U.S. FOOD & DRUG ADMINISTRATION

National Institutes of Health
Turning Discovery Into Health

August 27, 2019

The Honorable Brian Schatz
United States Senate
Washington, DC 20510-1105

Dear Senator Schatz:

Thank you for your March 20 letter requesting information on research and regulatory issues related to the therapeutic use of cannabis and cannabinoid compounds. The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) are committed to advancing research on the risks and potential benefits of cannabis for therapeutic uses, and we are pleased to share the following information about this important area of inquiry with you.

NIH's research portfolio includes epidemiologic, basic, and applied research on cannabis, its constituent compounds, and the endocannabinoid system through which cannabinoids act. Much of the current evidence on cannabis and health was synthesized in a National Academy of Sciences report, "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research,"[1] which was sponsored by the National Institute on Drug Abuse (NIDA), the National Cancer Institute (NCI), the Centers for Disease Control and Prevention, FDA, and other stakeholders. The report summarizes the evidence on the efficacy of cannabis or cannabinoids for chronic pain, as anti-emetics, and for improving patient-reported spasticity symptoms in multiple sclerosis, as well as evidence on the risks cannabis poses to respiratory health, brain development, and impaired driving.

Several NIH Institutes and Centers, including NIDA, the National Center for Complementary and Integrative Health (NCCIH), the National Institute of Neurological Disorders and Stroke, NCI, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases fund studies on the therapeutic potential of cannabis and cannabinoids as relevant to their respective missions. In fiscal year 2018, NIH estimates to have spent $148 million on cannabinoid research, broadly, and $38 million on therapeutics, specifically. NIH funds studies on delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), two of the cannabinoid components of the cannabis plant, for the treatment of pain, including chronic pain, back pain, and neuropathic pain caused by HIV. Several studies are also examining the endogenous signaling system that cannabinoids influence as a potential target for new pain and addiction therapies, including difficult-to-treat issues such as pain caused by sickle

[1] National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

cell disease or diabetic neuropathy. As part of these efforts, NIH recently reissued a funding opportunity announcement (FOA) titled "Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment," signaling its continued interest in this area. NIH supports research on the development of novel CBD therapies to further understanding of the therapeutic potential of CBD. NIH's research portfolio on cannabinoids has already helped to facilitate important therapeutic advances, providing some of the early basic and preclinical work on CBD as an epilepsy therapy. FDA's June 2018 approval of Epidiolex (cannabidiol oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome) demonstrates the potential for CBD drug development.

FDA also has demonstrated extensive support for drug development with cannabis and plant-derived cannabinoids. The Epidiolex development program received a fast track designation in FDA's Center for Drug Evaluation and Research. The new drug application for Epidiolex had been given a priority review and was approved in its first review cycle under the shortened review period for priority review of a new molecular entity. In addition, FDA has granted fast track designation for other cannabis-derived investigational new drug programs. FDA will continue to support development of drugs from the cannabis plant, and will continue to leverage its expedited programs (e.g., fast track, breakthrough therapy designation, etc.) to facilitate this drug development whenever the relevant standards are met.[2] This support includes the development of guidance for formulating and developing botanical drugs, and engagement with companies in formal industry meetings to discuss their planned or ongoing drug development programs for drugs derived from cannabis or containing cannabinoids.

NIH is also interested in disentangling the distinct therapeutic benefits and potential health risks of different component compounds within cannabis. Several studies across NIH are examining whether THC, CBD, and other cannabis components might have distinct profiles of risk and benefit. To further facilitate such research, in early 2019, NCCIH released an FOA titled "Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes," which focused on soliciting applications to study the therapeutic potential of non-THC/CBD components of cannabis as it relates to pain and nociception.

NIH also supports policy research on cannabis, including how it affects the use of other drugs. In 2017, NIAAA, NIDA, and NCI issued a program announcement for research on "Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes," which invites grant applications (through 2020) to study how changes in policy affect substance use. One project funded under this FOA is examining how local policies around both cannabis and opioids contribute to the use of both retail marijuana and prescription opioids within a particular jurisdiction. NIH is also supporting research to determine whether individuals in states with legalized medical marijuana transition to using cannabis as a replacement for prescribed controlled substances like opioids.

NIH and FDA strongly support the need for additional research on cannabis and its constituent

---

[2] For example, a drug may be granted breakthrough therapy designation "if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints" (21 U.S.C. 356(a)(1)).

compounds. A larger body of rigorous research, including on cannabis and cannabinoid products that are already in use or that could be developed into FDA-approved medications, is key to furthering our understanding of their potential medical benefits and risks. Research on cannabis as an alternative or adjunctive to opioids for treating pain conditions is ongoing; however, the study of cannabis as a treatment for opioid use disorder (OUD) is a gap area, with the exception of some work using CBD. At present, there are no clinical data showing that cannabis is effective for treating OUD (though there are other FDA-approved medications with established safety and efficacy that are underutilized),[3] and the current evidence on the use of cannabis to replace or reduce opioid use for pain is inconclusive. These are important areas for further research.

There are a variety of barriers to conducting research on cannabis and cannabinoids. First, through a contract with the University of Mississippi, which is the only entity registered with the Drug Enforcement Administration (DEA) to cultivate marijuana for research purposes, NIDA is the only source of marijuana permitted for use in research, thereby limiting the diversity of products and formulations available to researchers and slowing the development of cannabis-based medications.[4] Although the University of Mississippi supplies cannabis for clinical trials, it does not have the capacity to manufacture a broad array of cannabis-derived formulations for research or to supply these cannabis products for commercial development. It is not clear how entities seeking to develop these products for commercial purposes would demonstrate equivalency between the University of Mississippi cannabis used in clinical trials and the drug product that would ultimately be approved by the FDA for eventual marketing and sale. With this in mind, NIH and FDA support licensing additional entities to supply cannabis, including extracts and derivatives, to legitimate researchers and drug product developers in the United States.

Second, another barrier to advancing cannabis research is that, under federal law, researchers are unable to purchase strains of marijuana or products containing marijuana from state dispensaries (even with non-federal funds), resulting in a significant gap in our understanding of these products and their impact on health. Licensing additional entities to supply marijuana may improve the diversity of research products that more closely reflect what is currently consumed. In addition, NIH and FDA support enabling researchers holding Schedule I licenses for marijuana to obtain products from state authorized dispensaries. Such products could be used for basic or clinical research, provided such materials to be used in clinical studies also comply with FDA chemistry, manufacturing, and control requirements for materials to be used in research conducted under an investigational new drug application.

---

[3] National Academies of Sciences, Engineering, and Medicine. 2019. Medications for opioid use disorder save lives. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25310 .

[4] Marijuana is defined under the Controlled Substances Act as "all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include hemp or the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination." 21 U.S.C. § 802(16).

The continued placement of marijuana in Schedule I of the Controlled Substances Act creates significant administrative and cost challenges that slow this research and may deter scientists from pursuing cannabis research altogether. For example, researchers have reported that the registration process can take more than a year to complete, that the process of adding different cannabinoids (e.g., THC, and individual *cannabimimetics*) to a researcher's Schedule I registration is time consuming, and that differing interpretations of the Schedule I registration process among local DEA field offices as well as distinct federal and state registration requirements greatly complicate the process. To address these challenges, NIH and FDA recommend streamlining the process for conducting research with cannabis and other Schedule I substances.

Thank you again for your inquiry on cannabis and cannabinoid research and for soliciting our input on the barriers to conducting this research and how they could be addressed. Please do not hesitate to contact us if we can provide you with additional information on the role of NIH or FDA in advancing this important area of science.

Sincerely yours,

Norman E. Sharpless, M.D.
Acting Commissioner of
Food and Drugs

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health