the parts of hemp that grow above the ground and may contain cannabinoids including CBD (unlike the hemp seeds that do not produce cannabinoids). Hemp extracts are variably processed using different solvents and processes (such as decarboxylation, winterization, or distillation) and typically referred to as "full spectrum" and "broad spectrum" extracts, which are not formal titles in compendia. USP is currently examining major quality considerations for hemp aerial parts and its extracts. This includes nomenclature, fingerprint based on naturally occurring cannabinoid profile, limit for delta-9 THC, tests for CBD, tests for terpene profile, and limit for contaminants.

Hemp Seed as Food Products

The USP Food Ingredients Expert Committee developed the hemp seed oil and hemp seed protein food monographs for the *Food Chemicals Codex* (*FCC*). These monographs were published on March 1, 2022 and were effective June 1, 2022. USP continues to seek additional information to inform the total CBD limit[10] in these hemp seed monographs. We intend to host a virtual roundtable discussion, including stakeholders from FDA, Health Canada, ingredient manufacturers, and trade associations, to gain additional input on appropriate CBD limits in hemp seed products. We also intend to procure and test additional commercial hemp seed products to understand current levels of CBD in these products.

This document is for informational purposes for manufacturers and is intended to help address quality of cannabis, cannabis-derived products and cannabis-related compounds. Parties relying on the information in this document bear independent responsibility for awareness of, and compliance with, any applicable federal, state, or local laws and requirements.

[8] USP, https://www.usp.org/sites/default/files/usp/document/our-science/usp-delta-8-final-12-2-21.pdf.
[9] Gul W, Shahzadi I, Sarma N, Kim NC, ElSohly MA. Development and Validation of a GC-FID Method for the Quantitation of Δ 8-Tetrahydrocannabinol and Impurities Found in Synthetic Δ 8-Tetrahydrocannabinol and Vaping Products. Planta Med. 2024 Apr;90(4):316-332. https://pubmed.ncbi.nlm.nih.gov/38387478/
[10] The CBD total limit is ≤ 75 ppm.