USP Perspectives on Cannabis Quality

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Outline

- Introduce USP
- Need for quality controls and USP activities
- USP compendia and proposed cannabis standards – Overview
- Cannabis quality considerations
Mission
To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods
USP standards are set by Expert Volunteers

USP structure at a glance

- Council of the Convention
  - Membership
  - Resolutions
  - Engagement
  - Bylaws
  - Rules
  - Voting/elections

- Convention Membership
  - Elects BoT
  - Elects CoE
  - Adopts Resolutions
  - Amends Bylaws

- Board of Trustees (BoT) and Board Committees
  - Fiduciary
  - Strategy
  - Policy oversight
  - Risk management

- Council of Experts (CoE) and Expert Committees
  - Science and standards-setting decisions

- Expert Panels

- USP Staff
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Information needed on quality considerations for clinical research (see FDA draft guidance)

Varying results from invalid methods

Confusion from lack of a lexicon/glossary

Adulteration with synthetic cannabinoids

https://www.usp.org/dietary-supplements-herbal-medicines/cannabis
Six Years of Stakeholder Engagement

Timeline of Cannabis-Related Activities

- **2016**
  - Stimuli Article
  - Roundtable Discussion
  - USP Cannabis EP formed

- **2020**
  - State Regulators
  - Professional Associations
  - Trade Associations

- **2020-2022**
  - Patient Groups
  - Standards groups

**Notes:**
- The 2016 article analyzes the need for public, quality standards for medical cannabis products for patient safety, which lead to the EP formed that same year.
- The timeline highlights the development of standards and regulations, mentioning the involvement of various stakeholder groups including USP, CANRA, Americans For Safe Access, and more.
- Roundtable discussions and other collaborative efforts were key in achieving these milestones.
Federal regulators

- FDA
  - July 2019 – FDA cannabis docket, “Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds”
- USDA

State regulator (New York)

- Jan. 2021 – NY State proposed rule, “Cannabinoid Hemp”

Non-regulatory body (U.S. Hemp Authority)

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USP compendia and proposed cannabis standards – Overview

Compendia

- **CBD** – published proposed CBD drug substance monograph for *USP-NF* (comment period closed March 31, 2022)
- **General Chapter <1568>** Prospectus
- **HMC monograph** proposed (comment period open)
- **Hemp seed** – published hemp seed oil and hemp seed protein monographs in *FCC* (effective June 1, 2022)

Other Resources & Tools

- **Cannabis inflorescence for medical use** – published quality information in the *Journal of Natural Products*
- **Delta-8 THC and Impurities**
  - Published white paper
  - Impurity analysis for delta-8 THC in products, cannabinoid contaminants, and synthetic impurities in CBD
- **Hemp aerial parts and extracts**
  - Content of CBD, fingerprinting of cannabinoids, limit of delta-9 THC
- **Reference materials** for cannabis and cannabis-derived compounds
Critical Components of Botanical Quality

- Suitable nomenclature
- Definition: botanical characteristics
- Identity: orthogonal tests
- Strength and Composition
- Limits on contaminants
- Labeling

Specifications:
- Scientifically valid analytical methods
- Data-based acceptance criteria
- Suitable reference standards
CBD quality attributes

PF proposal for CBD API monograph – PF48(1) [Jan 2022]

- Tests for ID
- Assay
- Impurity limits
- Enantiomeric purity
- Suitable Reference Standards
<1568> Quality Considerations for Cannabis and Cannabis-derived Products for Clinical Research

Type of Posting: General Chapter Prospectus
Posting Date: 27-May-2022; updated 30-Jun-2022
Expert Committee: Botanical Dietary Supplements and Herbal Medicines (BDSHM)
Input Deadline: 31-Jul-2022

Proposed New Title: <1568> Quality Considerations for Cannabis and Cannabis-Derived Products for Clinical Research

Suggested audience: Organizations, manufacturers, suppliers, regulators, contract research organizations, clinical investigators involved in providing materials for clinical research using cannabis and cannabis-derived products.

Estimated Proposal PF: To be determined
Quality Attributes for Cannabis Inflorescence

Scientifically valid methods with acceptance criteria, supported by fit-for-purpose reference standards

- Identification of major chemotypes
  - Botanical and chromatographic tests

- Quantitation of cannabinoids and terpenes
  - LC and GC methods

- Limits for contaminants - pesticides, microbial load, aflatoxins, elemental contaminants

- Other quality attributes: sampling; water activity; FOM; ash values

- Labeling
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Proposed Cannabis Monograph Open for Public Comment in USP Herbal Medicines Compendium

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Rockville, Md., September 26, 2022 – The United States Pharmacopeia (USP) has opened a 90-day review period for their proposed Cannabis Species Inflorescence monograph in the Herbal Medicines Compendium (HMC), a laboratory quality standards testing reference used internationally. The proposed cannabis monograph provides scientifically validated 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.

“Cannabis is becoming more widely accepted around the world and is being widely researched by many international organizations for medicinal purposes. A key component of USP’s mission to improve global health is providing public standards and guidance to help ensure the quality of all medicines, including herbal medicines,” said Dr. Jaap Venema, USP’s Chief Science Officer.

During the HMC monograph review period, stakeholders, including manufacturers, researchers and regulators, are encouraged to evaluate the definition and constituents of interest, as well as methods and specifications for identification, composition and contaminants. Publicly available

https://hmc.usp.org/monographs/cannabis-species-inflorescence-0-1
Cannabinoid Profile for Identification

Olivetolic acid

Geranyl diphosphate

Divarinic acid

CBG

CBDA

THCA

CBCA

CBDVA

THCVA

CBD

Δ⁹-THC

CBC

CBDV

THCV

Δ⁸-THC

CBN
Criteria for Chemotype Classification

- **THC-dominant chemotype:**
  - principal peak for THCA
  - ratio of the total THC content to total CBD content is NLT 5:1
  - Contains NMT 1% of total CBD and NLT 1% of total THC.

- **CBD-dominant chemotype:**
  - principal peak for CBDA
  - ratio of the total THC content to total CBD content is NMT 1:5
  - contains NMT 1% of total THC and NLT 1% of total CBD

- **THC/CBD intermediate chemotype:**
  - two principal peaks for THCA and CBDA
  - ratio of the total THC content to total CBD content is NLT 0.2:1 and NMT 5:1
  - NLT 1% of total CBD and NLT 1% total THC
Tests for Identification and Cannabinoid Content
Quantitation of the Cannabinoids

• Contains NLT 80% and NMT 120% of the labeled amount (in mg/g) of the total THC or total CBD.
  • Calculation of “total THC” or “total CBD” takes into account the potential of acids to convert quantitatively to decarboxylated forms. For example: \[ \text{Total THC} = \text{THC} + 0.877 \times \text{THCA} \]

• Contains NLT 80% and NMT 120% of the labeled amount of all other cannabinoids measured (in mg/g) and present in an amount of 10 mg/g or more.

• For THC-dominant chemotype, the content of CBN is NMT 2% of the content of total THC. No unidentified peak in the Sample solution chromatogram exceeds the area of the CBN peak.
Dominant and Co-dominant Terpenes

- Caryophyllene-Limonene
- Caryophyllene
- Limonene
- Myrcene-Caryophyllene
- Myrcene-Caryophyllene-Limo
- Myrcene-Limonene
- Myrcene
- Terpinolene
- α-Pinene

Graph shows the parts per million (ppm) for various terpenes.
USP Reference Standards

**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 (1 mg/mL in acetonitrile and trimethylamine with stabilizer):
- 0.25 mg Tetrahydrocannabinolic Acid (THCA)
- 0.25 mg Cannabidiolic Acid (CBDA)
- 0.025 mg Tetrahydrocannabivarinic Acid (THCVA)
- 0.050 mg Cannabidivarinic Acid (CBDVA)
- 0.025 mg Cannabigerolic Acid (CBGA)

**USP Cannabinoids Mixture RS** 1 mL (1 mg/mL in methanol):
- 0.075 mg Delta-9-Tetrahydrocannabinol ($\Delta^9$-THC)
- 0.025 mg Delta-8-Tetrahydrocannabinol ($\Delta^8$-THC)
- 0.050 mg Cannabidiol (CBD)
- 0.025 mg Cannabinol (CBN)
- 0.025 mg Cannabichromene (CBC)
- 0.025 mg Cannabigerol (CBG)
- 0.025 mg Tetrahydrocannabivarin (THCV)
- 0.025 mg Cannabidivarin (CBDV)
Limits for Contaminants

- Pesticide residues – risk-based approach
- <232> Elemental Impurities–Limits for inhalation products
- <561> Articles of Botanical Origin: Test for Aflatoxins

• Microbial Enumeration Tests and Tests for Specified Microorganisms
  - <61> Microbiological Examination of Nonsterile Products
  - <62> Microbiological Examination of Nonsterile Products
  - <1111> Microbiological Examination of Nonsterile Products
  - <1223> Validation of Alternative Microbial Methods
Additional recommendations

- Sampling
- Control water activity
  - <1112> Application of Water Activity Determination to Nonsterile Pharmaceutical Products – control of water activity for reducing the susceptibility of formulations to microbial contamination.
  - <922> Water Activity
- <561> Articles of Botanical Origin describes the method of analysis of foreign organic matter
- Total Ash and Acid-insoluble Ash
  - <561> Articles of Botanical Origin
- Packaging and Storage
The Value of Public Standards

- Appropriate titles
- Useful definitions
- Validated methods
- Established limits

- Helps ensure a consistent approach to quality
- Provides scientific basis for reproducible clinical research
USP Cannabis resources

https://www.usp.org/cannabis

USP-NF General Chapters

USP publications

USP Reference Standards
Thank You