USP Perspectives on Cannabis Quality

Nandu Sarma, Ph.D.

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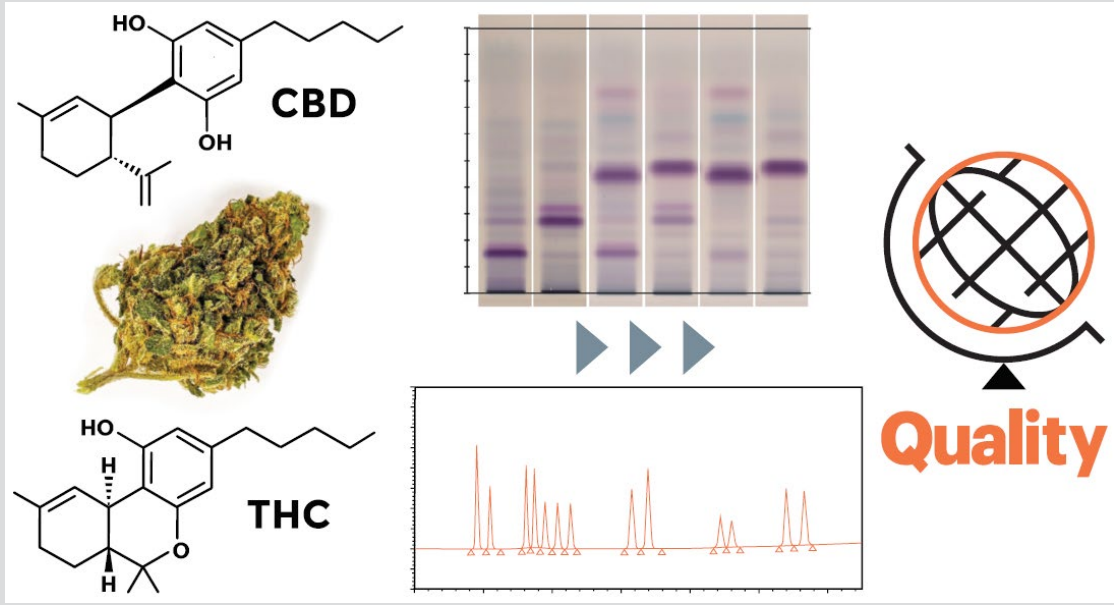


USP-ASTM Cannabis Workshop, December 07, 2022

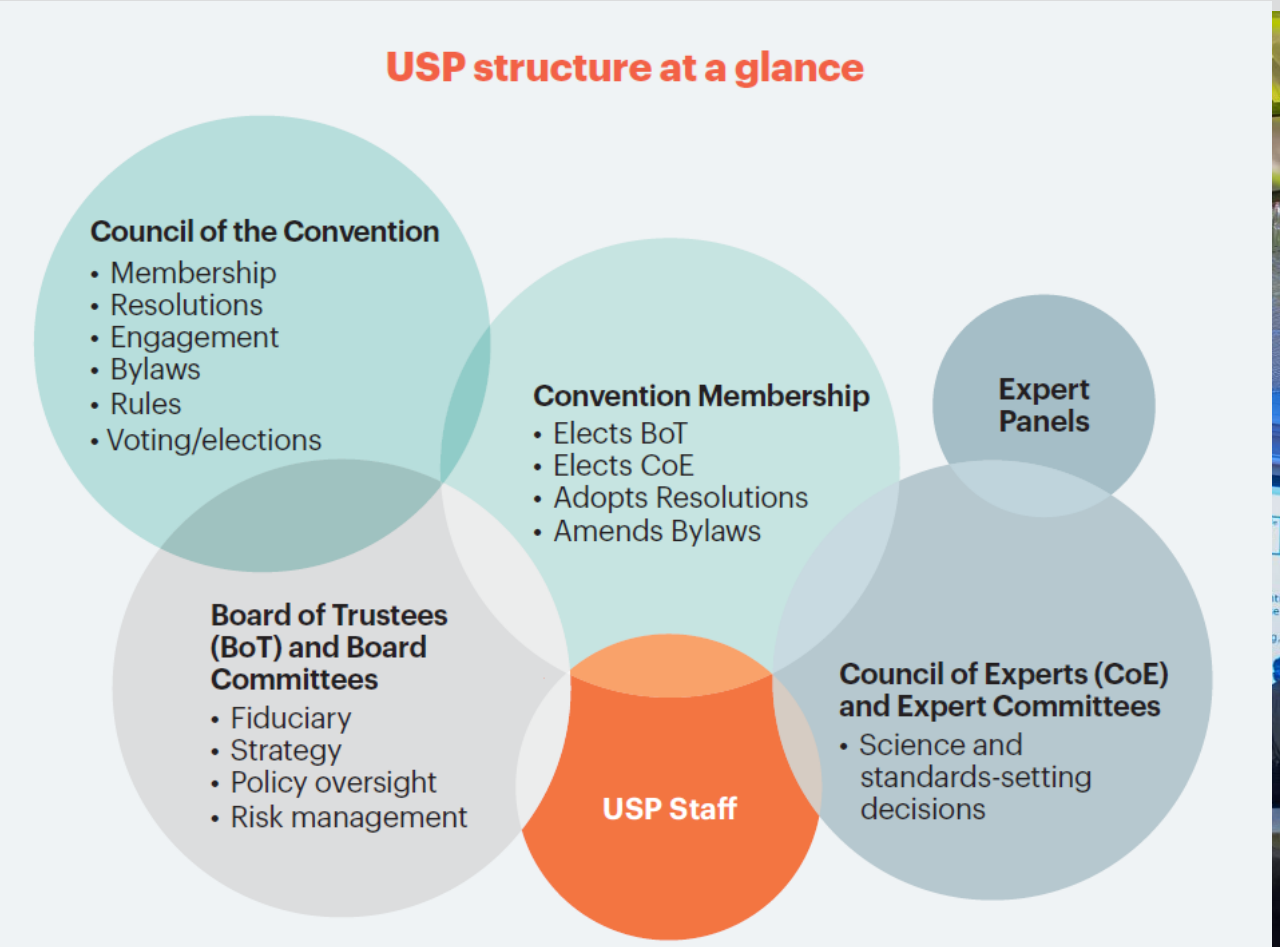
Outline

- Introduce USP
- Need for quality controls and USP activities
- USP compendia and proposed cannabis standards – Overview
- Cannabis quality considerations

Mission

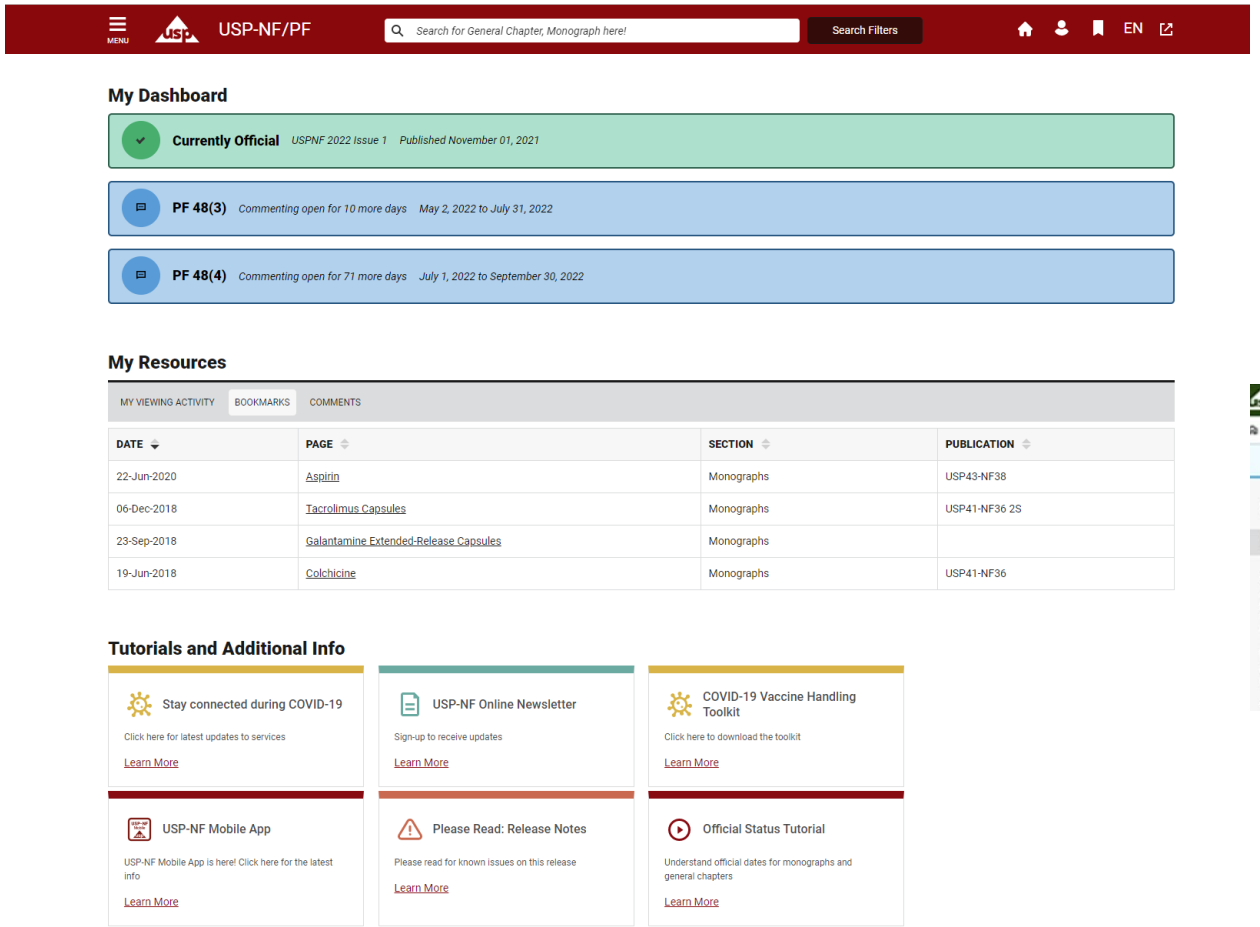
To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods

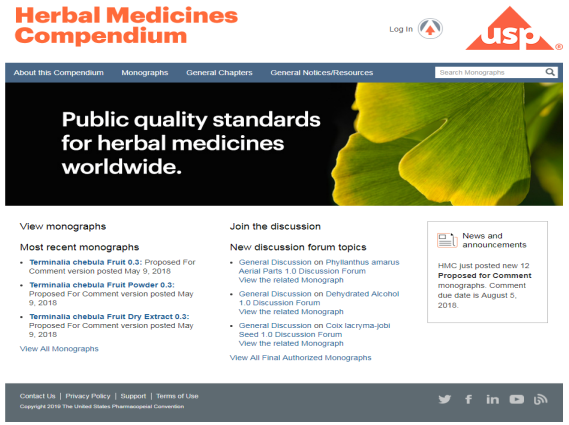
USP standards are set by Expert Volunteers

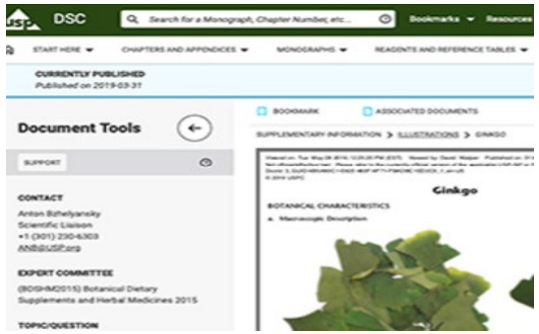


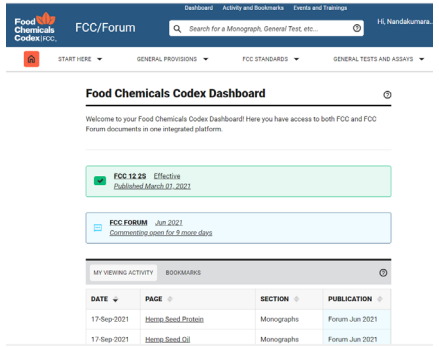
USP Compendia

USP standards used in over 140 countries









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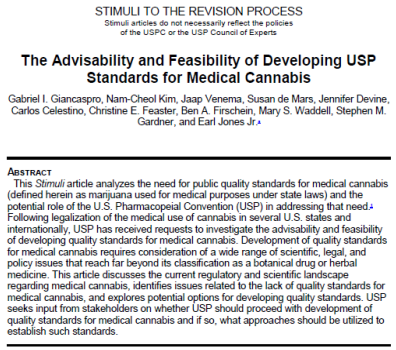
Articulating Quality Attributes for Cannabis Inflorescence to Help Prevent Harm to Patients

- 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


STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

The Advisability and Feasibility of Developing USP Standards for Medical Cannabis

Gabriel I. Giancaspro, Nam-Cheol Kim, Jaap Venema, Susan de Mars, Jennifer Devine, Carlos Celestino, Christine E. Feaster, Ben A. Firschein, Mary S. Waddell, Stephen M. Gardner, and Earl Jones Jr.

ABSTRACT

This *Stimuli* article analyzes the need for public quality standards for medical cannabis (defined herein as marijuana used for medical purposes under state laws) and the potential role of the U.S. Pharmacopeial Convention (USP) in addressing that need. Following legalization of the medical use of cannabis in several U.S. states and internationally, USP has received requests to investigate the advisability and feasibility of developing quality standards for medical cannabis. Development of quality standards for medical cannabis requires consideration of a wide range of scientific, legal, and policy issues that reach far beyond its classification as a botanical drug or herbal medicine. This article discusses the current regulatory and scientific landscape regarding medical cannabis, identifies issues related to the lack of quality standards for medical cannabis, and explores potential options for developing quality standards. USP seeks input from stakeholders on whether USP should proceed with development of quality standards for medical cannabis and if so, what approaches should be utilized to establish such standards.

Stimuli Article

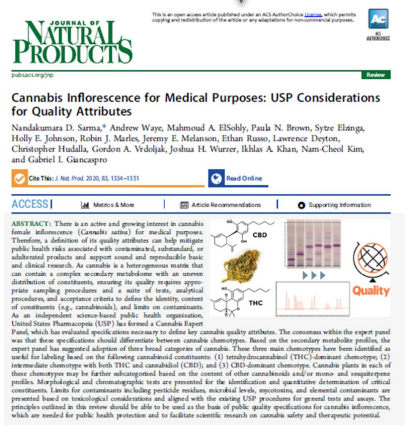
2016

Roundtable Discussion

2016

USP Cannabis EP formed

2020


JOURNAL OF NATURAL PRODUCTS

Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes

Nandakumara D. Sarma,* Andrew Waye, Mahmoud A. ElSohly, Paula N. Brown, Sytze Elzinga, Holly E. Johnson, Robin J. Marles, Jeremy E. Melanson, Ethan Russo, Lawrence Dryton, Christopher Hudalla, Gordon A. Vrdoljak, Joshua H. Wurzer, Ikhlas A. Khan, Nam-Cheol Kim, and Gabriel I. Giancaspro

ABSTRACT: There is an active and growing interest in cannabis female inflorescence (Cannabis sativa) for medical purposes. Therefore, a definition of its quality attributes can help mitigate public health risks associated with contaminated, substandard, or adulterated products and support sound and reproducible basic and clinical research. As cannabis is a heterogeneous matrix that can contain a complex secondary metabolome with an uneven distribution of constituents, ensuring its quality 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. As an independent science-based public health organization, United States Pharmacopeia (USP) has formed a Cannabis Expert Panel, which has evaluated specifications necessary to define key cannabis quality attributes. The consensus within the expert panel was that these specifications should differentiate between cannabis chemotypes. Based on the secondary metabolite profiles, the expert panel has suggested adoption of three broad categories of cannabis. These three main chemotypes have been identified as useful for labeling based on the following cannabinoid constituents: (1) tetrahydrocannabinol (THC)-dominant chemotype, (2) intermediate chemotype with both THC and cannabidiol (CBD), and (3) CBD-dominant chemotype. Cannabis plants in each of these chemotypes may be further subcategorized based on the content of other cannabinoids and/or mono and sesquiterpene profiles. Morphological and chromatographic tests are presented for the identification and quantitative determination of critical constituents. Limits for contaminants including pesticide residues, microbial levels, mycotoxins, and elemental contaminants are presented based on toxicological considerations and aligned with the existing USP procedures for general tests and assays. The principles outlined in this review should be able to be used as the basis of public quality specifications for cannabis inflorescence, which are needed for public health protection and to facilitate scientific research on cannabis safety and therapeutic potential.

2020-2022

CANNRA
CANNABIS REGULATORS ASSOCIATION

State Regulators

Trade Associations

AmericansFor SafeAccess

Patient Groups

Professional Associations

ASTM

Standards groups

AOAC INTERNATIONAL

USP Comments – Cannabis Quality

- Federal regulators
  - FDA
    - July 2019 – FDA cannabis docket, “Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds”
    - Sept. 2020 – FDA draft guidance, “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research”
  - USDA
    - Dec. 2019 – USDA interim final rule, “Establishment of a Domestic Hemp Production Program” (finalized Jan. 2021)
- State regulator (New York)
  - Jan. 2021 – NY State proposed rule, “Cannabinoid Hemp”
- Non-regulatory body (U.S. Hemp Authority)
  - Oct. 2020 – U.S. Hemp Authority Certification Program Standard

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- Cannabis quality considerations

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

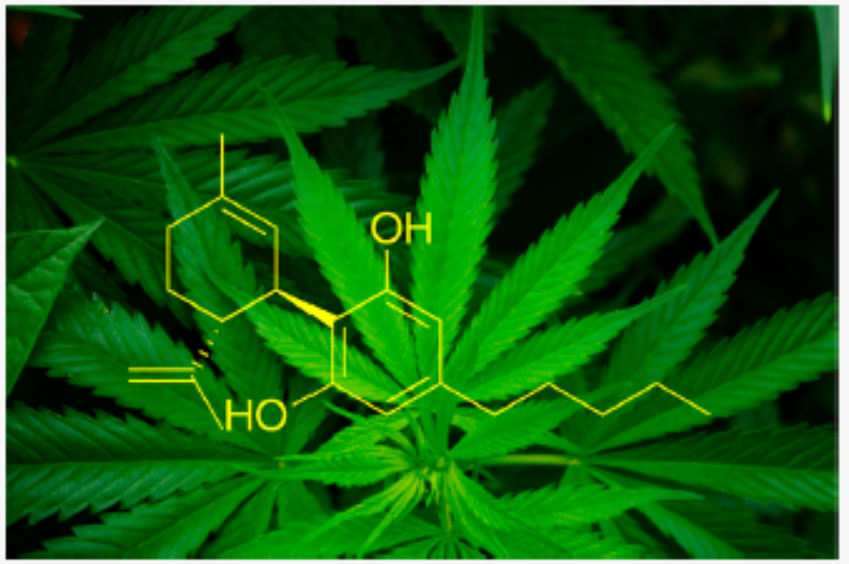
Critical Components of Botanical Quality

- 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*

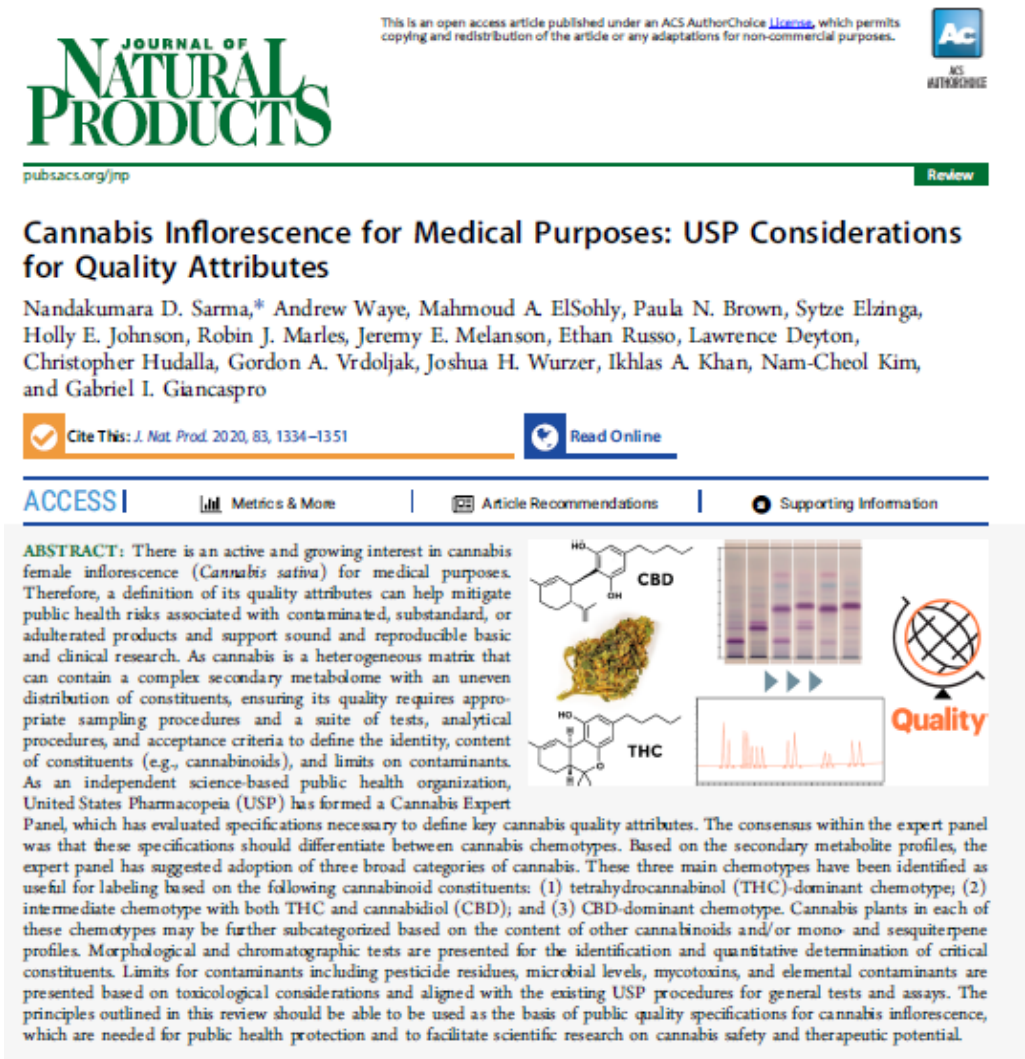
Suggested audience: Organizations, manufacturers, suppliers, regulators, contract research organizations, clinical investigators involved in providing materials for clinical research using cannabis and cannabis-derived products.

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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Review

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Cite This: J. Nat. Prod. 2020, 83, 1334−1351

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- **Cannabis quality considerations**

USP HMC monograph

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

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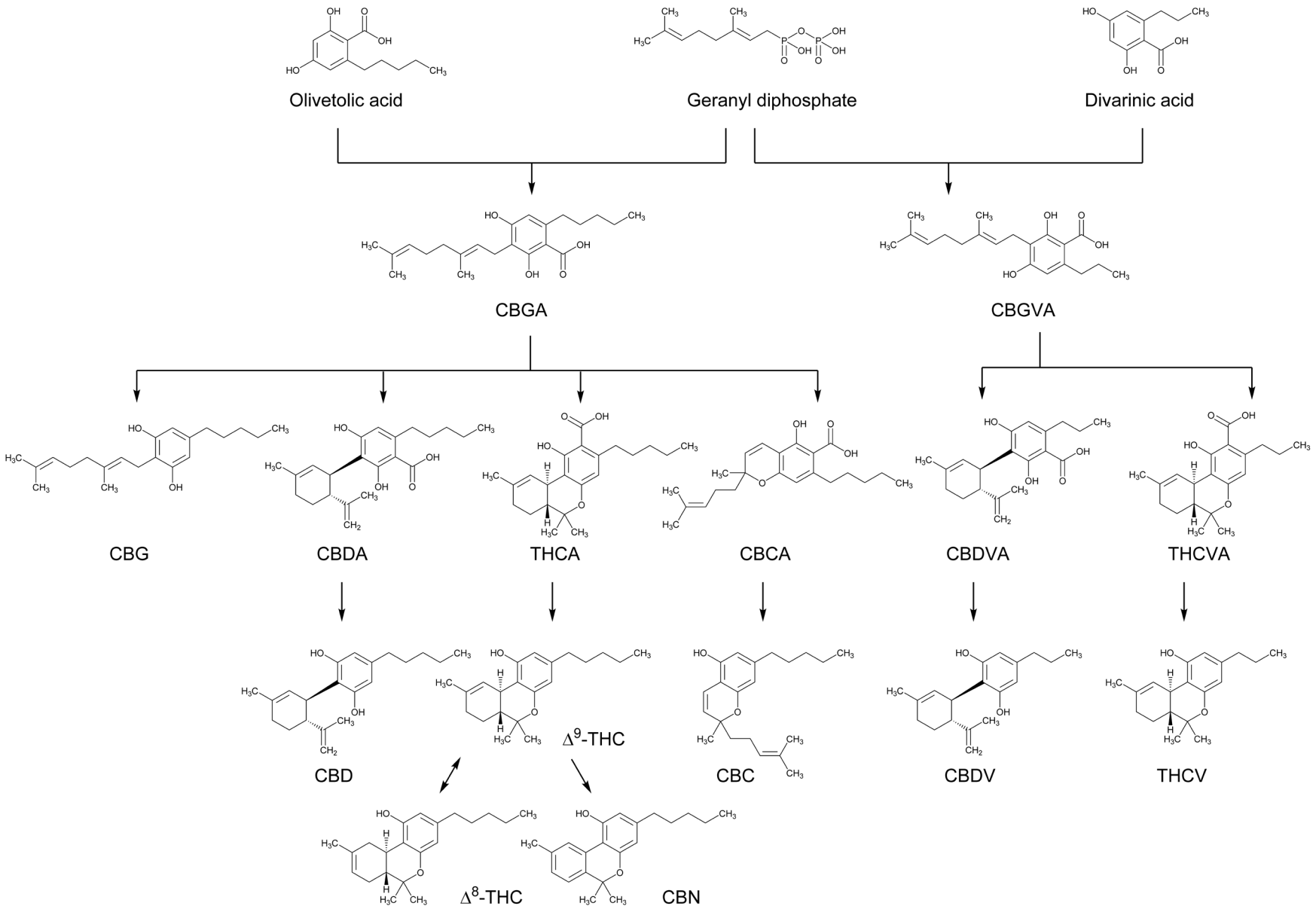
Rockville, Md., September 26, 2022 – The United States Pharmacopeia (USP) has opened a 90-day review period for their proposed *Cannabis* Species Inflorescence monograph in the *Herbal Medicines Compendium (HMC)*, a laboratory quality standards testing reference used internationally. The proposed cannabis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



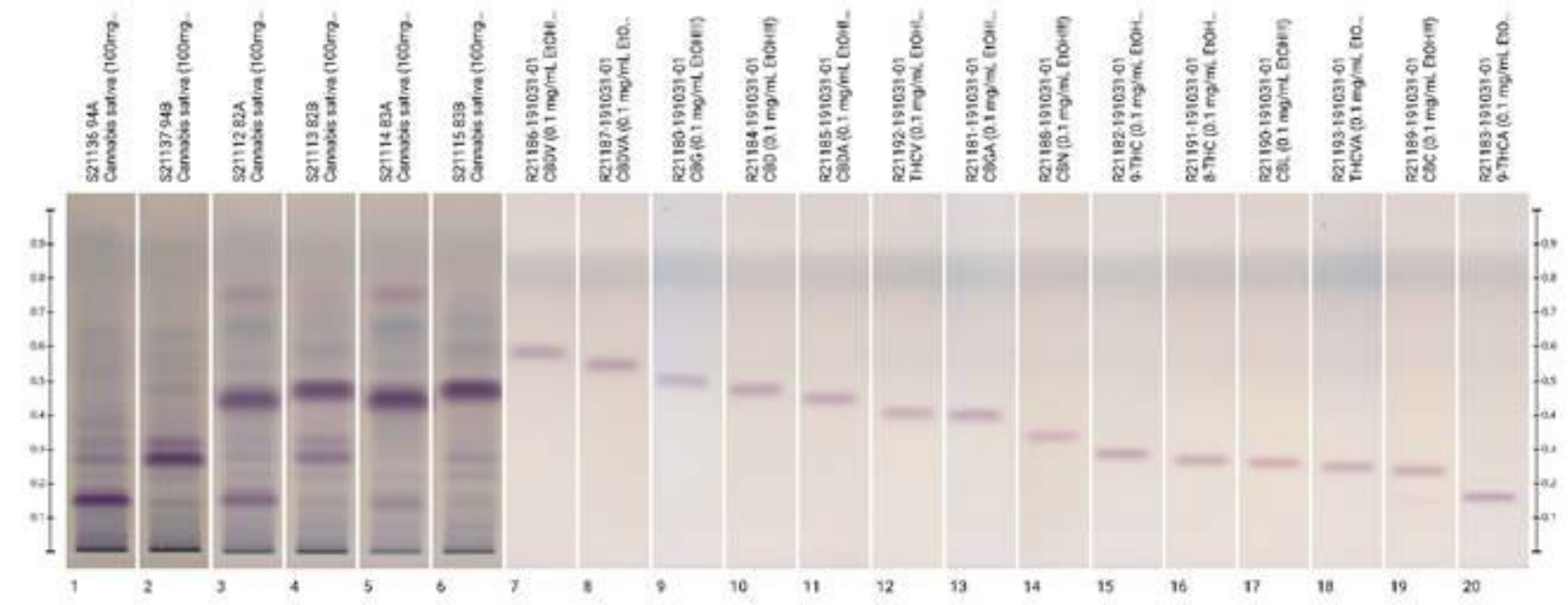
Criteria for Chemotype Classification

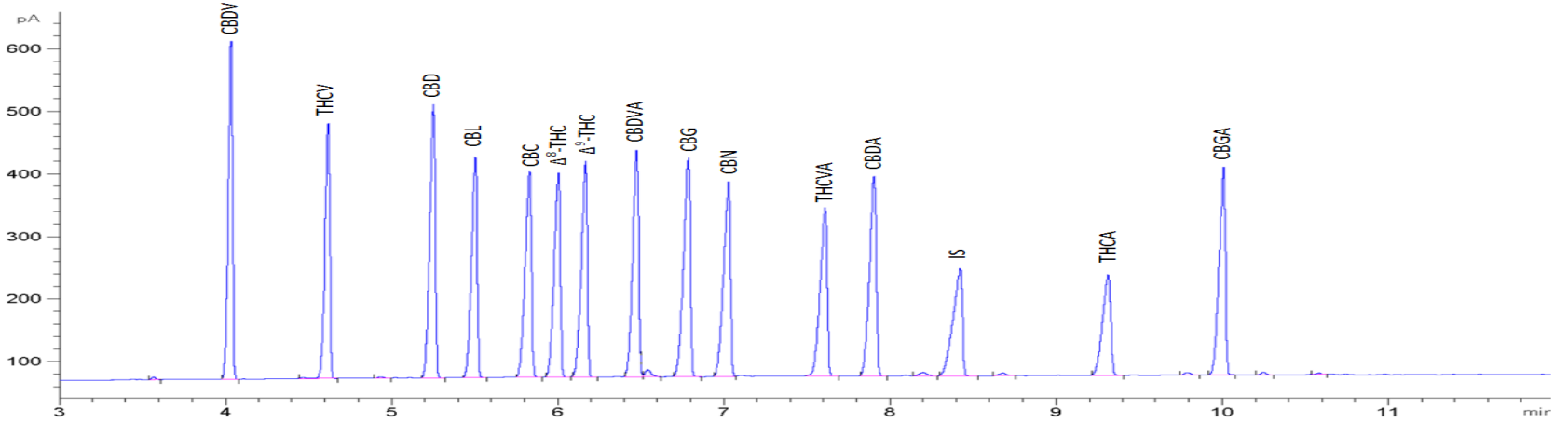
- THC-dominant chemotype:
  - principal peak for THCA
  - ratio of the total THC content to total CBD content is NLT 5:1
  - Contains NMT 1% of total CBD and NLT 1% of total THC.

- 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

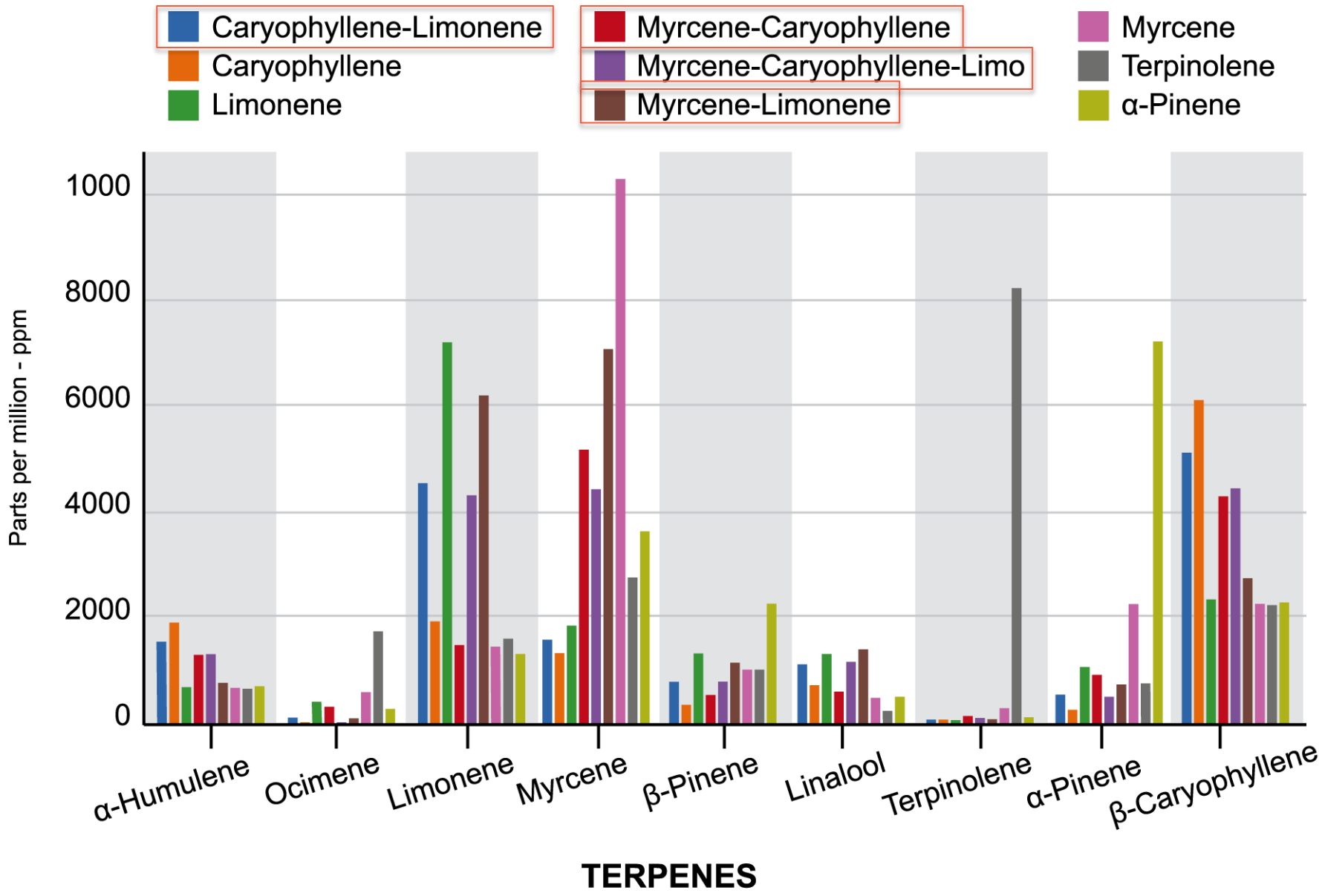




Quantitation of the Cannabinoids

- 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: $Total\ THC = THC + 0.877 * THCA$
- 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



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 (Δ^9-THC)
- 0.025 mg Delta-8-Tetrahydrocannabinol (Δ^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

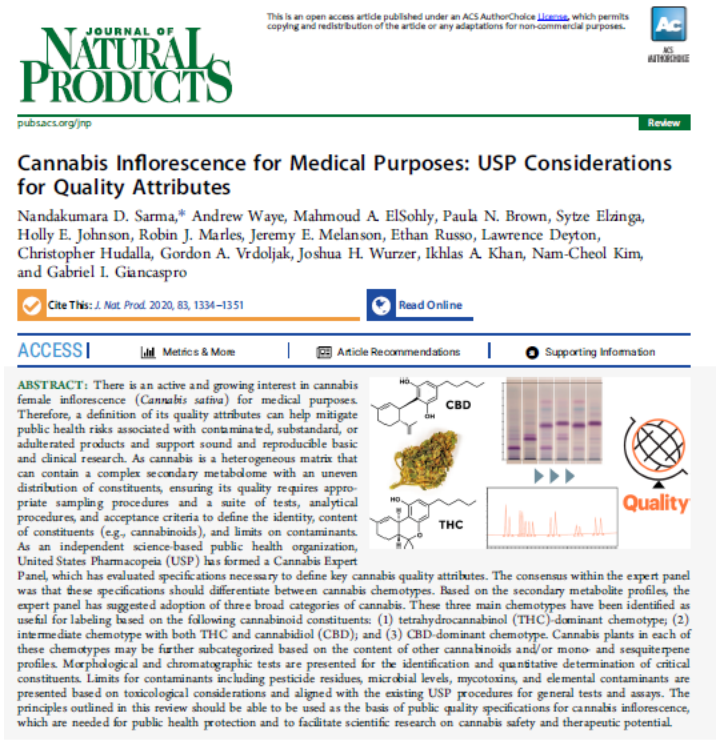
The Value of Public Standards

- 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



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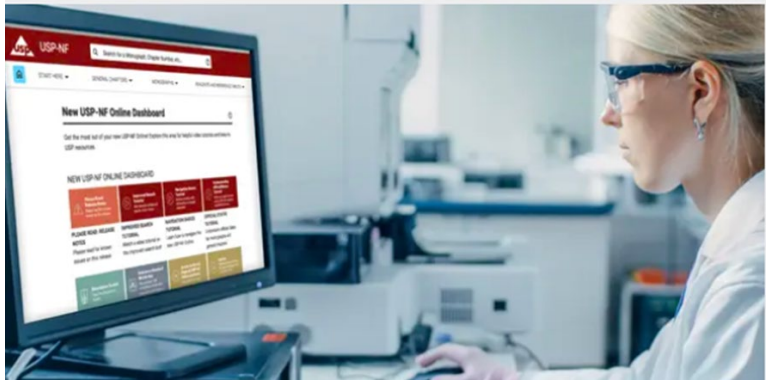
USP publications

USP Reference Standards



USP-NF General Chapters


Thank You