Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2020
Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (CMC)

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Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance outlines FDA's current thinking on several topics relevant to clinical research related to the development of drugs containing cannabis or cannabis-derived compounds.[2] Cannabis and cannabis-derived compounds that may be used in drug manufacturing include botanical raw materials, extracts, and highly purified substances of botanical origin. This guidance does not address development of fully synthetic versions of substances that occur in cannabis, sometimes known as cannabis-related compounds, which are regulated like other fully synthetic drugs. This guidance is limited to the development of human drugs and does not cover other FDA-regulated products.

The recommendations in this guidance are intended to provide clarity regarding a recent legislative change (see section III) and to address certain questions raised in a recent public hearing.[3] The guidance also introduces key FDA regulatory concepts to stakeholders who may be less familiar with FDA or our authorities than other drug developers.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For discussion of terms used in this guidance, see FDA and Cannabis: Research and Drug Approval Process at https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process.

[3] "Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds." Public hearing, May 31, 2019. https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds

II. BACKGROUND

Human drugs that contain cannabis and cannabis-derived compounds are generally subject to the same authorities and requirements, including quality standards, as FDA-regulated drug products containing any other substance. Under section 201(g) of the Food, Drug, and Cosmetic Act (FD&C Act), a drug is any product that is intended to diagnose, cure, mitigate, prevent, or treat a disease, or any product (other than food) intended to affect the structure or any function of the body.[4] This means any product (including one that contains cannabis or a cannabis-derived compound) marketed with a claim of therapeutic benefit, or with any other disease claim, is considered a drug. A drug that is not generally recognized[5] among experts as "safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" is a "new drug" under the FD&C Act and must be approved by the FDA for its intended use before it may be introduced into interstate commerce.[6] As part of drug development, sponsors may conduct clinical trials under an investigational new drug (IND) application to determine if a drug is safe and effective for a particular intended use. The IND application provides a mechanism for those developing a new drug to conduct studies and ship their proposed drug to clinical trial sites.[7] The data obtained from these studies may later become part of a new drug application (NDA), which is then used to formally propose that FDA approve a new drug for sale in the United States. Entities submitting an IND are referred to as *sponsors* or *investigators*,[8] while those submitting an NDA are referred to as *applicants*.[9] Early interaction with FDA may prevent clinical hold issues and aid sponsors in developing a complete IND.[10]

The 2018 Farm Bill (the Agriculture Improvement Act of 2018, Public Law 115-334) changed how cannabis is treated under the Controlled Substances Act (CSA). The bill created a new definition of *hemp*, which includes cannabis and derivatives or extracts of cannabis with no more than 0.3 percent by dry weight of the compound delta-9 tetrahydrocannabinol (THC) (see section III.C for further discussion).[11] The bill removed hemp from the definition of *marihuana*[12] provided in section 102 of the CSA,[13] which means that hemp is no longer a controlled substance under Federal law. However, botanical raw materials, extracts, and derivatives that contain

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[4] See 21 U.S.C. 321(g).

[5] In order for a drug product to be considered generally recognized as safe and effective (GRASE), (1) it must have been subjected to adequate and well-controlled clinical investigations that establish the product as safe and effective, and (2) experts must generally agree, based on those studies, that the drug product is safe and effective for its intended uses. The consideration of a product as GRASE generally must be supported by the same quality and quantity of scientific and clinical data necessary to support the approval of a new drug application.

[6] See sections 201(p), 301(d), and 505(a) of the FD&C Act.

[7] 21 CFR part 312. For general information about the different types of applications, see https://www.fda.gov/drugs/how-drugs-are-developed-and-approved/types-applications.

[8] 21 CFR 312.3

[9] 21 CFR 314.3

[10] See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] For a detailed discussion of the calculation of delta-9 THC content, including the proper treatment of measurement uncertainty, see USDA's interim final rule, "Establishment of a Domestic Hemp Production Program" (84 FR 58522, Oct. 31, 2019) and any succeeding regulations.

[12] The CSA uses the spelling *marihuana*; *marijuana* is a common alternative.

[13] See 21 U.S.C. 802.

cannabis or cannabis-derived compounds with delta-9 THC content above 0.3 percent by dry weight remain Schedule I controlled substances under the CSA.[14]

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 or cannabis-derived compound 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.

III. RECOMMENDATIONS

A. Sources of Cannabis

Sponsors, including sponsor-investigators, must meet all FDA requirements to conduct human clinical trials, regardless of the source of cannabis or any other botanical product under study in the trial.[15] The FDA website contains information, including guidance documents, to assist sponsors in preparing IND applications both generally[16] and for cannabis specifically.[17]

For many years, the National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP)[18] provided the only domestic federally legal source of cannabis for clinical research. Cannabis for the DSP is grown under contract by the University of Mississippi at the National Center for Natural Products Research. However, the changes made by the 2018 Farm Bill allow hemp to serve as a source of cannabis and cannabis-derived compounds for drug development if they do not contain delta-9 THC at more than 0.3 percent by dry weight. This change gives sponsors and investigators of clinical studies new options that do not involve the NIDA DSP.

In light of the changes made by the 2018 Farm Bill, FDA is clarifying its current thinking on sources of cannabis for clinical research:

- Currently, the NIDA DSP is the only domestic federally legal source of cannabis over the 0.3 percent delta-9 THC limit for clinical research.[19]

[14] For a list of controlled substances, see https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf.

[15] 21 CFR part 312

[16] For general information about the IND application process, see https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application.

[17] For information specific to cannabis, see https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process.

[18] For information about NIDA's DSP, see https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research.

[19] DEA is currently in the process of allowing additional growers to register with the DEA to produce and distribute cannabis for research purposes. For further information regarding the opening of DEA registration to bulk manufacturers of marihuana, see the *Federal Register* of August 12, 2016 ("Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States," 81 FR 53846) and August 27, 2019 ("Bulk Manufacturer of Controlled Substances Applications: Bulk Manufacturers of Marihuana," 84 FR 44920).

- Cannabis under the 0.3 percent delta-9 THC limit may be used for clinical research.

- Sponsors and investigators are encouraged to contact DEA with questions regarding controlled substances and the CSA.

B. Resources for Information on Quality Considerations

As part of an IND for any drug, including drugs that contain cannabis or cannabis-derived compounds, sponsors are expected to show that they can consistently manufacture a quality product. In each phase of clinical investigation, sponsors must submit sufficient information to ensure the identity, quality, purity, and potency or strength of the investigational drug.[20] The amount of information appropriate to meet this expectation will increase with successive stages of drug development. The guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008)[21] provides recommendations for phase 1 investigations, and the regulations at 21 CFR parts 210 and 211 govern current good manufacturing practice (CGMP) for phase 2 and phase 3 investigations, and marketed products.

Sponsors should provide quantitative data regarding phytochemicals that are present in their proposed product, including but not limited to, cannabinoids, terpenes, and flavonoids. Although the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015), does not address IND methods validation, sponsors preparing INDs may find the recommendations in this guidance helpful. In addition, please refer to the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (March 1995) for further recommendations regarding method validation. For a marketing application, submissions should include a detailed description of all analytical methods used, including justification of departures from compendial or other standard methods.

Guidance documents on pharmaceutical quality are available on FDA's website.[22] The United States Pharmacopeia (USP) and the National Formulary (NF) contain chapters on tests, equipment, and analytical methods for drug quality aspects such as identification, excipients, impurities, and microbiological controls for sterile as well as nonsterile products.[23]

The following additional principles and recommendations are particularly relevant for developing drugs that contain cannabis and cannabis-derived compounds:

- Cannabis is held to the same regulatory standards as any other botanical raw material, botanical drug substance, or botanical drug product. The general considerations and recommendations for botanical drugs contained in the guidance for industry *Botanical Drug Development* (December 2016) provide core principles for conducting clinical

[20] See 21 CFR 312.23 for the types of information required in an IND for each phase of a clinical study.
[21] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[22] For resources related to pharmaceutical quality, see https://www.fda.gov/drugs/development-approval-process-drugs/pharmaceutical-quality-resources and https://www.fda.gov/drugs/pharmaceutical-quality-resources/guidances-and-manuals-pharmaceutical-quality.
[23] https://www.uspnf.com/

research on botanical drugs, including drugs that contain cannabis and cannabis-derived compounds. In addition, FDA recommends that those pursuing drug development using cannabis or cannabis-derived compounds consider the following principles and documents:

- Adequate characterization of cannabis and cannabis-derived compounds, for example via a chemical fingerprint, is critical to ensuring batch-to-batch consistency.

- USP General Chapter <561> *Articles of Botanical Origin*, particularly regarding tests for residual pesticides, including any pesticides routinely used in the countries of origin of botanical raw materials.

- USP General Chapter <563> *Identification of Articles of Botanical Origin*.

- USP General Chapters <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*.

- USP General Chapter <232> *Elemental Impurities—Limits*.

- Quality tests, including those specific to dosage form, can be found in the topic-specific annexes to the ICH guidance for industry *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the International Conference on Harmonisation Regions* (February 2007) as well as various USP chapters.

- There may be drug scheduling considerations under the CSA for applicants pursing FDA approval of an NDA for a drug that contains cannabis or cannabis-derived compounds. FDA's review of the NDA may include an abuse potential assessment to inform labeling and to provide DEA with a scientific and medical evaluation of the drug's abuse potential.[24]

- As described in the guidance for industry *Botanical Drug Development*, IND sponsors may submit literature to support early clinical development. However, in general, the data contained in published studies regarding the chemical composition of test materials is not adequate for bridging to a proposed botanical drug product, as the particular botanical drug product under review may differ from the test material. In addition, the available literature may not sufficiently describe the botanical drug and its production. Therefore, FDA does not recommend that applicants pursuing FDA approval of an NDA rely on published literature in place of a full toxicology program to support development of a botanical drug product for phase 3 trials and beyond.

[24] See the guidance for industry *Assessment of Abuse Potential of Drugs* (January 2017).

  - The human major metabolite of cannabidiol, 7-COOH-CBD, is expressed disproportionately in humans compared to animals. While disproportionate metabolism is not limited to botanical products, FDA would like to make stakeholders aware that this is a known issue with certain cannabinoids.

- If a device is to be used in combination with a drug (e.g., when the product is delivered via an inhaler or other device), the product is considered to be a combination product[25] and must comply with the CGMP requirements in 21 CFR part 4, subpart A, including requirements for design controls (see 21 CFR 820.30).[26]

- Sponsors should consider selection of a container closure system carefully.[27] As drug development progresses, applicants pursuing FDA approval should provide adequate characterization and safety assessment of extractable and leachable compounds. The evaluation of these compounds under the specific conditions of use of the proposed drug, including identification of qualification thresholds, should be consistent with:

  - USP General Chapters <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* and <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*

  - Guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999)

  - Applicable dosage form-specific guidances

- Highly purified substances of botanical origin are considered analogous to conventional synthetic single-chemical active pharmaceutical ingredients (APIs) for the purposes of drug development, including nonclinical considerations,[28] and FDA review.[29] However, a naturally occurring compound isolated from a botanical source would be expected to have a different impurity profile from the corresponding synthetically produced cannabis-related compound, and impurities for the naturally occurring compound should be controlled accordingly.

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[25] A combination product is composed of two or more of the three types of medical products (i.e., drug, device, and biological product) that are either physically, chemically, or otherwise combined into a single-entity, copackaged together, or under certain circumstances distributed separately to be used together as a cross-labeled combination product. See 21 CFR 3.2(e).

[26] Further information about the CGMP requirements for combination products is available in the FDA guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

[27] For further information, see the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995).

[28] See in particular the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* (March 2006).

[29] For information about how FDA reviews drug applications, see https://www.fda.gov/drugs/development-approval-process-drugs/how-drugs-are-developed-and-approved and https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

C. Percent Delta-9 THC Calculation

Other than the specific change to the control status of hemp, scheduling decisions regarding controlled substances were not affected by the 2018 Farm Bill. Activities related to growing and manufacturing cannabis for use as an investigational drug for research must comply with CSA and DEA requirements[30,31] if the cannabis exceeds the threshold of 0.3 percent delta-9 THC by dry weight. Sponsors and investigators proposing drug development activities involving controlled substances should consult with DEA about the applicable requirements. Sponsors and investigators may find it useful to calculate the level of delta-9 THC in their proposed investigational drug product early in the development process to gain insight into the potential control status of their product.

Regardless of whether cannabis or a cannabis-derived compound meets the definition of *hemp*, sponsors and applicants should work with reliable laboratories for analytical testing. For Phase 1 studies, please refer to the guidance for industry *CGMP for Phase 1 Investigational Drugs* regarding methods development and laboratory controls. For phase 2 and 3 studies and for NDA submissions, laboratories (whether in house or under contract) must use validated analytical methods,[32] and applicants must provide those methods in their application.[33] The Agency may request additional chemistry, manufacturing, and controls information to assess drug substance and drug product quality during the development and submission processes.

Calculation of tetrahydrocannabinols content may provide sponsors and investigators with information about the composition of a proposed raw material, intermediate, drug substance, or drug product. The calculation in this section is not intended to alter the determination of a starting material for CGMP purposes as described in the guidance for industry *Botanical Drug Development* and the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016). It is important to note that the 0.3 percent delta-9 THC by dry weight threshold is not appropriate as a limit when considering tetrahydrocannabinols as impurities for quality control and application submission (i.e., chemistry, manufacturing, and controls) purposes. Quality-related calculations of tetrahydrocannabinols content will be evaluated during the IND evaluation and application review processes.

Sponsors using cannabis botanical raw materials in their drug development activities should refer to the U.S. Department of Agriculture (USDA) interim final rule, "Establishment of a Domestic Hemp Production Program" (84 FR 58522, October 31, 2019), or any superseding rule, for sampling[34] and testing[35] methods for evaluating the level of delta-9 THC in a cannabis botanical raw material.

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[30] See section 303(f) of the CSA.

[31] See 21 CFR 1301.18 and 1312.11 in particular. General regulations implementing the CSA can be found at 21 CFR parts 1300 et seq.

[32] 21 CFR 211.160; 21 CFR 211.22

[33] 21 CFR 314.50(d)

[34] See USDA's "Sampling Guidelines for Hemp Growing Facilities," available at https://www.ams.usda.gov/sites/default/files/media/SamplingGuidelinesforHemp.pdf.

[35] See USDA's "Testing Guidelines for Identifying Delta-9 Tetrahydrocannabinol (THC) Concentration in Hemp," available at https://www.ams.usda.gov/sites/default/files/media/TestingGuidelinesforHemp.pdf.

With respect to development of human drugs containing cannabis or cannabis-derived compounds, sponsors or applicants should provide the following information to FDA in their IND application, along with any other required information:

- Provide quantitative data, such as a certificate of analysis from a laboratory described in the USDA interim final rule, indicating the percent delta-9 THC by dry weight in their botanical raw material.

- Provide detailed descriptions of testing methods used to evaluate the level of delta-9 THC for phase 2 and phase 3 studies and marketing applications.

- Consider section 7.20, Rounding Rules, in the USP *General Notices and Requirements* when calculating and reporting the level of delta-9 THC to FDA.

In general, the composition of a botanical raw material is calculated as the amount of the compound(s) of interest naturally present relative to the dry weight of botanical raw material prior to extraction or other manufacturing steps. However, this type of dry weight calculation has limited utility for intermediates such as solutions, extracts in solution (whether aqueous or non-aqueous), and for finished products. Therefore, FDA recommends that sponsors, investigators, or applicants evaluating intermediates or finished products that contain cannabis or cannabis-derived compounds base the calculation of delta-9 THC percentage on the composition of the formulation with the amount of water removed, including any water that may be contained in excipients.

This recommended calculation should not be used for other purposes such as chemistry, manufacturing, or controls. Sponsors should submit documentation regarding the steps of this calculation when they submit the IND.

- For a solution-based material (intermediate, in-process material, or final drug product),

    1. Determine the density of the liquid formulation and convert 1 mL of the formulation to mass units (mg).

    2. Calculate water content (in mg) of each active and excipient component present in 1 mL of the formulation.

    3. Sum the water content (in mg) for all components present in 1 mL of the liquid formulation and subtract this amount from the total mass of 1 mL (from step 1). This is the water-adjusted total mass of 1 mL of the formulation.

    4. Calculate the mass, or mg amount, of delta-9 THC present in 1 mL of the liquid formulation.

    5. Calculate the percentage delta-9 THC by dividing the mass of delta-9 THC from step 4 by the total water-adjusted mass in step 3 and multiplying by 100.

- For a solid oral dosage form (e.g., tablet or capsule), this percentage is similarly calculated and would be the weight of delta-9 THC in the dosage unit divided by the total water-adjusted formulation weight multiplied by 100.

  - For oral capsules, the mass of the capsule itself should not be included in the denominator weight. Include only the capsule fill.

  - The water-adjusted formulation weight used in the calculation should reflect the removal (in mass units such as mg) of all water content present for each of the components, whether active or inactive, in the formulation.

- For either solutions or solids, use of the proposed or established specifications for the upper limit of water content for excipients that contain water, as opposed to a measured result from a sample, may be acceptable and would be a matter for review.

- We recommend that you consult DEA regarding the control status of cannabis or cannabis-derived materials or products that are under development. We note that intermediates or drug products that contain greater than 0.3 percent delta-9 THC by dry weight, even if the starting materials meet the definition of *hemp*, may no longer meet the definition of *hemp* and may be considered a Schedule I controlled substance.

- In addition, the drug product, including the dosing regimen, will be evaluated during the NDA review process for potential scheduling under the CSA.

- Some manufacturing processes may generate materials, such as intermediates or accumulated by-products, that exceed the 0.3 percent delta-9 THC by dry weight threshold even if the source material or finished product does not exceed the threshold. Sponsors, investigators, and applicants who anticipate generating such intermediates or by-products that may be shipped between manufacturing sites should contact DEA for recommendations.