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Seeing Past the Smoke: Regulatory Considerations for Public Health Research on Commercially Available Cannabis

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The legal status of cannabis products varies wildly across the United States. For example, a hypothetical journey beginning with a step across the Idaho border from Oregon moves one from a state where marijuana possession and use for both recreational and medical reasons is permissible to another where neither possession nor use of marijuana is legal for any purpose. Venturing further eastward into Montana flips the status of marijuana use and possession back once again to permissible for both recreational and medical use, but a continued journey east into North Dakota limits marijuana's possession and usage to purely medical purposes. Amidst this backdrop of inconsistent state policies, a trend towards greater enforcement leniency is evident throughout the United States. Recent years have seen a groundswell of states adopting legislation endorsing varying degrees of marijuana legalization and decriminalization.

As the trend towards cannabis legalization continues, learning more about the public health implications of marketed cannabis products takes on greater urgency.[1] However, researchers should be aware that complex regulatory paradigms govern research activities conducted with these substances. Researchers should carefully consider applicable regulatory obligations imposed by the U.S. Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and states and localities where research will occur before designing and implementing research protocols intended to study cannabis usage in human subjects. To the extent regulatory hurdles, designed for different purposes, inadvertently undermine the conduct of this important research, researchers and public health agencies may wish to advocate for regulatory change that would exempt this research from certain regulatory obligations.

FDA Considerations

Though many terms are often used interchangeably when referring to the iconic star-leafed plant, the term "cannabis" refers to a genus of plants containing types of material known colloquially as "hemp" and "marijuana." The active substances of most interest in these plants, found in varying strengths across different types of cannabis,[2] are delta-9-tetrahydrocannabinol (THC)[3] and cannabidiol (CBD). THC is best known for the psychoactive effects associated with recreational marijuana use, though THC, THC analogs, and CBD alike have been investigated for therapeutic use. To date, FDA has approved four prescription drug products related to cannabis: one derived from cannabis and three containing synthetic substances that are identical or similar to the THC found in cannabis.[4]

IND Application

The definition of "drug" under the Federal Food, Drug, and Cosmetic Act (FDCA), which governs all aspects of drug development, manufacture, research and distribution, includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and articles other than food that are "intended to affect the structure or any function of the body of man."[5] As a result, medical use of products containing either CBD, THC, or a mix of both is encompassed by the first category, while the recreational use of cannabis products that create a psychoactive effect would fall into the latter. Much of the research that an institution conducts involving use by study participants of any component of the cannabis plant for therapeutic purposes would qualify as a "clinical investigation," as it would be an "*experiment* in which a *drug* is administered or dispensed to, or *used involving*, one or more human subjects."[6]

Under FDA regulations, any time a clinical investigation is conducted with a drug, the research sponsor must evaluate whether an investigational new drug application (IND) must be submitted to FDA.[7] Experiments in which an investigator is providing any form of instruction or limitation regarding the administration of experimental products such as cannabis are likely to be considered regulated research by FDA.[8] Health systems and other research institutions may not be familiar with FDA requirements or may simply assume the research is not subject to those requirements if it is not intended to support an initial FDA approval of a specific drug product, a new use or other significant change to the labeling of an approved drug.[9] However, FDA strictly regulates research involving unapproved drugs and unapproved uses of approved drugs. Aside from the few FDA-approved cannabis-associated products mentioned above, cannabis products do not constitute drug products that are lawfully marketed in the United States. Accordingly, to maintain compliance with governing regulations, investigators conducting clinical investigations with cannabis may be required to submit an IND application or seek an IND waiver before proceeding with research activities.

IND requirements are largely designed to provide oversight for studies of substances for which FDA approval and commercialization is the ultimate goal, typically by the company sponsoring or funding the research. Such requirements may be an awkward fit for public health research. For example, the expectation that an IND provide details on the specific strength and composition of the investigational drug to be studied and how the product is manufactured may directly counter the context and aims of certain cannabis public health research activities.[10] Similarly, the requirement that the investigation sponsor demonstrate that the study drugs used by all subjects have identical strength and composition may be inconsistent with the goals of public health research.

In the context of public health cannabis research, the goal is often to study the larger public health implications associated with usage of many different products commonly used in a community (e.g., recreational cannabis consumption regardless of delivery vehicle, or cannabis vaping devices themselves). Accordingly, the composition or design of the investigational product can vary widely, and subjects may be permitted to self-dose to reach certain subjective treatment or recreational goals. In the context of such a study, there may be no attempt to control the study drug used because the goal of the study is not to obtain meaningful data about the characteristics of one particular product. When allowing subjects to choose any product, it is not possible to meet IND requirements for a full characterization of each individual product studied[11] because the products used would not be known to the investigators in advance.

While the impossibility of meeting the IND requirements for the public health study designs described above does not excuse investigators from compliance with applicable regulations, waivers from specific IND requirements can be sought. FDA also has channels for reaching out to the agency for feedback on whether an IND would be required or whether some requirements might be waived.[12]

IND waiver requests must contain at least one of the following: (a) an explanation why the sponsor's compliance with a specific IND requirement is unnecessary or cannot be achieved; (b) a description of an alternative submission or course of action that satisfies the purpose of the requirement; or (c) other information justifying a waiver.[13] Waivers may be granted if FDA finds that the proposed deviation from applicable requirements would "not pose a significant and unreasonable risk to human subjects of the investigation" and meets one of the following criteria: (1) the sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved; (2) the sponsor's proposed alternative satisfies the requirement; or (3) the applicant's submission otherwise justifies a waiver.[14]

While avenues for FDA engagement are available on whether an IND is required and for seeking a waiver from specific IND requirements, FDA may refuse a waiver request and demand that the study design be significantly revised to focus on just a few products for which the required information can be obtained prior to study initiation. This may be

problematic if changing the study design in the way FDA demands prevents researchers from conducting research they believe to be important to developing a macro-level understanding of the health effects of the types of cannabis products currently in real-world use. Thus, public health agencies and research institutions may wish to challenge overly broad interpretations of FDA authority that could inhibit research that advances understanding of the public health implications of community cannabis use. FDA should presumably not object to ceding jurisdiction in the context of observational public health studies conducted with products that are legal and widely available in the states where they are sold, when (1) product commercialization is not the goal, (2) the data to be gathered are wholly uncontrolled, (3) the research is intended to reflect impact on a community rather than an individual, and (4) the study does not increase risk to individual participants.

Cannabis: Not a Dietary Supplement

Researchers may try to argue that cannabis is used as a "dietary supplement" rather than a "drug" in their research because FDA does not require an IND for clinical investigations of "dietary supplements" when the intent of the investigation is to evaluate the dietary supplement's effect on the structure or function of the body.[15] A dietary supplement is defined as a product intended to supplement the diet that contains one or more substances that are considered dietary ingredients, including herbs or other "botanicals."[16] While cannabis is a "botanical" product, the definition of "dietary supplement" excludes products that contain substances that are approved as drugs.[17] As noted previously, FDA has approved drug marketing applications for synthetic or chemically related forms of CBD and THC.[18] FDA has thus concluded that THC and CBD products are excluded from the definition of a dietary supplement under 21 U.S.C. § 321(ff)(3)(B).[19] There is an exception to the applicability of this exclusion if the substance at issue was "marketed as" a dietary supplement or conventional food before the drug was approved or the new drug investigation was authorized. However, FDA has rejected the applicability of this exception for THC and CBD.[20] Accordingly, researchers who may wish to study edible forms of cannabis cannot avoid the reach of IND regulations by characterizing their products as dietary supplements.

DEA Considerations

In addition to considering FDA's regulatory authority over clinical investigations of recreational or medical cannabis use, researchers should evaluate any regulatory obligations arising out of the DEA's regulation of marijuana as a controlled substance. DEA maintains regulatory authority over any federally scheduled drug substances, even if those substances have been fully descheduled at the state level. Schedule I substances—the most tightly controlled category of controlled substances—are substances determined to have "a high potential for abuse . . . [with no] currently accepted medical use in treatment in the United States [and] a lack of accepted safety for use of the drug or other substance under medical supervision."[21] DEA currently includes "marihuana," "marihuana extract," and

"tetrahydrocannabinols" within this category.[22] As the 2018 Farm Bill removed hemp from the definition of marijuana, products meeting the definition of hemp are no longer considered Schedule I substances under the Controlled Substances Act (CSA).[23]

This is an area to watch closely as the Department of Health and Human Services (HHS) recently recommended that DEA reschedule marijuana to Schedule III.[24] This followed an October 2022 request from President Biden that HHS "review expeditiously how marijuana is scheduled under federal law."[25] DEA is currently considering HHS' recommendation. Rescheduling marijuana would likely allow for new avenues for research and medical uses, in part because DEA registration for research with substances outside of Schedule I is less onerous, and a single application can be used to approve a researcher to investigate substances in any of the Schedules II through V.[26]

DEA regulations require anyone who (among other things) distributes or dispenses any controlled substance to obtain a DEA registration, unless they are otherwise exempt for reasons such as personal use or procuring the controlled substance in the course of duties as a law enforcement officer.[27] As a result, researchers hoping to purchase and distribute cannabis products to study subjects must ensure compliance with DEA registration requirements. Once a researcher has complied with DEA registration requirements, controlled substances intended for research purposes must be acquired only through DEA-approved suppliers.[28] While this precludes the acquisition of cannabis for DEA-regulated research from community consumer storefronts, purchasing from DEA-approved suppliers is no longer quite as cumbersome a process as it once was. Through 2021, only one entity (the National Center for Development of Natural Products at the University of Mississippi) was permitted to cultivate research-grade cannabis. However, the 2022 Medical Marijuana and Cannabidiol Research Expansion Act included provisions to ease the ability for new cultivators to become DEA-approved, and there are currently at least seven such suppliers approved.[29]

Research protocols that do not involve the researcher handling marijuana products but instead call for research subjects to obtain their own cannabis through channels that are legal under applicable state law and consume such cannabis in a location that is not owned or maintained by the researcher may not be subject to DEA registration requirements. However, researchers should be mindful that dictating to subjects what kind of product to purchase or how to use the product may be viewed by FDA as rendering the study an "interventional" clinical investigation subject to FDA requirements, even if DEA requirements do not come into play.

State and Local Considerations

Researchers should also consider state and local requirements when planning their research activities.[30] While marijuana legality is sometimes conceived of as a binary yes/no question, in reality, the legal landscape is quite nuanced. Some states have fully

legalized the production, sale, and consumption of certain amounts of marijuana products, while others have banned these activities completely. Some states allow marijuana trade and consumption only for medical purposes, while others have decriminalized marijuana use and possession without necessarily legalizing it.

Some states additionally have agencies dedicated to the supervision of marijuana-related activities, akin to state-level alcohol control boards, and whose oversight and input should be considered in advance of any potential research activities.[31] By way of example, New York requires researchers working with investigational cannabis products to obtain a license from the state's Office of Cannabis Management.[32] Similarly, the state of Washington offers a research license by which holders may produce, process, and possess cannabis for clinical investigations or conduct research on the efficacy and safety of administering such as part of medical treatment.[33] There may also be more general state research requirements keyed to the federal scheduling of the investigational substance, such as in California, where researchers studying Schedule I or II substances should submit research information to the Research Advisory Panel of California for review.[34]

Conclusion

Research into the nature and health effects of commercially available cannabis, in its many forms, is of great interest to public health researchers. But before moving forward, researchers must be aware that cannabis *research* may be strictly regulated under federal, state, and local laws even when cannabis is easily accessible and legal for consumer *purchase and use* under state law. Running afoul of such regulations is not without risk. FDA can take regulatory enforcement action, like issuing a Warning or Untitled Letter or pursuing investigator disqualification, in the appropriate factual context. DEA may also issue Letters of Admonition, pursue fines/civil money penalties, or suspend research licenses and registrations if applicable requirements are not followed. Finally, the Department of Justice has the authority to pursue criminal or civil action under the FDCA, where a sponsor or investigator can be found to be causing the distribution of an unapproved new drug or where the study drug distributed is misbranded or adulterated. To ensure clinical study regulations do not present unnecessary obstacles to critical public health research, researchers and public health organizations focused on understanding the health effects of commercially available substances like cannabis may wish to open a dialogue with regulators to find an appropriate path forward to facilitate this kind of important research.

About the Authors

David Peloquin is a partner in Ropes & Gray's health care group based in Boston who advises clients on a wide range of legal and regulatory issues in the area of clinical research, data privacy, provision of health care services and related activities. David guides

clients through complex regulatory questions arising under the Common Rule and FDA regulations, data privacy regulations (including HIPAA, U.S. state privacy laws, and GDPR), and state and federal fraud and abuse laws and health care licensing requirements. David is also a member of the firm's digital health practice and frequently advises clients on the use of digital technologies in research and clinical settings. He frequently publishes and speaks on issues related to human subjects research, data privacy and digital health.

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**This article was shared with members of AHLA's Academic Medical Centers and Teaching Hospitals Practice Group.*

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[1] This article focuses on research activities aimed at understanding the health impacts of cannabis products available in the commercial marketplace as used in the ordinary course by consumers, rather than the use of such cannabis as a substitute for research-grade cannabis for the purposes of clinical investigation to support FDA approval for therapeutic use. However, the suggestions in this article are applicable to either instance.

[2] U.S. Food & Drug Administration, *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabinol (CBD)*, https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd (last visited Jan. 10, 2024) (defining hemp as a cannabis plant containing less than 0.3% THC and marijuana as a cannabis plant containing greater than 0.3% THC).

[3] While delta-9-THC is considered most responsible for the psychoactive effects associated with marijuana use, it is not the only form of THC in the plant. Some researchers have also sought to study delta-8-THC, a less potent compound with similar effects to delta-9-THC.

[4] *See supra* note 2. The four cannabis-related treatments are (1) Epidiolex (cannabidiol oral solution, a purified form of CBD); (2) Marinol (dronabinol oral capsules, a synthetic form of THC); (3) Syndros (dronabinol oral solution, a synthetic form of THC); and (4) Cesamet (nabilone capsules, a synthetically derived chemical with a structure like THC).

[5] 21 U.S.C. § 321(g)(1).

[6] 21 C.F.R. § 312.3(b) (emphasis added) (defining "experiment" as "any use of a drug except for the use of a marketed drug in the course of medical practice").

[7] *See* 21 C.F.R. § 312.2(a)-(b).; U.S. Dep't of Health & Human Services, *Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted without an IND*, FDA (Sept. 2013), https://www.fda.gov/media/79386/download (explaining when INDs are required and that INDs permit the interstate distribution or transport of drug products for which there is no approved marketing application).

[8] *See* U.S. Food & Drug Administration, *Warning Letter to Jon B. Cole, MD*, FDA (issued on May 5, 2021), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jon-b-cole-md-611902-05052021 (analyzing when an intervention crosses the line from medical treatment to clinical investigation).

[9] 21 C.F.R. § 312.2(b)(1)(i).

[10] U.S. Food & Drug Administration, *IND Applications for Clinical Investigations: Chemistry, Manufacturing, Control (CMC) Information*, FDA, https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-investigations-chemistry-manufacturing-and-control-cmc-information (last visited Jan. 10, 2024) (noting that such details typically include information on drug chemistry, manufacturing, and controls).

[11] *See, e.g.*, 21 C.F.R. § 312.23(a)(3)(i) (requiring the drug's name, active ingredients, pharmacological class, structural formula (if known), formulation of dosage forms, and route of administration); 21 C.F.R. § 312.23(a)(7)(i) (requiring a description of the "composition, manufacture, and control of the drug substance and the drug product").

[12] *See* 21 C.F.R. § 312.10; *see also* U.S. Food and Drug Administration, *IND Application procedures: Exemptions from IND Requirements*, FDA, (Oct. 9, 2015), https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-exemptions-ind-requirements (explaining that sponsors who are uncertain if their proposed investigation meets the criteria for IND exemption may be able to receive advice from FDA through informal communications like phone conversations or email, or submission of a written summary of the proposed investigation to the agency).

[13] 21 C.F.R. § 312.10(a).

[14] 21 C.F.R. § 312.10(b); *see also* New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8805 (Mar. 19, 1987), https://archives.federalregister.gov/issue_slice/1987/3/19/8728-8847.pdf#page=78 (noting that the preamble to the promulgation of the waiver regulations makes clear that their intent is to provide flexibility in complying with regulatory requirements but "does not authorize FDA to waive statutory requirements" and that regulatory requirement waivers require full sponsor compliance with their stated justifying condition).

[15] *See* U.S. Dep't of Health & Human Services, *Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted without an IND*, FDA (Sept. 2013), https://www.fda.gov/media/79386/download.

[16] 21 U.S.C. § 321(ff)(1).

[17] 21 U.S.C. § 321(ff)(3)(B).

[18] *See supra* note 2.

[19] *See id.*, *Questions and Answers*.

[20] *Id.*

[21] 21 U.S.C. § 812(b)(1).

[22] *See* Controlled Substances, at 13 (Dec. 23, 2023), https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf.

[23] *See* 21 U.S.C. § 802(16)(B) ("The terms 'marihuana' and 'marijuana' do not include — (i) hemp, as defined in section 1639o of title 7."); *see also* 7 U.S.C. § 1639o(1) ("The term 'hemp' means the plant Cannabis sativa L. and any part of that plant . . . with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.").

[24] Letter from Rachel L. Levine, Assistant Sec'y for Health, U.S. Dep't of Health & Human Services, to Anne Milgram, Adm'r, Drug Enforcement Administration (Aug. 29, 2023), https://www.dropbox.com/scl/fi/pw3rfs9gm6lg80ij9tja6/2023-01171-Supplemental-Release-1.pdf?rlkey=v5atj0tcnhxhnszyyzcwdcvvt&dl=0.

[25] *See* Statement from President Biden on Marijuana Reform, THE WHITE HOUSE (Oct. 6, 2022), https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/.

[26] 21 U.S.C § 823(g)(1)-(2); 21 C.F.R. § 1301.13(e)(1).

[27] 21 C.F.R. § 1301.11(a); 21 C.F.R. § 1301.22-26.

[28] 21 C.F.R. § 1305.06.

[29] Nat'l Ctr. for Complimentary & Integrative Health, *DEA-Approved Bulk Cannabis Suppliers,* https://www.nccih.nih.gov/grants/dea-approved-bulk-cannabis-suppliers.

[30] For purposes of this article, we assume that the cannabis procurement, consumption, and research activities are all taking place within the same state/jurisdiction. Other considerations may apply if inter-state/-jurisdiction travel is involved in the conduct of any of these steps.

[31] *See, e.g.*, New York State Office of Cannabis Mgmt., https://cannabis.ny.gov/.

[32] New York State Office of Cannabis Mgmt., *Apply for a Cannabis Research License*, https://cannabis.ny.gov/research.

[33] Washington State Liquor & Cannabis Bd., *Cannabis Research*, https://lcb.wa.gov/cannabis-license/mj-research.

[34] State of California Dep't of Justice: Office of the Att'y Gen., *2023 Guidelines*, https://oag.ca.gov/research/guide.