



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-D-1079]

Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research;
Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research.” This draft guidance outlines FDA’s current thinking on several topics relevant to the development of cannabis and cannabis-derived products: the source of cannabis and cannabis-derived compounds for clinical research; general quality considerations for developing drugs that contain cannabis and cannabis-derived compounds; and calculation of percent delta-9 tetrahydrocannabinol (THC) in botanical raw materials, extracts, and finished products. This draft guidance has been developed to help support clinical research into development of cannabis and cannabis-derived products.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2020-D-1079 for “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket

number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Amy Muhlberg, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 51, Rm. 3117, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 240-402-6901 or Cassandra Taylor, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 51, Rm. 4150, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 240-402-5290.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research.”

This draft guidance outlines FDA’s current thinking on several topics relevant to the development of drugs containing cannabis and cannabis-derived compounds: (1) the source of cannabis and cannabis-derived compounds for clinical research; (2) general quality considerations for developing drugs that contain cannabis and cannabis-derived compounds; and

(3) calculation of percent delta-9 THC in botanical raw materials, extracts, and finished products. This draft guidance has been developed to help support clinical research into development of drugs containing cannabis and cannabis-derived compounds.

Cannabis and cannabis-derived compounds have been the subject of interest from consumers, industry, researchers, the public, and regulators. The Agriculture Improvement Act of 2018, Public Law 115-334 (the 2018 Farm Bill), changed certain federal authorities relating to the production and marketing of cannabis and cannabis-derived compounds. Among other things, the 2018 Farm Bill removed *hemp* from Schedule I controls in the Controlled Substances Act (CSA). The 2018 Farm Bill also explicitly preserved FDA's authority to regulate products containing cannabis or cannabis-derived compounds under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). In doing so, Congress recognized FDA's important public health role with respect to all the products it regulates. Accordingly, consistent with the 2018 Farm Bill, drugs that contain cannabis and cannabis-derived compounds are subject to the same authorities and requirements as FDA-regulated products containing any other substance, regardless of whether the products fall within the definition of *hemp* under the 2018 Farm Bill.

The Drug Enforcement Administration (DEA) is the lead Federal agency for regulating controlled substances. FDA does not enforce the CSA or other laws within DEA's jurisdiction. Activities related to growing and manufacturing cannabis for use as an investigational drug for research must comply with CSA and DEA requirements if the cannabis exceeds the threshold of 0.3 percent delta-9 THC by dry weight. Sponsors and investigators are encouraged to contact DEA with questions regarding Schedule I cannabis or the CSA.

FDA held a public hearing¹ on May 31, 2019, to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds. The hearing was attended by more than 600 participants in person and over 2,300 joining remotely. Presentations by over 100 speakers represented a broad and diverse array of stakeholders. Nearly 4,500 comments were submitted to the docket associated with the hearing, and the docket's closing date was extended to accommodate greater participation. FDA developed this draft guidance in part to respond to issues and questions raised in the discussion at that hearing and in many of the public comments received.

Although the hearing was not exclusively about cannabidiol (CBD), this compound was a key discussion topic. FDA and many stakeholders have concerns about marketed products that contain CBD, including concerns about potential contamination and inaccurate or misleading labeling. FDA would like to reiterate that EPIDIOLEX[®] (cannabidiol) is the sole FDA-approved² product derived from an extract of the cannabis plant.

Many sponsors initiating clinical research for drugs containing cannabis and cannabis-derived compounds may be unclear regarding, or unfamiliar with, applicable drug quality expectations. In general, drugs containing cannabis and cannabis-derived compounds are subject to the same authorities and requirements as drugs containing any other substance. Drugs intended for human use are evaluated by FDA's Center for Drug Evaluation and Research (CDER³) to ensure that drugs marketed in the United States are safe and effective for their intended uses and

¹ "Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds"; <https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds>.

² See Epidiolex drug approval package and labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm.

³ FDA's Center for Biologics Evaluation and Research (CBER) also has regulatory responsibilities with respect to the review of human drugs.

will be manufactured in a manner that ensures quality. CDER has published extensive regulations and guidance documents regarding the drug development and review process. In addition, FDA's website contains useful explanations regarding drug research and development. Finally, CDER's Small Business and Industry Assistance helps small pharmaceutical businesses and industry navigate the wealth of information that FDA offers, and assists in understanding the regulation of human drug products.

FDA's support of drug development extends to drugs containing cannabidiol and other compounds found in cannabis. One important element is encouraging drug developers to meet with FDA early in their development programs--ideally, before submitting an investigational new drug (IND) application. The pre-IND meeting is an opportunity to obtain FDA input on research plans and required content for an IND submission. The pre-IND meeting can be valuable in planning a drug development program, especially if sponsors' questions are not fully answered by guidances and other information provided by FDA. Early interactions with FDA staff through a pre-IND meeting can answer sponsors' questions related to a specific drug development program and provide information that will assist them in preparing complete IND applications. Efficient use of FDA resources can lead to more efficient drug development.

The FDA web page "FDA and Cannabis: Research and Drug Approval Process" (available at <https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process>) provides the basic roadmap for conducting clinical research at FDA using cannabis and cannabis-derived compounds. The resources on this page may be helpful to those interested in better understanding FDA processes for conducting clinical trials using cannabis and cannabis-derived compounds.

Calculating the amount of a substance in a botanical raw material by dry weight is a standard procedure. However, the calculation of dry weight for an extract or solid oral dosage form is less familiar to many stakeholders than the standard calculation for botanical raw materials. Therefore, the draft guidance recommends calculating delta-9 THC by dry weight in intermediates and drug products by removing the water content, including water contained in excipients. We invite comment from the public on this recommended approach. In addition, FDA invites public comment on the appropriate manufacturing controls over materials that cross under the 0.3 percent delta-9 THC by dry weight threshold during the production of a drug that contains cannabis or cannabis derived compounds.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

FDA tentatively concludes that this draft guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required.

However, this draft guidance refers to previously approved FDA collections of information. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR Parts 312 and 314 for submission and approval of applications for investigational drugs and new drugs have been approved under OMB control

numbers 0910-0014 and 0910-0001 respectively; and current Good Manufacturing Practices for Finished Pharmaceuticals as outlined in 21 CFR Parts 210 and 211 have been approved under OMB control number 0910-0139.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs> or <https://www.regulations.gov>.

Dated: July 16, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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