

# **FDA Role in Regulation of Cannabis Products**

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# Disclaimer



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# Biography

As Deputy Director for Regulatory Programs, in the Center for Drug Evaluation and Research at the FDA, Dr. Throckmorton shares the responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter, and generic drugs in the United States. He is committed to ensuring that the benefits of approved drugs outweigh their known risks. Among his responsibilities in CDER, Dr. Throckmorton works on issues related to controlled substances, including cannabis and cannabis-derived products.

Dr. Throckmorton received his medical degree from the University of Nebraska Medical School and completed his residency and fellowship at Case Western Reserve University and Yale University, respectively. Prior to coming to the FDA in 1997, he conducted basic science research and practiced medicine at the Medical College of Georgia, Augusta, Georgia and Augusta Veterans Administration Hospital.

# FDA Responsibilities

## Regulated Products include:

**Human Foods** (e.g., conventional foods, dietary supplements, food additives)

**Drugs** (including prescription and non-prescription)

**Biologics** (e.g., vaccines, blood and blood products)

**Medical Devices** (e.g., tongue depressors, pacemakers)

**Electronic Products that give off radiation** (e.g., microwave oven, X-ray equipment)

**Cosmetics** (e.g., skin moisturizers, lipsticks, eye and facial make-up, nail polish, cleansing shampoos)

**Veterinary Products** (e.g., animal foods, animal drugs)

**Tobacco Products** (e.g., cigarettes, smokeless tobacco)

# FDA Authority



Federal Food, Drug & Cosmetic Act (FD&C Act)

- Federal law enacted by Congress
- Along with other federal laws it establishes legal framework within which FDA operates

FDA regulations

- Develops regulations based on law set forth in FD&C Act or other laws under which FDA operates
- FDA regulations can be found in Title 21 of the Code of Federal Regulations ([21 CFR](#))

FDA guidance

- Follows procedures required by its “Good Guidance Practice” regulation to issue FDA Guidance
- Describe FDA’s current thinking on a regulatory issue



# FDA Role in Regulation of Cannabis Products



## Cannabis-derived compounds

- Compounds occurring naturally in the plant – like **CBD** and **THC**
- These compounds are extracted directly from the plant
- Can be used to manufacture drug products
- Example: highly-purified CBD extracted from the plant
- Agency approved one cannabis-derived drug product: Epidiolex (cannabidiol)

## CANNABIS

- *Cannabis sativa* L. is a plant that contains over 80 different naturally occurring compounds called “cannabinoids”
- Two well-known cannabinoids:
  - **Cannabidiol (CBD)**
  - **Tetrahydrocannabinol (THC)**
- Plants are grown to produce varying concentrations of cannabinoids – **THC** or **CBD**
- These plant variations are called cultivars

## Cannabis-related compounds

- These synthetic compounds are created in a laboratory
- Can be used to manufacture drug products
- Some synthetic compounds may also occur naturally in the plant and some may not
- Examples: Synthetically-derived dronabinol (also naturally occurring) and nabilone (not naturally occurring)
- Agency approved 3 synthetic cannabis-related drug products: Marinol & Syndros (dronabinol), Cesamet (nabilone)

# Regulatory Landscape : The Agriculture Improvement Act of 2018 (Farm Bill)



- Gives US Department of Agriculture (USDA) **authority** to issue federal regulations and guidelines concerning hemp production. **Individual States or tribes** desiring primary regulatory authority over hemp production must submit a plan to USDA
- **Removed hemp from the definition of marijuana** in the Controlled Substances Act (CSA)
  - Hemp: defined as cannabis (*Cannabis sativa* L.), and derivatives of cannabis, with extremely low (not more than 0.3 percent on a dry weight basis) concentrations of delta-9 THC
- **Marijuana is still regulated by DEA** under Schedule 1 of the CSA

# The Farm Bill's Impact on FDA Authorities

- **FDA's authorities** under the FDCA and section 351 of the PHS Act were **specifically preserved by the Farm Bill**
- Cannabis and cannabis-derived products are **subject to the same authorities and requirements** as FDA-regulated products **containing any other substance**
  - Allows hemp to serve as a source of cannabis and cannabis-derived compounds for drug development without CSA controls, if the investigational drug **does not contain delta-9 THC at more than 0.3 percent by dry weight**



# Overview of FDA Drug Authority



- Under the FD&C Act:
  - Any product, including a cannabis product (hemp or otherwise), that is marketed with a claim of therapeutic benefit, or with any other disease claim, is considered to be a drug
  - Generally, a new drug must be approved by the FDA for its intended use before it may be introduced into interstate commerce (limited exceptions, e.g., certain OTC drugs)

# THC and CBD: Active ingredients in approved drugs



- [Sec. 301\(ll\) of the FD&C Act \(21 U.S.C. § 331\)](#)- paraphrased
  - It is **prohibited** to introduce into interstate commerce any food that contains an active ingredient (such as **THC or CBD**) in an approved drug product or in a potential drug for which substantial clinical investigations have been instituted and made public.
- CBD and THC **cannot** be added to foods under the FD&C Act
  - This prohibition applies regardless of whether the substances are hemp-derived
- CBD and THC products **are excluded** from the definition of dietary supplements under [FD&C Act Section 201\(ff\)\(3\)\(B\)](#)

# Cannabis Drug Development



- When used under clinical trial, cannabis and cannabis-derived compounds must meet all FDA requirements for [IND applications](#), which includes 3 broad areas
  1. Animal Pharmacology and Toxicology Studies
  2. Manufacturing Information
  3. Clinical Protocols and Investigator Information
- Development of drugs has focused on using compounds in cannabis: CBD, THC
- **Four products approved:**
  1. Marinol (dronabinol) (1985): nausea from cancer chemotherapy → Schedule III
  2. Cesamet (nabilone) (1985 (2006)): nausea & neuropathic pain → Schedule II
  3. Syndros (dronabinol) (2016): nausea from cancer chemotherapy → Schedule II
  4. Epidiolex (CBD) (2018): for childhood seizures & TSC → [No longer controlled](#)

# Cannabis Drug Development Draft Guidance



- On July 21<sup>st</sup>, 2020 FDA published Draft Guidance [Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research](#)
- Cannabis and cannabis-derived compounds can be used in clinical research
  - Under an Investigational New Drug (IND) application to study a specific therapeutic indication

## Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research Guidance for Industry

### *DRAFT GUIDANCE*

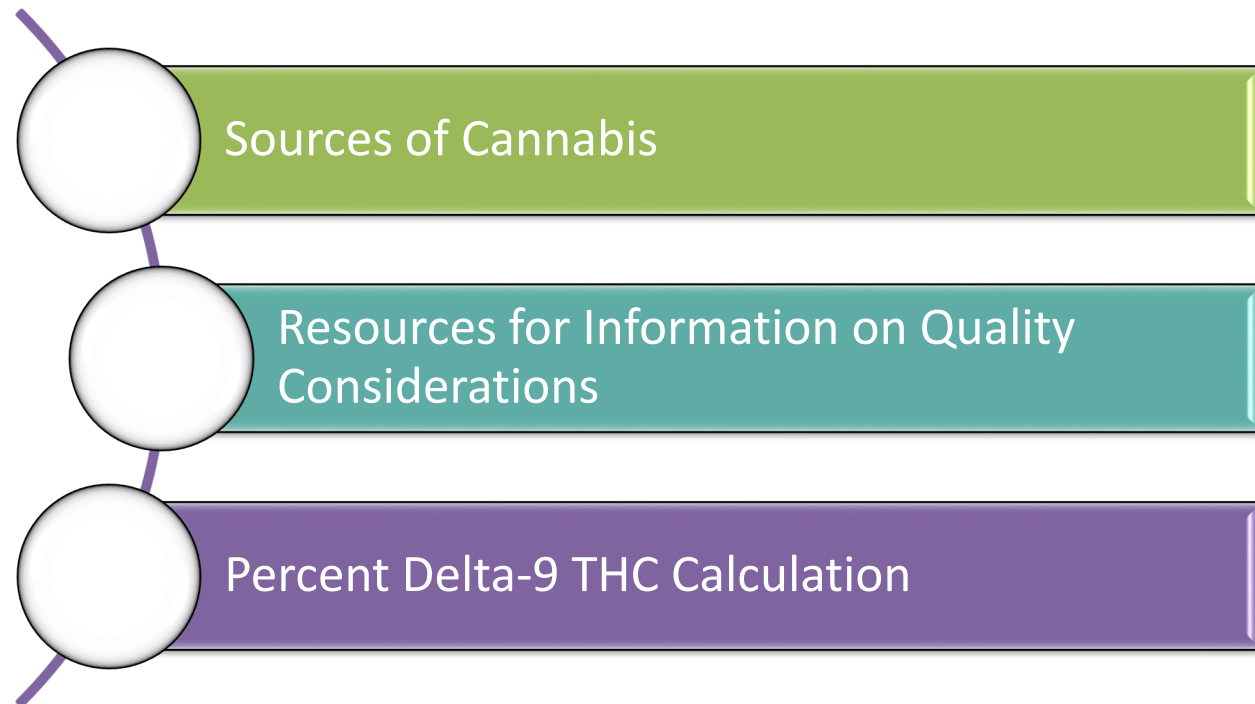
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Amy Muhlberg at 240-402-6901 or Cassandra Taylor at 240-402-5290.

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)



# FDA Authority Over Foods for Humans and Animals & Food Additives



## Foods:

- Exceptions to §301(l):
  - If article was **marketed in food before the drug was approved** or **before the substantial clinical investigations** involving the drug had been authorized.
    - *Note: FDA has examined the available evidence and concluded that this exception does not apply to CBD*
  - FDA can also create an exception to 301(l) through **notice and comment rulemaking**.
- All ingredients in human and animal food must be **approved food additives or GRAS** for their intended use in the intended species.

## Food Additives:

- At this time, there are **no approved food additive uses** for any substances derived from hemp and we are **unaware of any basis to conclude that CBD is GRAS** for its use in human or animal food.
  - This includes a lack of available safety data related to-food producing animal use (residues in meat, milk, eggs).

# FDA Work on Cannabis



**FDA's Cannabis Product Committee (CPC) - a cross-Agency collaboration**

**FDA**

**Office of the Commissioner**



**Office of Regulatory Affairs**





# FDA's CBD Work Plan

A vertical timeline graphic on the left side of the slide, consisting of a purple line with four white circular nodes. Each node is connected to a horizontal bar of a different color (green, teal, blue, and purple) containing text.

Develop a comprehensive **research agenda that includes stakeholder input** to address data gaps related to preclinical and clinical data needs identified based on scientific review of CBD safety data.

Evaluate potential new pathways for CBD products, while **evaluating issuance of an enforcement policy** and **continuing with WLs** and enforcement as needed to address public health risks

Respond to **mandated Reports to Congress**

Continue to **engage and communicate** with consumers, federal and state regulators, as well as other stakeholders.

# Scientific Uncertainties for CBD

- Effects of cumulative and long-term human exposure
- Effects in susceptible populations: children, pregnant/lactating mothers, elderly
- Reversibility of adverse nonclinical effects (e.g., males, pediatric patients)
- Drug-drug interaction data
- Pharmacology and toxicology of 7-COOH-CBD
  - Metabolic profile across toxicology species (rabbit, nonhuman primate)
- Impact of excipients in marketed consumer products on bioavailability (e.g., topicals/transdermals, smoking or vaping)

# Other FDA Activities: Warning Letters Related to CBD Products



- FDA issued **numerous Warning Letters** from 2015 to present, including after passage of the Farm Bill:
  - Unapproved new drugs [§§201(p), 301(d), and 505(a)]
  - Misbranded drugs [§§301(a) and 502(f)(1)]
  - Illegally marketed food [§301(l), 402(a)(2)(C)(i), and 301(a)]
  - Illegally marketed supplements [§201(ff)(3)(B)]
  - Unapproved new animal drugs [§§301(a) and 501(a)(5)]
- FDA **posted lab results** for dozens of CBD products cited in the warning letters.
  - In many cases, the CBD content did not match the labeled claims and some products did not contain any CBD

# 9/14/21 Consumer Update on delta-8 THC

Delta-8 tetrahydrocannabinol, also known as delta-8 THC, is a psychoactive substance found in the Cannabis sativa plant, of which marijuana and hemp are two varieties.

## 5 things you should know about delta-8 THC

1. Delta-8 THC products have not been evaluated or approved by the FDA for safe use and may be marketed in ways that put the public health at risk.
2. The FDA has received adverse event reports involving delta-8 THC-containing products.
3. Delta-8 THC has psychoactive and intoxicating effects.
4. Delta-8 THC products often involve use of potentially harmful chemicals to create the concentrations of delta-8 THC claimed in the marketplace.
5. Delta-8 THC products should be kept out of the reach of children and pets.

# Adverse Event Reporting

## How to report complaints and cases of accidental exposure or adverse events

- If you think you are having a serious side effect that is an immediate danger to your health, call 9-1-1 or go to your local emergency room. Health care professionals and patients are encouraged to report complaints and cases of accidental exposure and adverse events to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:
- Call an FDA [Consumer Complaint Coordinator](#) if you wish to speak directly to a person about your problem.
- Complete an [electronic Voluntary MedWatch form](#) online or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the form, or submit by fax to 1-800-FDA-0178.
- Complete a [paper Voluntary MedWatch form](#) and mail it to the FDA.
- To report adverse events in animals to FDA's Center for Veterinary Medicine, please download and submit Form FDA 1932a found at: [www.fda.gov/ReportAnimalAE](http://www.fda.gov/ReportAnimalAE).

# Other FDA Activities: Real-World Data



FDA Voices Blog: [Better Data for a Better Understanding of the Use and Safety Profile of Cannabidiol \(CBD\) Products](#)

## A Practical Framework for Robust, Collaborative CBD Data Projects to Inform Public Health Decisions

Here, we describe a framework for the FDA's work in the development of research projects that lay the methodological groundwork for high quality RWD science on the safety and use of CBD products. These research projects would be aimed at building upon currently existing independent state and national quality and safety monitoring efforts, observational study data models, and novel data sources to develop more robust capabilities and methods for CBD data collection and analysis.



Amy Abernethy, M.D., Ph.D.

We know from experience that collaborative projects with researchers across government, academia, and the private sector can stimulate rapid progress in the development of rigorous methods for collecting and analyzing RWD. Most recently, in the context of COVID-19, collaborative research projects between the FDA and outside data experts have focused on using RWD to improve analytical methods and inform the public health response to the pandemic.

It is important to note that there are research questions for which RWD research projects are unlikely to substitute for certain types of traditional studies. We do not expect that analyses of observational data will substitute for other types of studies in certain contexts. For example, appropriately designed animal studies can address

toxicological issues that are difficult to study in humans, such as chronic, developmental, and reproductive toxicity.

However, we strongly believe that RWD, when collected and analyzed using rigorous methods, can be important for moving the science forward—including by aiding hypothesis generation and by refining the design of follow-up studies. For example, RWD may identify new potential adverse events or subpopulations of CBD users that should be the focus of follow-up studies.



## Other FDA Activities: Real-World Data

- [FDA Voices Blog](#) includes:
  - FDA ongoing work on CBD
  - Engagement with stakeholders on CBD issues
  - FDA's CBD product sampling and testing activities
  - Additional work is needed to build data on CBD use and safety
  - Practical framework for robust, collaborative CBD data projects to inform public health decisions
- FDA thinks real-world data (RWD) on CBD use and safety has a crucial role alongside data from other types of studies to fill the current gaps

# Summary and Conclusions



- FDA has a well-defined role to play in the regulation and development of products containing cannabis and cannabis-derived compounds
- FDA continues to support scientific and rigorous testing and approval of drugs derived from cannabis and to support **robust scientific research** into understanding the **therapeutic uses and safety** of non-drug cannabis products
- FDA is actively exploring potential **regulatory pathways** for the **lawful marketing** of appropriate cannabis-derived products
- FDA is **committed to protect and promote the public health** with respect to products containing cannabis and cannabis-derived compounds, including enforcement action when needed

