Process for Conducting Interventional Research with Cannabis

Glossary of Terms

CMC	Chemistry, Manufacturing, and Controls
CSA	Controlled Substances Act
DEA	Drug Enforcement Administration
DMF	Drug Master File
FDA	Food and Drug Administration
IND	Investigational New Drug
LOA	Letter of Authorization
NIDA	National Institute of Drug Abuse
NDA	New Drug Applications
PT	Pharmacology and Toxicology

Approaching the process for conducting research with cannabis can be a daunting task. Cannabis continues to be classified as a Schedule I drug. Consequently, strict laws in place require that investigators must cooperate with federal agencies, namely the FDA and DEA, in order to acquire approval, licensure, and legal exemptions as well as access to an approved, reliable cannabis source to carry out that research.

The purpose of this guide is to explain each step of the process with the necessary background information, explanations, and links to resources.

Step 1: Contact NIDA for specific information on medicinal cannabis strains

The purpose of this step is to obtain information regarding specific available cannabis strains to be studied, including their chemistry, manufacturing, and controls (CMC) information that will be included in both the FDA IND application and the DEA registration application for a Schedule I License.

The National Institute on Drug Abuse (NIDA), a division of the National Institute of Health, allows and funds studies pertaining to the therapeutic uses of cannabis and its chemical constituents. NIDA contracts with the University of Mississippi to grow cannabis intended for research study use. The University of Mississippi has been the *only* grower to legally supply researchers with cannabis. However, given the proliferation of public interest in marijuana's potential to treat various symptoms and diseases, the DEA released its intent to expand the number of DEA-registered marijuana growers and manufacturers beyond NIDA. Though a restricted effort, this will allow a more diverse array of growers to supply consistent, research-grade marijuana to researchers in the United States. However, to date, no additional growers have been approved by the DEA.

NIDA's Drug Supply Program (DSP) makes studying Schedule 1 substances possible for researchers by providing legal access to substances otherwise unattainable, financially inaccessible, or unavailable.

Once registered with the DEA in compliance with the Controlled Substances Act (Step 3, below), then a request to NIDA accompanied by necessary documents may be submitted (Step 7, below).

For further information on NIDA's DSP:
NIDA Drug Supply Program Catalog (25th edition, last updated May 2016)

For details on specific DSP batches and contact information for marijuana product availability and content, follow this link: Marijuana Plant Material Available from the NIDA Drug Supply Program

Step 2: Obtain approval from an accredited Institutional Review Board (IRB)

An IRB-approved protocol is required to pass all subsequent regulatory steps.

Step 3: Obtain LOA from NIDA

A Letter of Authorization (LOA) will be used to reference the CMC information found on NIDA's Drug Master File (DMF) filed with the FDA. A LOA is obtained from the DMF holder (in this case NIDA), which will then be submitted in the IND application Section 1.4.2 (See **Step 5**).

A DMF is a FDA submission providing detailed, confidential information regarding one or more drugs used for humans.

STEP 4: Obtain an IND from the FDA

The role of the FDA is to ensure that drugs being used in research are sound and effective for their intended use. Although the FDA is aware of the interest in the potential of cannabis to treat a wide array of medical conditions, the agency has not approved botanical cannabis as a safe and effective drug. An Investigational New Drug, or IND, application must be submitted to the FDA for any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease prior to marketing in the US. The IND provides the FDA with information pertaining to:

- **Clinical Research Study Protocol**: The study plan; determines the extent to which human subjects are being exposed to risks in a trial, as well as providing details of the study.
- **Clinical Investigator Qualifications**: Ensures that investigators (licensed health care professionals) who will oversee drug administration to study participants, are qualified to carry out their necessary responsibilities during clinical trials.
- **Manufacturing Information**: Gives information pertaining to chemical composition and stability of drug, manufacturing controls, and whether the manufacturer can produce the drug in consistent supply.
- **Preclinical Toxicology and Pharmacology Data**: Provides data on whether the product being researched is safe for human use and any previous studies involving the drug.

The IND is the method by which a sponsor can be granted legal exemption by the FDA to legally transport a study agent across state lines to research locations.

This link provides step-by-step instructions to Request a Pre-Assigned Application Number

Need more help before diving into the application process or solving IND data issues?
The FDA may provide pre-IND consultations in the early drug development stages to facilitate communication and provide support for various parts of the IND application.

Upon submission of the IND application, the FDA will issue an IND number and confirm receipt of the application within **3 business days**. That begins a 30-day application review period by the FDA. If the FDA requires more information or requests changes they will do so with official correspondence during that 30-day review period. If no correspondence is received, the proposed research may proceed.

Step 4a: The IND application

The following table is used to provide researchers with information regarding IND application submission procedures, application procedures, and application reporting for periodically updating the FDA.

IND application forms may be found here and explanations for each IND application component may be found here. More information for filling out the CMC information is found here as well as for pharmacology and toxicology (PT).

If applicable, the IND application must include the LOA from NIDA (see **Step 4)** to reference the CMC information in the FDA's DMF.

Once the IND application is complete, it may be mailed to the FDA -- Submitting the IND application.

Step 5: FDA reviews the IND application

Review may take up to **30 days** from the time when the FDA receives the IND application, during which time the study sponsor must wait before starting any trials. The sponsor may proceed with the clinical investigation once the FDA has notified the sponsor of its approval.

Step 6: Contact DEA for Registration Application for Schedule I License

New applicants who do not already possess DEA registration must complete DEA Form 225: New Application for Registration for research. This form can be submitted online or via mail.

You must have IRB approval and an active IND prior to submitting the DEA Schedule I license application.

If renewing registration, applicants must complete DEA Form 225a (DEA Registration Renewal Form Login)

If you have a DEA Schedule I license, you must submit the protocol to DEA for approval before initiating the study.

Further registration information (categories and fees)
Registration applications Q&A
Protocol for "Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances": Section 1301.18 of Title 21 Code of Federal Regulations

Step 7: Contact NIDA to obtain cannabis once FDA completes IND review and the DEA registration is received

NIDA: Ordering Guidelines for Marijuana and Marijuana Cigarettes

Source:
U.S. Food and Drug Administration. (2017). "Marijuana Research with Human Subjects". https://www.fda.gov/newsevents/publichealthfocus/ucm421173.htm

Further Reading:

FDA and Marijuana: FDA's role in the drug approval process, how the FDA supports sound scientific research

Botanical Drug Development: Guidance for Industry (FDA CDER)

"DEA speeds up application process for research on Schedule I Drugs"

"Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States"

"Pot and Politics: Investigating Barriers to Medical Marijuana Legalization"

"Medical Marijuana Research News"

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