VIA ELECTRONIC SUBMISSION

July 22, 2024

Drug Enforcement Administration
Attn: DEA Federal Register Representative/DPW
8701 Morrissette Drive
Springfield, Virginia 22152

Re: Schedules of Controlled Substances: Rescheduling of Marijuana (Docket No. DEA-2024-0059; A.G. Order No. 5931-2024)

Dear Sir/Madam,

USP-Rockville
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The United States Pharmacopeia (USP) is pleased to provide comments on the proposed rule *Schedules of Controlled Substances: Rescheduling of Marijuana* (Proposed Rule) related to the transfer of marijuana (cannabis) from Schedule I of the Controlled Substances Act (CSA) to Schedule III of the CSA. USP is an independent, scientific, global non-profit organization founded in 1820 and dedicated to building trust in medicines through rigorous science, public quality standards, and a range of programs to help advance the supply of quality medicines. We are governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry organizations, as well as dozens of government agencies, who together comprise the USP Convention.[1] Nearly 1000 experts from the scientific and healthcare community volunteer on USP's Expert Committees to establish nearly 5000 public quality standards for medicines, foods, and dietary supplements.[2]

USP acknowledges the broad scope of legal and regulatory complexities associated with cannabis and cannabis-derived compounds and supports approaches that will aid in a regulatory pathway for medical products by facilitating research into the health effects of cannabis and its constituents, drug development, and potential U.S. Food and Drug Administration (FDA) approval of quality products. USP respects and supports the scientific and medical evaluation of marijuana and recommendation of the Department of Health and Human Services (HHS) to reschedule cannabis from a Schedule I to Schedule III controlled substance, as well as the efforts of the U.S. Department of Justice and the Drug Enforcement Administration (DEA) to initiate rulemaking to reschedule cannabis.

As the proposed rescheduling of marijuana is considered, USP offers the following comments for consideration:

1. **Public quality standards for cannabis and cannabis-derived compounds are an essential part of the conversation to help prevent harm to patients and ensure public trust in products.**

[1] USP's governing bodies, in addition to the Council of the Convention, include its Board of Trustees and Council of Experts.
[2] USP publishes two legally recognized Official Compendia of the United States, combined into a single publication, the *United States Pharmacopeia-National Formulary* (*USP-NF*). The *USP-NF* includes more than 800 dietary-supplement and dietary ingredient related documentary standards and approximately 200 physical reference standards to verify that products and their ingredients can pass tests indicating adherence to quality standards. USP also publishes a compendium of food ingredient standards in the *Food Chemicals Codex* (*FCC*) and standards for herbal ingredients used in herbal medicines in the *Herbal Medicines Compendium (HMC).*

2. **Rescheduling can help support medical research and characterization of cannabis and cannabis-derived products.**

Quality standards are critical if cannabis is rescheduled

Public quality standards set forth requirements related to nomenclature, identification criteria, strength and composition criteria, purity testing, limits on contaminants, and robust, scientifically valid quality testing methods. When utilized, these standards provide transparency and validated methods for testing and assist with identification of adulterated and potentially dangerous botanical articles. The establishment of quality attributes and analytical tools for cannabis and cannabis-derived compounds is particularly important due to variability, quality issues related to these botanical articles, potential health hazards with certain articles, and the increase in the number of cannabis products that exist in the marketplace.

Quality standards can be universally and consistently applied by manufacturers and researchers, which means a given botanical article should have the same quality and safety profile from each plant source. For each product, manufacturers compare their product to the published acceptance criteria to standardize the amount of active drug material contained in their products. **Establishing and standardizing accurate descriptions, appropriate nomenclature, and validated analytical testing of cannabinoid content for regulatory purposes is critical for cannabis and cannabis-derived compounds and helps provide transparency to healthcare practitioners and patients about the products they are consuming, building public trust in these products, and improving public health.**

USP standards and resources for cannabis

As noted in the Proposed Rule, cannabis was first described in the *USP* in 1850 and remained in the *USP* until 1942.[3] As an "official compendium" under the Federal Food, Drug, and Cosmetic Act, USP's compendial standards for strength, quality, and purity are generally mandatory for drugs marketed in the United States, including Schedule III drug substances and drug products. In recent years, USP has been working with independent experts from industry, academia, regulatory agencies, and healthcare practitioners to protect public health and promote sound research by establishing a framework for the consistent characterization of cannabis for medical use.

Several relevant standards exist in USP compendia or are in active development, including:

- USP General Chapter <1568> *Cannabis Quality Attributes for Clinical Investigations*, which is proposed with intent to align with the recent FDA final guidance[4] on the topic;[5]
- A Cannabis Species Inflorescence proposed monograph is available for public comment in the *Herbal Medicines Compendium*; and[6]

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[3] Brinckmann JA, Marles R, Schiff P, et al. Quality Standards for Botanicals — Legacy of USP's 200 Years of Contributions. 2020:51-65. https://www.usp.org/news/quality-of-botanical-supplements

[4] U.S. Food and Drug Administration. Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research: Guidance for Industry, January 2023. Accessed at https://www.fda.gov/media/164690/download

[5] United States Pharmacopeial Convention. <1568> Quality Considerations for Cannabis and Cannabis-Derived Products for Clinical Research. USP-NF 2024; www.uspnf.com. Accessed March 14, 2024.

[6] United States Pharmacopeial Convention. 2024. https://hmc.usp.org/monographs/cannabis-species-inflorescence-0-1?_gl=1*mvt4f*_gcl_au*NjMzNTA5NzEuMTcxNjkwNjA0Ng..*_ga*MzIxNDMzMTkyLjE2NDA3MDk1NTA.*_ga_DTGQ04CR27*MTcxODk4NDMwOS41NTMuMS4xNzE4OTg4MDc3LjAuMC4w. Accessed June 21, 2024.

- Hemp seed oil and hemp seed protein monographs are published in the *Food Chemical Codex.*[7,8]

Additionally, USP has non-compendial scientific resources available, including:

- Cannabis inflorescence for medical use quality information published in the *Journal of Natural Products;*[9]
- A recent paper detailing the public health concerns about delta-8 THC and impurities;
- Impurity analysis methods for delta-8 THC products and synthetic impurities published in the journal *Planta Med*;[10] and
- Availability of reference materials for analytical testing of cannabis and cannabis-derived compounds.[11]

Rescheduling can help support characterization of cannabis and cannabis-derived compounds

A change in scheduling could allow for a less burdensome pathway to further facilitate clinical research, medicine development, and the understanding of cannabis and cannabis-derived compound pharmacology and toxicology. **If a rescheduling is finalized, it is imperative to help ensure the quality of investigational materials through public standards that clearly articulate quality attributes and allow for consistent characterization.** The National Institute on Drug Abuse (NIDA) strongly supports the need for a standardized measure to facilitate research on cannabis and cannabis-derived articles and to enable comparison of articles.[12]

Further, as concentrations of Δ9-tetrahydrocannabinol (THC) increase and the type and number of cannabis and cannabis-derived products grows, the need for additional research to better characterize the cannabis article(s) in them also increases. Reports have indicated that analytical tests quantifying the amount of Δ9-THC in cannabis products can yield inconsistent results because of insufficient standardization of sample preparation and testing methods.[13,14] This underscores the importance of public quality standards for these investigational materials, as one of the considerations for the 8-factor analysis by HHS and DEA includes assessment of concerns related to quality. Public quality standards provide tools to address the variability associated with complex chemical profile of cannabis described in these assessments.

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[7] Hemp seed oil. Food Chemicals Codex 14th Edition. 2024.
[8] Hemp seed protein. Food Chemicals Codex 14th Edition. 2024.
[9] Sarma ND, Waye A, ElSohly MA, et al. Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes. Journal of Natural Products. 2020;83(4):1334-1351.
[10] 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.
[11] United States Pharmacopeia. Supporting the quality of cannabis for medical use. 2022; https://www.usp.org/cannabis. Accessed June 21, 2024.
[12] Volkow, N. D., and Weiss, S. R. B. (2020) Importance of a standard unit dose for cannabis research. Addiction, 115: 1219–1221. https://doi.org/10.1111/add.14984.
[13] Azwell T, Ciotti C, Adams A, Pauli GF. Variation among hemp (Cannabis sativus L.) analytical testing laboratories evinces regulatory and quality control issues for the industry. Journal of Applied Research on Medicinal and Aromatic Plants. 2022;31:100434.
[14] Jikomes N, Zoorob M. The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products. Scientific reports. 2018;8(1):4519.

Rescheduling can help support medical research and patient safety

While the health effects of cannabis and cannabis-derived products have been documented by groups including the National Academies of Sciences, Engineering, and Medicine,[15] ongoing research aims to enhance the consistency of cannabinoid analyses,[16] explore daily intake limits,[17] and better understand the potential harms and benefits of cannabis and cannabis-derived products.[18] Increased use of cannabis products in patients with co-morbid conditions has also raised questions about potential drug-drug interactions between cannabis and other prescribed medications.[19,20] **Because of the numerous pharmacologically active compounds in cannabis and cannabis-derived products currently available, validated and standardized analytical testing methods are critical to ensure consistency and patient safety.**

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USP appreciates the opportunity to provide comments on the proposed rescheduling of marijuana and to highlight the essential role of quality standards when considering a change in scheduling. Thank you again for the opportunity to share our perspectives. If you have any questions or would like additional follow-up, please do not hesitate to reach out to Amy B. Cadwallader, PhD, Director, Regulatory and Public Policy Development at Amy.Cadwallader@usp.org or by phone at (301) 692-3567.

Sincerely,

Anthony Lakavage, J.D.
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Secretary, USP Convention and Board of Trustees
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[15] National Academies of Sciences, Engineering, Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press; 2017.
[16] Azwell T, Ciotti C, Adams A, Pauli GF. Variation among hemp (Cannabis sativus L.) analytical testing laboratories evinces regulatory and quality control issues for the industry. Journal of Applied Research on Medicinal and Aromatic Plants. 2022;31:100434.
[17] Henderson RG, Vincent M, Rivera BN, Bonn-Miller MO, Doepker C. Cannabidiol safety considerations: Development of a potential acceptable daily intake value and recommended upper intake limits for dietary supplement use. Regulatory Toxicology and Pharmacology. 2023;144:105482.
[18] Hall W, Leung J, Carlini BH. How should policymakers regulate the tetrahydrocannabinol content of cannabis products in a legal market? Addiction (Abingdon, England). 2023;118(6):998-1003.
[19] Brown JD. Potential Adverse Drug Events with Tetrahydrocannabinol (THC) Due to Drug-Drug Interactions. J Clin Med. 2020;9(4).
[20] Kocis PT, Vrana KE. Delta-9-Tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions. Medical Cannabis and Cannabinoids. 2020;3(1):61-73.