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FDA and Cannabis: Research and Drug Approval Process

Public Health Focus

Expanded Access

The FDA understands that there is increasing interest in the potential utility of cannabis for a variety of medical conditions, as well as research on the potential adverse health effects from use of cannabis.

To date, the FDA has not approved a marketing application for cannabis for the treatment of any disease or condition. The agency has, however, approved one cannabis-derived drug product: Epidiolex (cannabidiol), and three synthetic cannabis-related drug products: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). These approved drug products are only available with a prescription from a licensed healthcare provider. Importantly, the FDA has not approved any other cannabis, cannabis-derived, or cannabidiol (CBD) products currently available on the market.

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CANNABIS

- *Cannabis sativa L.* is a plant that contains over 80 different naturally-occurring compounds called "cannabinoids"
- Two well-known cannabinoids:
  - **Cannabidiol (CBD)**
  - **Tetrahydrocannabinol (THC)**
- Plants are grown to produce varying concentrations of cannabinoids – **THC** or **CBD**
- These plant variations are called cultivars

Cannabis-derived compounds

- Compounds occurring naturally in the plant – like **CBD** and **THC**
- These compounds are extracted directly from the plant
- Can be used to manufacture drug products
- Example: highly-purified CBD extracted from the plant

Cannabis-related compounds

- These synthetic compounds are created in a laboratory
- Can be used to manufacture drug products
- Some synthetic compounds may also occur naturally in the plant and some may not
- Examples: synthetically-derived dronabinol (also naturally occurring) and nabilone (not naturally occurring)

FDA has approved Epidiolex, which contains a purified form of the drug substance cannabidiol (CBD) for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. That means FDA has concluded that this particular drug product is safe and effective for its intended use.

The agency also has approved Marinol and Syndros for therapeutic uses in the United States, including for nausea associated with cancer chemotherapy and for the treatment of anorexia associated with weight loss in AIDS patients. Marinol and Syndros include the active ingredient dronabinol, a synthetic delta-9- tetrahydrocannabinol (THC) which is considered the psychoactive intoxicating component of cannabis (i.e., the component responsible for the "high" people may experience from using cannabis). Another FDA-approved drug, Cesamet, contains the active ingredient nabilone, which has a chemical structure similar to THC and is synthetically derived. Cesamet, like dronabinol-containing products, is indicated for nausea associated with cancer chemotherapy.

FDA is aware that unapproved cannabis and/or unapproved cannabis-derived products are being used to treat a number of medical conditions including, AIDS wasting, epilepsy, neuropathic pain, spasticity associated with multiple sclerosis, and cancer and chemotherapy-induced nausea. Caregivers and patients can be confident that FDA-approved drugs have been carefully evaluated for safety, efficacy, and quality, and are monitored by the FDA once they are on the market. However, the use of unapproved cannabis and cannabis-derived products can have unpredictable and unintended consequences, including serious safety risks. Also, there has been no FDA review of data from rigorous clinical trials to support that these unapproved products are safe and efficacious for the various therapeutic uses for which they are being used.

FDA understands the need to develop therapies for patients with unmet medical needs, and does everything it can to facilitate this process. FDA has programs such as Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review that are designed to facilitate the development of and expedite the approval of drug products. In addition, the FDA's expanded access (sometimes called "compassionate use") statutory and regulatory provisions are designed to facilitate the availability of investigational products to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy available, either because the patients have exhausted treatment with or are intolerant of approved therapies, or when the patients are not eligible for an ongoing clinical trial. Through these programs and the drug approval process, FDA supports sound, scientifically-based research into the medicinal uses of drug products containing cannabis or cannabis-derived compounds and will continue to work with companies interested in bringing safe, effective, and quality products to market.

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FDA Supports Sound Scientific Research

The FDA has an important role to play in supporting scientific research into the medical uses of cannabis and its constituents in scientifically valid investigations as part of the agency's drug review and approval process. As a part of this role, the FDA supports those in the medical research community who intend to study cannabis by:

1. Providing information on the process needed to conduct clinical research using cannabis.
2. Providing information on the specific requirements needed to develop a human drug that is derived from a plant such as cannabis. In December 2018, the FDA updated its Guidance for Industry: Botanical Drug Development, which provides sponsors with guidance on submitting investigational new drug (IND) applications for botanical drug products. The FDA also has issued "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research, Draft Guidance for Industry."
3. Providing specific support for investigators interested in conducting clinical research using cannabis and its constituents as a part of the IND or investigational new animal drug (INAD) process through meetings and regular interactions throughout the drug development process.
4. Providing general support to investigators to help them understand and follow the procedures to conduct clinical research through the FDA Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance group.

To conduct clinical research that can lead to an approved new drug, including research using materials from plants such as cannabis, researchers need to work with the FDA and submit an IND application to CDER. The IND application process gives researchers a path to follow that includes regular interactions with the FDA to support efficient drug development while protecting the patients who are enrolled in the trials. An IND includes protocols describing proposed studies, the qualifications of the investigators who will conduct the clinical studies, and assurances of informed consent and protection of the rights, safety, and welfare of the human subjects. The FDA reviews the IND to ensure that the proposed studies, generally referred to as "clinical trials," do not place human subjects at an unreasonable risk of harm. The FDA also requires obtaining the informed consent of trial subjects and human subject protection in the conduct of the clinical trials. For research intending to develop an animal drug product, researchers would establish an INAD file with the Center for Veterinary Medicine (CVM) to conduct their research, rather than an IND with CDER.

FDA is committed to encouraging the development of cannabis-related drug products, including CBD. Those interested in cannabis-derived and cannabis-related drug development are encouraged to contact the relevant CDER review division and CDER's Botanical Review Team (BRT) to answer questions related to their specific drug development program. The BRT serves as an expert resource on botanical issues and has developed the Botanical Drug Development Guidance for Industry to assist those pursuing drug development in this area. FDA encourages researchers to request a Pre-Investigational New Drug application (PINDI) meeting to discuss questions related to the development of a specific cannabis-derived and cannabis-related drug product.

Please note that certain cultivars and parts of the *Cannabis sativa L.* plant are controlled under the Controlled Substances Act (CSA) since 1970 under the drug class "Marihuana" (commonly referred to as "marijuana") (21 U.S.C. 802(16)). "Marihuana" is listed in Schedule I of the CSA due to its high potential for abuse, which is attributable in large part to the psychoactive intoxicating effects of THC, and the absence of a currently accepted medical use in the United States. From 1970 until December of 2018, the definition of "marihuana" included all types of *Cannabis Sativa L.*, regardless of THC content. However, in December 2018, the Agriculture Improvement Act of 2018 (also known as the Farm Bill) removed hemp, a type of cannabis that is very low in THC (cannabis or cannabis derivatives containing no more than 0.3% THC on a dry weight basis), from controls under the CSA. This change in the law may result in a more streamlined process for researchers to study cannabis and its derivatives, including CBD, that fall under the definition of hemp, a result which could speed the development of new drugs containing hemp.

Conducting clinical research using cannabis-derived substances that are considered controlled substances under the CSA often involves interactions with several federal agencies. For example:

- Protocols to conduct research with controlled substances listed in Schedule I are required to be conducted under a site-specific DEA investigator registration. For more information, see 21 CFR 1301.18.
- National Institute on Drug Abuse (NIDA) Drug Supply Program provides research-grade marijuana for scientific study. Through registration issued by DEA, NIDA is responsible for overseeing the cultivation of marijuana for medical research and has contracted with the University of Mississippi to grow marijuana for research at a secure facility. Marijuana of varying potencies and compositions along with marijuana-derived compounds are available. DEA also may allow additional growers to register with the DEA to produce and distribute marijuana for research purposes. DEA that, as the result of a recent amendment to federal law, certain forms of cannabis no longer require DEA registration to grow or manufacture.
- Researchers work with the FDA and submit an IND or INAD application to the appropriate CDER divisions or other center offices depending on the therapeutic indication or population. If the research is intended to support the approval of an animal drug product, an INAD file should be established with CVM. Based on the results obtained in studies conducted at the IND or INAD stage, sponsors may submit a marketing application for formal approval of the drug.

Cannabis Study Drugs Controlled Under Schedule I of the CSA (greater than 0.3% THC on a dry weight basis)

Step 1 ▲

Sponsor obtains pre-IND number through CDER review division to request a pre-IND meeting. For new animal drug research, a sponsor may engage with CVM to establish an INAD file. A pre-IND meeting with CDER is optional, and an opportunity to obtain FDA guidance on sponsor research plans and required content for an IND submission.

Step 2 ▼

Step 3 ▼

Step 4 ▼

Step 5 ▼

Step 6 ▼

Step 7 ▼

For nonclinical research, including research conducted under an INAD file submitted established with CVM, there is no requirement of prior authorization of the protocol by FDA before the investigators may proceed with a protocol registration application submitted to DEA. For these nonclinical protocols, investigators may immediately pursue investigator and study site licensure, and protocol registration with DEA, so they may then obtain their Schedule I cannabis-derived study drug from supplier.

Cannabis Study Drugs Containing Hemp (no more than 0.3% THC on a dry weight basis)

Step 1 ▲

Sponsor obtains pre-IND number through CDER review division to request a pre-IND meeting. For new animal drug research, a sponsor may engage with CVM to establish an INAD file. A pre-IND meeting with CDER is optional, and an opportunity to obtain FDA guidance on sponsor research plans and required content for an IND submission.

Step 2 ▼

Step 3 ▼

Step 4 ▼

Step 5 ▼

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FDA's Role in the Drug Approval Process

The FDA's role in the regulation of drugs, including cannabis and cannabis-derived products, also includes review of applications to market drugs to determine whether proposed drug products are safe and effective for their intended indications. The FDA's drug approval process requires that clinical trials be designed and conducted in a way that provides the agency with the necessary scientific data upon which the FDA can make its approval decisions. Without this review, the FDA cannot determine whether a drug product is safe and effective. It also cannot ensure that a drug product meets appropriate quality standards. For certain drugs that have not been approved by the FDA, the lack of FDA approval and oversight means the safety, effectiveness, and quality of the drug – including how potent it is, how pure it is, and whether the labeling is accurate or false – may vary considerably.

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Additional Resources

- Product-Specific Guidance for Generic Drug Development: Draft Guidance on Cannabidiol Oral Solution (PDF - 42KB)
- Cannabis Clinical Research: Drug Master Files (DMFs) & Quality Considerations Webinar
- Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research, Draft Guidance for Industry
- FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD): Questions and Answers
- Development & Approval Process (Drugs)
- From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process
- FDA Center for Drug Evaluation and Research Small Business and Industry Assistance group
- CVM Small Business Assistance
- National Institutes of Health (NIH): Guidance on Procedures for Provision of Marijuana for Medical Research
- National Institute on Drug Abuse's (NIDA) Role in Providing Marijuana for Research
- Drug Enforcement Administration - Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances
- International Narcotics Control Board: Single Convention on Narcotic Drugs (1961)
- National Institute on Drug Abuse (NIDA): Ordering Guidelines for Marijuana and Marijuana Cigarettes

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