APhA
2215 Constitution Avenue, NW • Washington, DC 20037-2985

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Scientific Data and Information about Products Containing Cannabis or Cannabis Derived Compounds; Public Hearing; Request for Comments (Docket No. FDA-2019-N-1482)

Dear Sir/Madam:

The American Pharmacists Association ("APhA") appreciates the opportunity to submit comments in response to the Food and Drug Administration (FDA) Public Hearing and Request for Comments, "Scientific Data and Information about Products Containing Cannabis or Cannabis Derived Compounds". APhA, founded in 1852 as the American Pharmaceutical Association, represents nearly 60,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, physicians' offices, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings and the uniformed services.

APhA supports FDA's efforts to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds. APhA appreciates FDA's decision to carefully evaluate cannabis and cannabis-derived compounds in FDA-regulated products before producing a decision or new position on specific regulatory questions. However, APhA does support regulatory changes that further facilitate research related to the efficacy and safety associated with the use of cannabis and its various components. For APhA's policy specific to medical marijuana and cannabis, please see Appendix 1.

A. Health and Safety Risks

1. *Safety Concerns*

    i. Research Needs

APhA appreciates FDA's efforts to gain information about specific patient safety concerns related to cannabis and cannabis-derived products. As FDA is aware, pharmacists rely on a product's labeling and communications from FDA regarding safety concerns. Peer-reviewed publications and education provided by FDA, professional associations or other organizations also help inform pharmacists. APhA members indicated research is currently lacking regarding

specific levels of cannabis and cannabis-derived compounds that cause safety concerns (including drug interactions), and in terms of how the mode of delivery (e.g., ingestion, absorption, inhalation, transdermal) affects safety and exposure to cannabis and cannabis-derived compounds, particularly long-term effects in various age-group populations. Despite certain products being accessible to consumers within states, Federal requirements tend to limit researchers' ability to study more broadly availability cannabis and cannabis-derived products. Consequently, research is also lacking in this area.

In addition, APhA members recommended FDA consider safety concerns and relevant use information of different forms of cannabidiol (CBD) (e.g., oil-based solutions, crystalline derivatives (or solid forms), edibles, suppositories, topicals). APhA also members noted the need for pharmacokinetic studies that correlate blood levels with therapeutic efficacy and adverse effects for most cannabis and cannabis-derived products. Further research is needed in this area to determine dosing regimens.

ii. Risk of Misuse

At the May 31 Public Meeting presenters indicated issues in identifying the amount of CBD and tetrahydrocannabinols (THC) in products currently available to consumers. Given this concern and the popular recreational use of such products, particularly those containing THC, APhA notes there could be increased rates of misuse or unguided use. APhA encourages FDA to study and identify strategies to prevent such misuse from occurring and consider strategies to determine the extent to which misuse currently occurs and the circumstances under which it occurs. This information will be helpful in identifying strategies to limit misuse. Pharmacists play an important role in educating patients and consumers about different products related to their health; however, a lack of information (including labeling) can make counseling more difficult and ultimately increases risks to those using cannabis and cannabis-derived products.

iii. Interactions

As FDA is likely aware, there are several factors that can impact the safety and effectiveness of a medication. During the May 31 Public Meeting, concerns regarding drug-drug interactions were raised by multiple presenters. APhA encourages FDA to consider other types of interactions (e.g., interactions with food, alcohol, and dietary supplements) and how the route of administration impacts such interactions. Information pertaining to interactions should be shared with health care practitioners and individuals using cannabis and cannabis-derived products, among other stakeholders.

iv. Communications Regarding Health and Safety Risks

As FDA identifies safety concerns, APhA encourages the agency to also consider how those concerns are communicated to health care practitioners, patients and consumers. For example, patients may perceive certain products as being less risky because safety information is not included or readily available. For instance, patients may equate the purported non-psychoactive properties of CBD with safety. On the topic of CBD, it is important to educate the

public about the differences between the FDA-approved cannabidiol compound, and the other CBD oil/CBD-infused products.

Although FDA has exercised enforcement authority (e.g., warning letters) in regards to firms marketing unapproved new drugs that allegedly contain CBD, we encourage the agency to enhance enforcement efforts and communications to consumers. As previously noted, patients may improperly perceive cannabis and cannabis-derived products that are readily available to also be safe and effective. It is imperative that patients consult with their health care provider before using any of these cannabis or cannabis-derived products. APhA believes it should be made clear that patients should not use cannabis or cannabis-derived products as substitutes for their current medications without a discussion with their health care provider. FDA could play an important role in advancing this messaging.

In addition, APhA notes the important role health care practitioners, such as pharmacists, play in educating patients about safety concerns and medications. APhA members indicated that it can be difficult to provide counseling to patients for a variety of reasons, including a lack of research and education. APhA members, including student pharmacists, are interested in learning more about safety concerns and benefits related to cannabis and cannabis-derived products, particularly those that were rescheduled in the Agriculture Improvement Act of 2018 (hereinafter "2018 Farm Bill"). As more information is available, APhA believes educating clinicians will be crucial to patient safety and safe and effective use.

Lastly, APhA recognizes how difficult it may be for FDA to send warning letters or engage in other methods of enforcement to each firm marketing unapproved new drugs, especially given the rapid growth of the market. However, APhA is concerned consumers may not be aware of practices that warrant FDA enforcement. Therefore, when considering communication to consumers about safety concerns, APhA encourages also communicating enforcement activity and information about improper marketing to consumers and healthcare providers. Use of traditional and enhanced communication routes like professional associations and social media could help reach broader audiences.

2. *Special Human Populations*

APhA supports FDA's efforts to consider the needs and risks of special populations who may be deliberately or inadvertently targeted, in its decision-making process. Consistent with FDA's past efforts, APhA encourages FDA to review risks and benefits specific to special populations (e.g., children, elderly, pregnant or lactating women) and to also identify how to decrease risks associated with cannabis or cannabis-derived products. For example, child-resistant packaging and more standardized labeling may help mitigate risks more prevalent in special populations. Cannabis or cannabis-derived products targeted to children (e.g. fruit rollups and gummies) require immediate attention.

3. *Safety Information Collection*

As noted at the May 31 Public Meeting, surveillance information pertaining to cannabis and cannabis-derived products is lacking and when it is collected, may be collected by different sources that do not share information. As FDA considers a regulatory framework for cannabis and cannabis-derived products, APhA recommends addressing surveillance and identifying options to obtain more robust safety data. To the extent practicable, APhA encourages FDA to utilize and promote current systems rather than develop systems unique to cannabis and cannabis-derived products. Making health care practitioners and consumers aware of reporting options and information relevant to include in reports may help increase the quantity and quality of surveillance information.

From a clinical perspective, APhA advocates that the pharmacist collect and document information in the pharmacy patient profile about patient use of cannabis and its various components and provide appropriate patient counseling. However, it is important to note that pharmacy systems are typically not interoperable with other medical record systems or registries, especially as pertaining to non-pharmaceutical products and services.

4. Options to Support Drug Development from Cannabinoids

As FDA considers options to support drug development involving cannabinoids, APhA believes it is important for FDA to be aware of barriers to cannabinoid-related research when the active pharmaceutical ingredient is derived from cannabis. In addition to comments raised at the May 31 Public Meeting, APhA is aware of several different organizations, such as the Council on Governmental Relations (COGR), that have identified research barriers associated with cannabis and hemp (e.g., inability to accept funds from the cannabis industry for research and DEA requirements). Although APhA has not yet formally endorsed COGR's findings, we appreciate the perspectives of research universities and affiliated medical centers and independent research institutes. APhA recommends FDA review recommendations from groups like COGR to determine whether the agency has authority to make changes to facilitate research, or if there is an opportunity to work collaboratively with other regulators to address these barriers to support research.

B. Manufacturing and Product Quality

APhA members are aware that manufacturing and product quality are important factors for patients and consumers to consider before using any cannabis or cannabis-derived product. However, particularly for unapproved products, pharmacists are often unable to know a product's quality or easily find information pertaining to quality. APhA members support FDA identifying standards related to manufacturing and product quality. Health care providers, including pharmacists, and patients should be able to easily determine or infer whether a product does or does not meet such standards.

Once standards are identified, APhA recommends FDA provide education to inform health care providers, patients and consumers of these standards and how they can check whether such standards are satisfied by manufacturers. As the cannabis and cannabis-derived product

market continues to grow, factors such as product loyalty could result in recurring use and sale of products that may not adhere to quality standards. APhA recommends FDA swiftly address issues related to product quality to protect public health and safety.

C. Marketing/Labeling/Sales

1. Informing consumers of risks

APhA believes there are a variety of options FDA should consider employing to inform consumers about risks associated with cannabis and cannabis-derived products, including in the directions for use and warnings. Such information conveyed in labeling should be evidence-based and clear for consumers and health care practitioners to understand and apply. In the labeling, FDA may also need to consider how best to disclose the presence of THC and the amount of both THC and CBD in the marketed product.

In addition, since there are many different types of advertising tools and claims, APhA believes it is important FDA determine (e.g., obtain consumer and other stakeholder input, review relevant literature) the extent to which this information could be misinterpreted by consumers. FDA's Office of Prescription Drug Promotion (OPDP) could also play an important role by dedicating resources to more actively look for and take actions against advertisements that violate the law. Such efforts may help ensure products misleading customers do not enter or remain on the market. APhA recognizes how difficult it may be for FDA to send warning letters or engage in other methods of enforcement to each firm marketing unapproved new drugs, but consumers may not be aware of practices that warrant FDA enforcement. Therefore, when considering communication to consumers about safety concerns, APhA encourages also communicating enforcement activity and information about improper marketing to consumers and healthcare providers through traditional and enhanced communication routes like professional associations and social media.

APhA suggests FDA educate industry and others about the specifics of laws related to advertisement and promotion but in the context of cannabis and cannabis-derived products. APhA believes it could be particularly helpful for FDA to distinguish between claims made by manufacturers of approved prescription drugs versus those made by manufacturers of dietary supplements or non-approved products. In making such communications, APhA recommends FDA consider how state laws could also impact patient perceptions of different uses of cannabis and cannabis-derived products. Reducing patient confusion should be among FDA's efforts when considering marketing, labeling and sales.

APhA also encourages FDA to consider the source from which consumers learn about and obtain cannabis and cannabis-derived products. Consistent with FDA's attention to online pharmacy, APhA recommends FDA consider how the BeSafeRx campaign can be utilized to inform the public about illicit cannabis and cannabis-derived product sales online. APhA members have indicated patients purchase cannabis and cannabis-derived products online, including those purporting to solely contain CBD. Currently, little information is available regarding such online sales.

2. Conditions, Restrictions or Other Limitations

As FDA is aware, there are many different state laws addressing cannabis and hemp. Such laws may use variable terms or be otherwise inconsistent with the recently enacted 2018 Farm Bill. For example, in certain states pharmacists may be instructed by their board of pharmacy not to sell cannabis or cannabis-derived products, including products falling within the definition of "hemp" under the 2018 Farm Bill. Alternatively, some states have laws specific to CBD (generally with a specified, low-level of THC) to allow use of such products for certain medical purposes not approved by the FDA. Therefore, variable interpretations and definitions of state and federal laws may result in limitations regarding both the location of sale and the products that may be sold.

Differences among Federal and state laws may also pose barriers for regulators seeking to identify effective strategies for protecting public health. For example, state-imposed conditions, restrictions or other limitations (e.g., registries/patient ID cards, medical conditions, patient age, healthcare practitioner involvement) may be applicable to a different scope of products and circumstances between states. As a result, it may be difficult determine whether a limitation or other conditions could be replicated to mitigate specific risks.

Based on discussions from the May 31 Public Meeting and related blog posts by FDA,[1] other than liver injury, it is not clear which specific risks FDA aims to mitigate. Therefore, as FDA considers implementing different conditions, restrictions or other limitations, APhA encourages the agency to more clearly identify risks associated with cannabis and cannabis-derived products and then consider mechanisms to reduce such risks or otherwise prevent harm.

APhA also notes stigma may place implicit limitations on patient use and access. For example, research in California regarding the use of medical marijuana found that stigmatization of medical marijuana has a "profound effect on how patients seek treatment, and whether they seek medical marijuana treatment at all."[2] Consumers who do not feel comfortable talking to their health care providers may be at additional risk but also lose the potential benefit of working with their provider to consider alternative treatments. Therefore, as FDA considers a regulatory framework, APhA recommends FDA identify opportunities to prevent stigma in the interest of patient care.

APhA is sensitive to FDA's need to balance careful regulatory decision-making, including those to support drug development, with public health protections. However, APhA is concerned that risks to patients will only proliferate as more unregulated products come to market. APhA urges FDA to prioritize a regulatory strategy that focuses on protecting patients but also providing health care practitioners with relevant information needed to help provide care. Should you have any questions or wish to gain insights from pharmacists, please contact,

[1] Food and Drug Administration, (June 2019). "FDA is Committed to Sound, Science-based Policy on CBD", available at: https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fda-committed-sound-science-based-policy-cbd

[2] Satterlund, T.D., Lee, J.P. & Moore, R.S. (2015). Stigma among California's Medical Marijuana Patients, *Journal of Psychoactive Drugs*, 47(1), 10-17.

APhA
2215 Constitution Avenue, NW • Washington, DC 20037-2985

Jenna Ventresca, Director, Health Policy, by email jventresca@aphanet.org or phone (202) 558-2727.

Sincerely,

Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO

APhA
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Appendix 1:

Marijuana

Role of the Pharmacist in the Care of Patients Using Cannabis

1. APhA supports regulatory changes to further facilitate clinical research related to the clinical efficacy and safety associated with the use of cannabis and its various components.
2. APhA encourages health care provider education related to the clinical efficacy, safety, and management of patients using cannabis and its various components.
3. APhA advocates that the pharmacist collect and document information in the pharmacy patient profile about patient use of cannabis and its various components and provide appropriate patient counseling.
4. APhA supports pharmacist participation in furnishing cannabis and its various components when scientific data support the legitimate medical use of the products and delivery mechanisms, and federal, state, or territory laws or regulations permit pharmacists to furnish them.
5. APhA opposes pharmacist involvement in furnishing cannabis and its various components for recreational use.

(JAPhA N55(4): 365 July/August 2015)

Medicinal Use of Marijuana

1. APhA supports research by properly qualified investigators operating under the investigational new drug (IND) process to
explore fully the potential medicinal uses of marijuana and its constituents or derivatives.
2. APhA opposes state by state, marijuana specific, or other drug specific legislation intended to circumvent the federal laws and regulations pertaining to
    (a) marketing approval of new drugs based on demonstrated safety and efficacy, or;
    (b) control restrictions relating to those substances having a recognized hazard of abuse.

(Am Pharm NS20(7):71 July 1980) (Reviewed 2003) (Reviewed 2006)(Reviewed 2011)(Reviewed 2015)