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

Guidance for Industry

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

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

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Contains Nonbinding Recommendations

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This guidance represents 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 office 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 human drugs containing cannabis or cannabis-derived compounds.[2] As defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), *drug* includes 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.[3] In general, this means any product (including one that contains cannabis or cannabis-derived compounds) marketed with a claim of therapeutic benefit, or with any other disease-related claim, is considered a drug. To be legally marketed in interstate commerce, drugs that are not biological products generally must either (1) receive premarket approval by FDA through the new drug application (NDA) or abbreviated new drug application (ANDA) process, or (2) for certain over-the-counter nonprescription drugs, meet the requirements in the FD&C Act for marketing without an approved NDA or ANDA.[4] The recommendations in this guidance are intended for products that meet the legal definition of a drug under the FD&C Act.

Cannabis and cannabis-derived compounds that may be used in manufacturing human drugs include botanical raw materials, extracts, and highly purified substances of botanical origin. This guidance provides recommendations for sponsors interested in developing such cannabis and cannabis-derived compounds for use in human drugs for clinical research. This guidance does not address development of fully synthetic versions of substances that occur in cannabis, sometimes known as cannabis-related compounds (e.g., dronabinol), which are regulated like other fully synthetic drugs. This guidance is limited to the development of drugs for human use and does not cover other FDA-regulated products.

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

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

This guidance addresses the legal definitions and regulatory controls related to cannabis (see section II), and it addresses certain questions raised in a public hearing about drugs containing cannabis and cannabis-derived compounds.[5] 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.

II. BACKGROUND

The Agriculture Improvement Act of 2018 (Public Law 115-334), often referred to as the 2018 Farm Bill, changed how cannabis is treated under the Controlled Substances Act (CSA). The 2018 Farm Bill, which is generally implemented by the U.S. Department of Agriculture (USDA),[6] defines *hemp* as including 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).[7] The bill removes hemp from the definition of *marihuana*[8] provided in section 102 of the CSA,[9] which means that hemp is no longer a controlled substance under Federal law. However, at this time, botanical raw materials, extracts, and derivatives that contain 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.[10]

The Drug Enforcement Administration (DEA) is the lead Federal agency for regulating controlled substances. 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 compounds exceed the threshold of 0.3 percent delta-9 THC by dry weight.[11] When submitting an investigational new drug (IND) application, sponsors should consider the delta-9 THC content to determine the controlled substance status of any botanical raw materials, drug substances, and drug products covered by the submission.[12] FDA does not enforce the CSA or regulations within DEA's jurisdiction. Sponsors, investigators, and manufacturers are encouraged to contact DEA with questions regarding the control status under

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[5] "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

[6] The USDA administers Federal laws regarding hemp production.

[7] For a detailed discussion of the calculation of total delta-9 THC content (i.e., delta-9 THC and tetrahydrocannabinolic acid (THCA)), including the proper treatment of measurement uncertainty, see 7 CFR 990.1 and 990.25 and any succeeding regulations.

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

[9] See 21 U.S.C. 802(16).

[10] See 21 CFR 1308.11 Schedule I (d)(31)(i).

[11] See 21 CFR 1318.

[12] As defined in 21 CFR 314.3

the CSA of the cannabis or cannabis-derived materials (e.g., botanical raw materials, drug substances, and drug products) and applicable DEA regulatory requirements for Schedule I cannabis-derived materials.

The 2018 Farm Bill preserved FDA's authority to regulate products containing cannabis or cannabis-derived compounds under the FD&C Act and section 351 of the Public Health Service Act. Human drugs that contain cannabis and cannabis-derived compounds (regardless of whether the products fall within the definition of *hemp* under the 2018 Farm Bill) are generally subject to the same authorities and requirements, including quality standards, as FDA-regulated drug products containing any other substance. As part of drug development, sponsors may conduct clinical trials under an IND to determine if a drug is safe and effective for a particular intended use.[13] The IND provides a mechanism for those developing a new drug to conduct studies and ship their proposed drug to clinical trial sites.[14] The data obtained from these studies may later become part of an 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*,[15] while those submitting an NDA are referred to as *applicants*.[16] Early interaction with FDA may prevent clinical issues and aid sponsors in developing a complete IND.[17]

III. RECOMMENDATIONS

Sponsors, including sponsor-investigators, must meet all FDA requirements to conduct human clinical trials, regardless of their source of cannabis or any other botanical product under study in the trial.[18] FDA's website contains information, including guidance documents, to assist sponsors in preparing INDs both generally[19] and for cannabis specifically.[20] This section describes FDA's recommendations regarding sources of cannabis for clinical research and resources for information on quality and control status considerations.

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[13] Clinical trials conducted under an IND are generally divided into three phases: phase 1 includes the initial introduction of the investigational drug into humans; phase 2 includes studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition; phase 3 includes expanded studies that are intended to further assess the safety and effectiveness of the drug to evaluate the overall benefit-risk relationship of the drug. For more information on the phases of an investigation, see 21 CFR 312.21.

[14] 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.

[15] 21 CFR 312.3

[16] 21 CFR 314.3

[17] 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.

[18] 21 CFR part 312

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

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

A. Sources of Cannabis

For many years, the National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP)[21] 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. While the NIDA DSP continues to be a domestic federally legal source of cannabis over the 0.3 percent delta-9 THC threshold for clinical research, it is no longer the only federally legal source.[22] This development gives sponsors and investigators of clinical studies new sourcing options that do not involve the NIDA DSP.[23] Additionally, 7 CFR 990 and the changes made by the 2018 Farm Bill allow hemp, as defined in the bill[24] (i.e., cannabis at or below 0.3 percent delta-9 THC on a dry weight basis), to serve as a source of cannabis and cannabis-derived compounds for drug development.

In light of the developments described above, FDA is clarifying its current thinking on sources of cannabis for clinical research:

- Sources of cannabis with not more than 0.3 percent delta-9 THC on a dry weight basis and those over 0.3 percent delta-9 THC on a dry weight basis may be used for clinical research if deemed to be of adequate quality by FDA when reviewed as part of an IND (see section III.B).

- Sponsors and investigators may use the NIDA DSP as a source of cannabis over the 0.3 percent delta-9 THC threshold, or they may use other sources authorized by DEA to provide Schedule I cannabis materials for research. Sponsors can find DEA regulations for importation of controlled substances in 21 CFR 1312. A list of DEA-authorized growers of Schedule I cannabis is available online.[25] We refer sponsors and investigators to the DEA for guidance and answers to frequently asked questions about cannabis production and sources for research.

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 demonstrate the identity, quality, purity, and potency or strength of the investigational drug.[26] The amount of information appropriate to meet this expectation increases with successive stages of drug development. The guidance for industry *Content and Format of Investigational New*

[21] For information about NIDA's DSP, see https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research.
[22] See 21 CFR 1318 for information on procedures governing the registration of manufacturers seeking to plant, grow, cultivate, or harvest marihuana.
[23] The Medical Marijuana and Cannabidiol Research Expansion Act (Public Law 117-215) includes provisions related to cannabidiol and marijuana registration, research applications, and research protocols. The statute is not specifically addressed in this guidance, which focuses on quality considerations for human drug development.
[24] See 7 U.S.C. 1639o.
[25] See https://www.deadiversion.usdoj.gov/drugreg/marihuana.html.
[26] See 21 CFR 312.23 for the types of information required in an IND for each phase of a clinical study.

Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products (November 1995) provides recommendations for what data to provide for phase 1 investigations, and the guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008) provides recommendations for how to follow current good manufacturing practice (CGMP) for drugs in phase 1 clinical investigations.[27] The regulations in 21 CFR parts 210 and 211 govern CGMP for phase 2 and phase 3 investigations and for marketed drug products. The guidance for industry *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information* (May 2003) contains FDA's recommendations for how to address chemistry, manufacturing, and controls (CMC) in phase 2 and phase 3 investigations. Sponsors must provide a description of the investigational drug substance, which should include quantitative data regarding phytochemicals that are present in their proposed drug including but not limited to cannabinoids, terpenes, and flavonoids.[28] Although the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015) does not address method validation in an IND, sponsors preparing INDs may find the recommendations in this guidance helpful. In addition, sponsors can refer to the International Conference on Harmonization (ICH) draft guidance for industry *Q2(R2) Validation of Analytical Procedures* (August 2022)[29] for further recommendations regarding method validation. For a marketing application (e.g., an NDA), submissions must include a detailed description of all analytical methods used.[30] When an applicant proposes a departure from compendial or other standard methods relevant to the drug, the applicant should include justification for these departures in the application.

Guidance documents on pharmaceutical quality are available on FDA's website.[31] The United States Pharmacopeia (USP) and the National Formulary (NF)[32] contain chapters on tests, equipment, and analytical methods for drug quality aspects such as identification, excipients, impurities, and microbiological controls for nonsterile (e.g., non-aqueous inhalation drugs, oral drugs) and sterile (e.g., aqueous inhalation drugs[33]) products. The draft guidance for industry *Microbiological Quality Considerations in Non-Sterile Drug Manufacturing* (September 2021)[34] contains additional information on control of objectionable microorganisms[35] in nonsterile products.

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

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[27] 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.

[28] See 21 CFR 312.23(a)(7)(iv)(a) and the guidance for industry *Botanical Drug Development* (December 2016) for information regarding quantitative description of the drug substance used in the drug product.

[29] When final, this guidance will represent the FDA's current thinking on this topic.

[30] See 21 CFR 314.50(d).

[31] 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.

[32] https://www.usp.org

[33] See 21 CFR 200.51.

[34] When final, this guidance will represent the FDA's current thinking on this topic.

[35] See 21 CFR 211.113(a). The term *objectionable microorganisms* as used here refers to organisms that are objectionable due to their detrimental effect on products or their potential harm to patients, or it refers to an objectionable total number of organisms. See the *Federal Register* of Sep. 29, 1978 (43 FR 45053).

- Cannabis and cannabis-derived compounds are 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 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 <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests.*

    - USP General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms.*

    - USP General Chapter <71> *Sterility Tests.*

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

    - Tests for residual pesticides should include pesticides routinely used in the botanical raw materials' countries of origin. See USP General Chapter <561> *Articles of Botanical Origin* for further information.

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

    - USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.*

    - USP General Chapter <1225> *Validation of Compendial Procedures.*

- 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 ICH Regions* (February 2008) and in various USP chapters.

- Highly purified substances of botanical origin are considered analogous to conventional synthetic single-chemical active pharmaceutical ingredients for the purposes of drug

development (including nonclinical considerations)[36] and FDA review.[37] 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.

- 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[38] and must comply with the CGMP requirements in 21 CFR part 4, subpart A, including requirements for design controls (see 21 CFR 820.30).[39]

- Sponsors and applicants should consider selection of a container closure system or device constituent part carefully. As drug development progresses, applicants pursuing FDA approval should generate adequate characterization information and safety assessment data for extractable and leachable compounds to support a marketing application. However, when there are specific concerns (e.g., pediatric patient populations, device-related concerns), data to justify the safety should be submitted earlier in development. In these cases, FDA recommends submitting these data early in the IND phase and sponsors are encouraged to discuss the container closure system or device with the review division. The evaluation of extractable and leachable compounds under the specific conditions of use of the proposed drug, including identification of qualification thresholds, should be consistent with:

  - USP General Chapter <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*

  - USP General Chapter <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)

- As described in the guidance for industry *Botanical Drug Development*, IND sponsors may submit literature to support early clinical development. However, in general,

[36] 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).

[37] 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.

[38] 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).

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

chemical composition information found in published studies of test materials is not adequate for bridging to a proposed botanical drug product because the particular botanical drug product under review may differ from that of the published study. 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 data from a full toxicology program to support development of a botanical drug product for phase 3 trials and beyond.

- Assays to characterize the metabolic profile of major cannabinoids in humans and in toxicology species should be developed early to avoid delays in development. Metabolism data are often not available for most cannabinoids. Human-specific and disproportionate metabolites (i.e., human metabolite levels that are higher than animal levels) should be adequately characterized for safety prior to phase 3 clinical studies.[40] The major human metabolite of cannabidiol, 7-COOH-CBD, is expressed disproportionately in humans compared to animals; FDA recommends dedicated toxicology studies for this metabolite.

C. Considerations of Control Status Under the CSA

The 2018 Farm Bill's change to hemp's control status[41] has significantly reduced DEA's regulatory requirements for cannabis and cannabis-derived compounds that fall under the definition of *hemp*. However, if the cannabis does not meet the definition of *hemp* (i.e., it exceeds the threshold of 0.3 percent delta-9 THC by dry weight), activities related to growing and manufacturing cannabis for use as an investigational drug for research must still comply with applicable CSA and DEA requirements.[42,43,44] Sponsors and investigators proposing drug development activities involving controlled substances should consult DEA about the applicable requirements. Sponsors and investigators may find it useful to calculate the delta-9 THC content in their proposed cannabis or cannabis-derived investigational drug product early in the development process to gain insight into their product's potential abuse liability and control status.

Calculating the delta-9 THC content may provide sponsors and investigators with information about the control status of a proposed botanical raw material, intermediate, drug substance, or drug product. However, sponsors and investigators should not rely on the 0.3 percent delta-9

[40] See the FDA guidance for industry *Safety Testing of Drug Metabolites* (March 2020) and the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: Questions and Answers (March 2013)*.
[41] See 21 CFR 1308 for further information on the control status of cannabis and 7 CFR 990 for further information on the domestic hemp production program.
[42] See 21 CFR 1318.
[43] See section 303(f) of the CSA.
[44] See 21 CFR 1301.18 and 1312.11 in particular. General regulations implementing the CSA can be found in 21 CFR parts 1300 et seq.

THC by dry weight threshold when evaluating tetrahydrocannabinols as impurities for the purposes of quality control and application submission (i.e., CMC) (see section B).[45]

Sponsors using cannabis botanical raw materials in their drug development activities must comply with 7 CFR 990 (or any superseding regulations). Sponsors should also refer to USDA guidelines for sampling[46] and for testing[47] methods for evaluating the level of delta-9 THC in a cannabis botanical raw material.

An IND for a human drug containing cannabis or cannabis-derived compounds should include, along with any other required information, quantitative data (such as the analyses described in 7 CFR 990.3(a)(3) and 7 CFR 990.25 and any subsequently created regulations) indicating the percent delta-9 THC by dry weight in the botanical raw material.

In general, the percentage of delta-9 THC in botanical raw materials is calculated as the amount of delta-9 THC (and tetrahydrocannabinolic acid (THCA)) naturally present in a sample of the material relative to the dry weight of the botanical raw material sample prior to extraction or other manufacturing steps. However, this type of dry weight calculation has limited utility for intermediates such as solutions or extracts in solution (whether aqueous or non-aqueous) and for finished products of various dosage forms. Therefore, FDA recommends that sponsors, investigators, or applicants evaluating intermediates or finished products that contain cannabis or cannabis-derived compounds base the calculation of total delta-9 THC percentage (i.e., the THCA and THC[48]) on the composition of the formulation with the amount of water removed,[49] including any water that excipients may contain.

The recommended calculation for delta-9 THC content should not be used for other purposes such as CMC.

Sponsors should submit documentation regarding the steps of the delta-9 THC calculation when they submit the IND.

- For a solution-based material:

    1. Obtain a sample of the solution and determine its mass.

    2. Calculate the water content (in mass units) of the sample of the solution.

    3. Calculate the mass, or mg amount, of delta-9 THC (as total THC, combined with mass-adjusted THCA) present in the sample.

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[45] See 21 CFR 312.23 for the types of information required in an IND for each phase of a clinical study, and 21 CFR 314.50 for NDA content and format.
[46] See USDA's "Sampling Guidelines for Hemp Growing Facilities," available at https://www.ams.usda.gov/sites/default/files/media/SamplingGuidelinesforHemp.pdf.
[47] 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.
[48] See 7 CFR 990.3(a)(3).
[49] See USP General Chapter <731> *Loss on Drying* for the calculation of the Loss on Drying value and General Chapter <921> *Water Determination* for the calculation of water content (Karl Fisher method).

4. Calculate the percentage delta-9 THC *on a dry weight basis* by dividing the mass of total delta-9 THC by the water-adjusted mass of the sample, adjusted to exclude the mass of the sample attributed to water present in the sample, as follows (M = mass):

$$\text{THC percentage } = \frac{M_{(THC)}}{M_{(sample)} - M_{(water)}} \times 100$$

- 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 the experimentally determined water content present in the dosage unit.

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

- Cannabis-derived drug products may raise concerns about drug abuse liability. During the NDA review process, FDA may need to evaluate such a product for potential scheduling, or for transfer to a different control schedule (i.e., rescheduling), under the CSA. Please refer to the guidance for industry *Assessment of Abuse Potential of Drugs* (January 2017) for detailed considerations of data that you should collect during the IND stage of development so that you are able to provide a complete data package with your NDA submission. FDA's review of the NDA may include an abuse potential assessment to inform drug product labeling and to provide DEA with a scientific and medical evaluation of the drug's abuse potential to allow for drug scheduling or rescheduling under the CSA, if necessary.