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Client Alert Commentary

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FDA Finalizes Quality Recommendations for Cannabis in Clinical Investigations

FDA provides recommendations on sources of cannabis in clinical research, resources for information on quality, and control status considerations under the Controlled Substances Act.

Key Points:

- The Food and Drug Administration (FDA) highlighted recommendations and applicable resources for sponsors intending to use cannabis and cannabis-derived compounds in investigational clinical drug research.
- Although the 2018 Farm Bill removed "hemp" as a controlled substance, sponsors growing and manufacturing cannabis or cannabis-derived compounds with a higher than 0.3% delta-9 tetrahydrocannabinol (THC) by dry weight must still comply with the Drug Enforcement Administration's (DEA's) rules regarding controlled substances.

On January 23, 2023, FDA issued its Final Guidance, Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research. The guidance summarizes FDA's current thinking on assuring the quality of cannabis or cannabis-derived compounds used in clinical research. It provides recommendations for clinical sponsors and investigators interested in researching cannabis and cannabis-derived compounds derived from botanical origin. Notably, the development or manufacture of fully synthetic versions of cannabis-related compounds falls outside the scope of this guidance, which are regulated like other fully synthetic drugs.

Background on Cannabis — Hemp Legislation

In December 2018, then-President Trump signed into law the Agriculture Improvement Act of 2018 (Public Law 115-334), also known as the 2018 Farm Bill. The 2018 Farm Bill amended how cannabis (hemp) is treated under the Controlled Substances Act (CSA). It defines hemp as including cannabis and derivatives or extracts of cannabis with no more than 0.3% by dry weight of the compound delta-9 THC.[1] The bill amended the definition of the term marihuana/marijuana by removing hemp from Section 102 of the CSA — meaning that hemp was no longer a controlled substance under federal law.[2] That said, botanical raw materials, extracts, and derivatives containing cannabis or cannabis-derived compounds with delta-9 THC content above 0.3% by dry weight remain Schedule I controlled substances under the CSA, which are regulated by the DEA.

The 2018 Farm Bill did not change 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 (PHSA). Therefore, human drugs containing cannabis and cannabis-derived compounds are subject to FDA's general pharmaceutical drug regulatory framework. Specifically, during the drug development process, sponsors conduct clinical studies under an Investigational New Drug (IND) Application to determine whether a drug is safe and effective for a particular intended use. Importantly, the IND provides a pathway for those developing a new drug to conduct the clinical studies and/or to ship a drug under investigation — that would otherwise be prohibited — to clinical trial sites. The data obtained from these studies typically becomes part of the basis for FDA to determine safety and effectiveness, and to ultimately approve the marketing of a new drug in the United States.

FDA's Recommendations on Cannabis Quality for Clinical Research

Regardless of the source of cannabis or any other botanical product under study in a clinical trial, sponsors and investigators must meet all of FDA's requirements to conduct human clinical trials. This FDA guidance outlines general recommendations related to the sources of cannabis used in clinical research; resources for information on quality; and control status considerations under the CSA. The key points in each category are summarized below.

Appropriate Sources of Cannabis

FDA clarified that sources of cannabis for clinical research may include the following:

- Sources of cannabis with no more than 0.3% delta-9 THC on a dry weight basis and those over 0.3% delta-9 THC on a dry weight basis may be used for clinical research if FDA deems them to be of adequate quality when reviewed as part of an IND.

- Sponsors and investigators may also use the National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP)[3] as a source of cannabis over the 0.3% 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 importing controlled substances in 21 C.F.R. § 1312. A list of DEA-authorized growers of Schedule I cannabis is available online.[4]

Resources for Information on Quality Considerations

FDA explained that, as part of an IND for any drug, sponsors are expected to show that they can consistently manufacture a quality product. The agency indicated that during each phase of clinical investigation, sponsors must provide FDA with sufficient information that demonstrates the identity, quality, purity, and potency or strength of the investigational drug.

To help sponsors better understand the type of information required for an IND application, FDA provided multiple references to resources, including identifying several FDA guidance documents related to INDs and clinical studies, including the following:

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products (November 1995)

- CGMP for Phase 1 Investigational Drugs (July 2008)

- INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information (May 2003)

- Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)
- Q2(R2) Validation of Analytical Procedures (August 2022)
- Microbiological Quality Considerations in Non-Sterile Drug Manufacturing (September 2021)
- Botanical Drug Development (December 2016)
- Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (February 2008)
- Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)

FDA also provided references to several chapters of the United States Pharmacopeia (USP) and National Formulary (NF), which contain chapters on tests, equipment, and analytical methods for drug quality aspects related to identification, excipients, impurities, and microbiological controls for nonsterile and sterile products. The USP and NF also outline a number of recommendations that are particularly relevant for developing drugs containing cannabis or cannabis-derived compounds.

Considerations of Control Status Under the CSA

Although the 2018 Farm Bill changed hemp's status as a controlled substance, thereby significantly reducing DEA's regulatory oversight for hemp derived products, activities related to growing and manufacturing cannabis that do not meet the definition of hemp (i.e., cannabis of higher than 0.3% delta-9 THC by dry weight) for use as an investigational drug must still comply with applicable CSA and DEA requirements. Therefore, FDA recommends that sponsors and investigators intending to use cannabis with a THC content above that threshold consult with DEA regarding its specific requirements.

Takeaways

This FDA guidance points to several useful resources that clinical trial sponsors of drugs containing cannabis and cannabis-derived compounds may use when preparing their IND applications. As indicated in the guidance, utilizing cannabis and cannabis-derived compounds from botanical ingredients (rather than synthetic ingredients) poses special challenges for ensuring that the investigational drugs meet FDA's requirements for identity, quality, purity, and potency or strength. This guidance provides several technical recommendations that the industry should consider as it moves forward in researching cannabis and cannabis-derived compounds in human clinical studies.

If you have questions about this Client Alert, please contact one of the authors listed below or the Latham lawyer with whom you normally consult:

J. Benneville (Ben) Haas
ben.haas@lw.com
+1.202.637.1084
Washington, D.C.

J. Seth Olson
seth.olson@lw.com
+1.202.637.2119
Washington, D.C.

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Endnotes

[1] The US Department of Agriculture generally implements the 2018 Farm Bill. *See* 7 U.S.C. § 1639o(1).

[2] *See* 21 U.S.C. § 802(16).

[3] For more information about NIDA's DSP, see https://nida.nih.gov/research-topics/marijuana/nidas-role-in-providing-cannabis-research.

[4] *See* https://www.deadiversion.usdoj.gov/drugreg/marihuana.htm.