VIA ELECTRONIC SUBMISSION

August 18, 2023

The Honorable Cathy McMorris-Rodgers
Chair, House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member, House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Bernie Sanders
Chair, Committee on Health, Education, Labor and Pensions
428 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Bill Cassidy
Ranking Member, Committee on Health, Education, Labor and Pensions
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Subject: Request for Information Regarding the Food and Drug Administration Regulation of Cannabidiol Products

Dear Senators Sanders and Cassidy and Representatives McMorris-Rodgers and Pallone:

The United States Pharmacopeia (USP) is pleased to provide feedback to the bicameral, bipartisan request for information regarding the Food and Drug Administration (FDA) regulation of cannabidiol (CBD) products. In recent years, there has been an increase in the number of cannabis and cannabis-derived compounds on the U.S. market. As such, there is a critical and growing need for standardizing the quality attributes for cannabis and related products to help protect patients and consumers from harm.

Fundamentally, USP believes that products containing cannabis and cannabis-derived compounds, including CBD, marketed in the United States, should be required under the law to adhere to science-based, transparent public quality standards.

Due to the significant increase in the number of cannabis products and growing rates of use by consumers in the United States, adherence to quality standards is imperative to address the documented quality-related issues present in these products, the accompanying concerns of consumer harm, and the inherent variability of botanical products, including those containing CBD.

Founded in 1820, USP is an independent, scientific, global non-profit organization 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, which are published in the *United States Pharmacopeia – National Formulary (USP-NF)*. *USP-NF* includes more than 800 dietary-supplement and dietary-ingredient related documentary standards and approximately 200 physical reference standards to verify that a product and its ingredients can pass tests indicating adherence to quality standards. USP quality standards serve as benchmarks that consist of tests and other

[1] USP's governing bodies, in addition to the Council of the Convention, include its Board of Trustees and Council of Experts.

measures to determine potency, purity, identity, and quality of medicines, dietary supplements, dietary ingredients, and foods. One of USP's areas of expertise and focus is the development of quality standards for botanical ingredients, including analytical testing methods and requirements to help ensure their identity, purity, strength, and limits on contaminants.

Quality standards set forth requirements related to nomenclature, identification criteria, strength and composition criteria, purity testing, limits on contaminants, and robust, scientifically valid, transparent quality testing methods.

When utilized, these standards provide transparency and validated methods for product testing and assist with identification of adulterated and potentially dangerous products. In addition, the standards list acceptance criteria, which act as upper and lower limits for certain attributes of these products. For each product, manufacturers compare their product to the published acceptance criteria to standardize the amount of active drug material or dietary supplement ingredients contained in their products. This provides consumers, healthcare practitioners, and patients with transparency on the products they are consuming.

USP greatly appreciates the opportunity to provide feedback on the request for information regarding FDA regulation of CBD products. USP urges the committees to consider requiring adherence to scientifically valid, public quality standards as the committees contemplate regulatory reforms. Below, please see our response to several of the questions posed in the request for information.

Current Market Dynamics

Question 3: How is the lack of national standards for CBD products affecting the market?

Answer: A critical and growing need exists for standardizing the quality attributes for products containing cannabis and cannabis-derived compounds[2] to help protect patients and consumers from harm.[3] As more products become available and are sourced more broadly, and as states continue to adopt initiatives that are expanding access to cannabis and cannabis-derived compounds such as CBD, potential exposure to – and associated risk of harm from – contaminated, substandard, or super-potent products is increasing. Other impacts are described below.

When public quality standards are available, they can be universally and consistently applied by different manufacturers, which means a given product should have the same quality and safety profile from one manufacturer to the next. Without these public quality standards, manufacturers may use confidential, proprietary, and non-transparent specifications which can result in dramatic variations in quality and safety between manufacturers. Use of a common set of quality standards throughout the industry provides transparency on the quality expectations for the ingredients and products for manufacturers and regulators. Public standards help regulators

[2] *Cannabis sativa L.* (cannabis) is a plant that contains over 100 different naturally occurring compounds called "cannabinoids." Cannabis-derived compounds are compounds occurring naturally in the plant, like cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), that are extracted directly from the plant. Cannabis-derived compounds that may be used in manufacturing human drugs include botanical raw materials (BRMs), extracts, and highly purified substances of botanical origin. Cannabis-related compounds are synthetic compounds created in a laboratory and can be used to manufacture drug products. Some may also occur naturally in the plant. Hemp is a legal term defined by the 2018 Agricultural Improvement Act (Farm Bill) and is generally defined as *Cannabis sativa* L. and any part of the plant with a delta-9 THC concentration of not more than 0.3% on a dry weight basis.

[3] With respect to the legal status of cannabis and cannabis-derived compounds, USP defers to applicable federal and state government authorities.

protect public health by providing scientifically validated tests to ensure the identity, constituent composition, and strength of cannabis and cannabis-derived products. Public standards can be used to monitor product quality and facilitate consistent manufacturing of products, which helps limit exposure to toxic substances, pathogenic microorganisms, and harmful additives. In addition, USP public quality standards are flexible and reflect the current state of knowledge because they evolve with public health needs and are continuously revised to accommodate innovation and technological advances.

Disparate Approaches to Oversight: In the absence of certain national standards, states have sometimes adopted their own approaches to oversight of cannabis and cannabis-derived products.[4] The application of inconsistent regulatory frameworks and uneven approaches to quality standards can put consumers at risk due to differing quality parameters, which can result in variable amounts of cannabis, cannabis-derived compounds, and contaminants in products. These inconsistent results complicate the efforts of healthcare practitioners to care for their patients and highlight the urgent need to mitigate the public health risk from lack of uniform oversight for cannabis and cannabis-derived products by introducing national-level guidelines based on conventional risk assessment methodologies.[5,6]

Inconsistent Manufacturing Leads to Inconsistent Product Composition: Botanical quality is impacted by several variables, including plant genetics, cultivation, collection, and post-harvest conditions. Cannabis nomenclature is complex, and there is disagreement about the number of species. USP's approach is to name all cannabis material *Cannabis sativa* L., which includes subspecies, varieties, and chemotypes. Even within the same chemotype and growing conditions, there can be considerable variation in cannabinoid content. This presents a challenge to maintaining consistent quality across products. Recent research notes that composition data are reported inconsistently due to an insufficient standardization of sample preparation and testing methods, increasing the likelihood of erroneous product information.[7] 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 could provide information on the quality attributes and materials used in the manufacture of products. This information can also help manufacturers meet Current Good Manufacturing Practices (CGMP) and other manufacturing requirements.

Limits for Contaminants in Cannabis Are Not Appropriately Defined: Contaminants, including pesticide residues, microbial load, aflatoxin levels, organic solvents, and elemental contaminants, present significant risks to the quality and safety of cannabis and cannabis-derived products. Research has reported inconsistency in cannabis-borne contaminant regulation, increasing risk of contaminant exposure from cannabis and cannabis-derived products, and a need for a unified, national regulatory approach to mitigate the public health risk of cannabis contamination based on scientific data.[8] Risk-based limits for contaminants should be based on the assessment of available information from multiple sources. Tests and assays

[4] As of 2022, twenty-one states, three U.S. territories, and the District of Columbia have legalized recreational use of cannabis. Thirty-seven states, four U.S. territories, and D.C. have legalized medical use of the drug. Each has unique regulations.
[5] Pruyn SA, Wang Q, Wu CG, Taylor CL. Quality Standards in State Programs Permitting Cannabis for Medical Uses. Cannabis Cannabinoid Res. 2022;7(6):728-735.
[6] Jameson LE, Conrow KD, Pinkhasova DV, et al. Comparison of State-Level Regulations for Cannabis Contaminants and Implications for Public Health. *Environmental Health Perspectives.* 2022;130(9):097001.
[7] 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.
[8] Jameson LE, Conrow KD, Pinkhasova DV, et al. Comparison of State-Level Regulations for Cannabis Contaminants and Implications for Public Health. *Environmental Health Perspectives.* 2022;130(9):097001.

contained in public quality standards provide analytical methods and acceptance criteria to control contaminants and may be useful for quality assurance.

Public Health Concern from Synthetic Cannabis-Related Compounds: Delta-8 tetrahydrocannabinol (delta-8 THC), a psychoactive substance, is one of the hundreds of cannabinoids produced naturally by the cannabis plant. Delta-8 THC is not found in significant amounts in the cannabis plant but has recently been found in concentrated amounts in products available for purchase in retail outlets.[9] To obtain the concentrations of delta-8 THC claimed in the marketplace, potentially harmful chemicals are used to manufacture the compound using hemp-derived CBD. Delta-8 THC is associated with adverse health outcomes and little research evaluating the pharmacology and toxicology of the compound is available. Since the proliferation of delta-8 THC, other THC isomers (e.g., delta-10 THC) are emerging in the marketplace. Public quality standards can provide analytical methods to detect and control for the presence of these adulterants in products and highlight the public health concerns associated with them.

Pathway

Question 4: Please comment on the concerns FDA has raised with regard to regulating most CBD products through existing pathways (i.e., conventional foods, dietary supplements and cosmetics), and FDA's view that there is a need for a new regulatory pathway for CBD products. If existing regulatory pathways are sufficient for regulating CBD products, please explain how these existing pathways can be used to address the concerns raised by FDA, as appropriate.

Answer: USP supports the development of a regulatory pathway specific for cannabis products or specific guidance for the application of an existing regulatory process for oversight of cannabis containing products. USP believes any pathway should require adherence to scientifically valid, public quality standards.

Scope

Question 5: How should CBD and/or cannabinoid-containing hemp products be defined? What compounds should be included and excluded from a regulatory framework?

Answer: The terms "hemp" and "hemp-derived CBD" should be defined to specify the source of the article used and to differentiate the hemp-derived CBD from synthetically derived CBD. Such definitions will help to identify the substance to which the name applies, and the name that should be used consistently by healthcare professionals and regulators. Suitable definitions are critical to ensure that products derived from the cannabis plant, which is a highly variable botanical, meet the regulatory definition of "hemp" and to address public health concerns associated with synthetically-derived compounds, as noted in Question 3. The cannabinoid constituents of the hemp plant material, such as CBD, cannabigerol (CDG), cannabidivarin (CBDV), delta-8 THC, delta-10 THC, and other minor cannabinoids constituting more than 1% of the content, should be characterized and clearly labeled to minimize confusion due to the differences between the several hemp varieties that are being developed to produce cannabinoids.

[9] Bozman ME, Manoharan SVRR, Vasavada T. Marijuana variant of concern: Delta 8-tetrahydrocannabinol (Delta-8-THC, Δ8-THC). Psychiatry Research Case Reports. 2022;1(2):100028.

USP standards can help to ensure that the quality of two ingredients obtained from different processes have similar identity, strength, and limits on contaminants. CBD can be obtained from natural sources or semisynthetic derivatives, and it should be noted that chemically identical substances will exhibit the same biological properties, regardless of their origins. However, the same substance can present safety concerns due to high amounts of exposure or prolonged periods of exposure, especially if it contains impurities from the synthesis, extraction, or purification processes, which may differ depending on whether the starting material was synthetic or natural. The use of public quality standards will ensure the quality of both synthetically derived and cannabis-derived constituents, including setting appropriate limits for impurities.

While the term “intoxicating” could be subject to different interpretations, the cannabinoids that are known to bind and activate the cannabinoid receptors in the brain are very well known. Analytical methods are available to accurately quantitate these cannabinoids, and they should be identified and labeled as such in consumer products.

Terms such as “full spectrum” and “broad spectrum” extracts are also subject to different interpretations. Definitions and quality specifications for each term should be defined.

Additionally, USP recommends that definitions for “cannabis,” “cannabis product,” and “hemp-derived CBD” clearly articulate the appropriate regulatory paradigm for each product.

Question 7: How has the absence of federal regulation over CBD created a market for intoxicating, synthetically-produced compounds, such as Delta-8 THC, THC-O, THC-B, HHC-P, and others?

Answer: Delta-8 THC is not found in significant amounts in the cannabis plant but has recently been found in concentrated amounts in products available for purchase in retail settings. Depending on the method of synthesis, delta-8 THC products may contain cannabinoid contaminants or unknown impurities that are not naturally occurring in cannabis or hemp plants. Based on the analysis of the reported adverse events, both FDA and the U.S. Centers for Disease Control and Prevention (CDC) have expressed public health concern from synthetic cannabis-related compounds, such as delta-8 THC.[10] Delta-8 THC is associated with adverse health outcomes, and little research is available evaluating the pharmacology and toxicology of the compound.

Since the proliferation of delta-8 THC, other THC isomers (e.g., delta-10 THC) are emerging in the marketplace. To help prevent patient and consumer harm resulting from exposure to substandard, contaminated, or adulterated cannabis products, rigorous, scientific evaluation of the quality attributes of cannabis and hemp materials is required, including characterization of identity, composition, and purity. In addition, systematic and properly controlled clinical investigations on delta-8 THC and other THC isomers are needed to mitigate risks to public health prior to their release on the market. The availability of suitable analytical methods will help ensure high quality materials are used in such studies, resulting in the increased reproducibility and applicability of preclinical and clinical data.

[10] Bozman ME, Manoharan SVRR, Vasavada T. Marijuana variant of concern: Delta 8-tetrahydrocannabinol (Delta-8-THC, Δ8-THC). Psychiatry Research Case Reports. 2022;1(2):100028.

Federal-State Interaction

Question 9b: In the absence of federal regulation or enforcement over CBD products, many states have established state regulatory programs to safeguard public health and create market certainty for industry participants. Which standards, if any, should Congress look to as models?

Answer: Considering the safety concerns related to CBD, a federal framework that provides safeguards for consumer safety is needed. USP believes that a core element of that framework is adherence to public quality standards which include scientifically validated analytical methods and data-based acceptance criteria for establishing identity, purity, and limits on contaminants. Therefore, USP urges Congress to establish a federal framework that requires adherence to public quality standards.

While states have begun to establish regulatory frameworks around hemp-derived CBD products, a patchwork of state regulations makes it difficult to apply any one standard across all 50 states. Federal action on hemp-derived CBD products would enable more certainty nationwide.

USP, which is recognized in federal law as the official compendial quality standards for medicines and dietary supplements, has researched and disseminated scientific information on key quality and safety considerations for cannabis containing products. This guidance has been published in reputable scientific journals. USP's public quality standards for medicines and dietary supplements are established by committees of scientific experts (comprised of nearly 800 scientists) along with over 200 FDA government liaisons. USP's standard setting committees are prepared to leverage this platform and the scientific research already developed to establish public quality standards for a range of cannabis containing products.

Quality

Question 20: How should Congress create an FDA-implemented framework to ensure that manufacturers provide appropriate consumer protections and quality controls?

Answer: Due to public health concerns associated with CBD products, USP recommends that any framework implemented for the regulation of CBD products should require that manufacturers adhere to public quality standards to help protect consumers from poor-quality products. As noted above in the answer to Question 3, public standards help regulators protect public health by providing scientifically validated tests to ensure the identity, constituent composition, and strength of cannabis and cannabis-derived products. Public standards can be used to monitor product quality and facilitate consistent manufacturing of products, which helps limit exposure to toxic substances, pathogenic microorganisms, and harmful additives. In addition, USP public quality standards are flexible and reflect the current state of knowledge because they evolve with public health needs and are continuously revised to accommodate innovation and technological advances.

Summary

Any and all regulatory pathways for products containing cannabis and cannabis-derived substances, including CBD, should require adherence to science-based, public quality standards. USP is positioned to provide trusted, scientifically-based public quality standards for CBD products marketed to consumers and patients in the United States, as it has for medicines and supplements for nearly 100 years.

Adherence to public quality standards is particularly important for cannabis and cannabis-derived products due to their variability, potential for quality problems, the significant increase in availability and usage of these products, and the potential for harm to patients.

Thank you for your consideration of USP's perspectives. If you have any questions or would like additional follow up, please do not hesitate to reach out to Joseph M. Hill, Director, U.S. Government Affairs at Joe.Hill@USP.org or 202-361-4163.

Sincerely,

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