U.S. FOOD & DRUG ADMINISTRATION

Cannabis Clinical Research: Drug Master Files (DMFs) & Quality Considerations

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SBIA Webinar

Learning Objectives

- Gain understanding of FDA's role in regulating cannabis products and Farm Bill's impact on FDA authorities
- Explain the general botanical drug development process
- Elaborate on best practices for conducting clinical research with cannabis and cannabis-derived compounds
- Learn the who, what, when and how of Drug Master Files (DMFs)
- Discuss how to use the DMF pathway in cannabis clinical research
- Present examples on how to use DMFs
- Provide FDA resources to stakeholders

Overview

- FDA Responsibilities and Authority
- 2018 Farm Bill's Impact on FDA Authorities
- FDA's Role in Regulation of Cannabis Products
- Cannabis Drug Development
- Botanical Raw Materials
- Cannabis Drug Development Guidance
- Drug Master Files (DMFs)
- Summary

The United States Food and Drug Administration (FDA)

- Protecting the public health by, for example:
  - ensuring that the foods it regulates are safe, wholesome, sanitary and properly labeled
  - ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use, are safe and effective
- Ensuring cosmetics and dietary supplements are safe and properly labeled
- Advances the public health by helping to speed product innovations
- Regulates tobacco products

https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm

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 Basics: https://www.fda.gov/aboutfda/transparency/basics/ucm194909.htm

The Farm Bill's Impact on FDA Authorities

- FDA's authorities under the FD&C Act and section 351 of the Public Health Service (PHS) Act were **specifically preserved by the Farm Bill**
  - Cannabis and cannabis-derived products, including products containing CBD, are subject to the same authorities and requirements as FDA-regulated products containing any other substance

- FDA authorities include:
  - Scientific and regulatory support for research on **potential therapeutic uses** of CBD products and **approval of CBD drug products** that are safe and effective
  - **Regulation of CBD products** (e.g., as foods including dietary supplements, drugs, cosmetics)
  - **Enforcement actions as necessary** against violative CBD products, particularly those that present serious human or animal health risks

Agriculture Improvement Act of 2018 ("Farm Bill," Pub L. No: 115-1072)

The Farm Bill's Impact on FDA Authorities

- Many products containing CBD **are illegal under the Food, Drug, and Cosmetic Act** (e.g. illegal to make therapeutic claims unless an approved drug, illegal to put in food or dietary supplements)

- FDA's jurisdiction over other products is heavily dependent on the facts and circumstances
  - Lotions, soap, or other cosmetics containing CBD might be lawful depending on the circumstances
  - CBD in a vaping product may fall outside FDA's jurisdiction unless the vaping product makes a therapeutic claim, or if there is a tobacco ingredient in the vaping fluid
  - Oils or other products labeled "pure CBD" without any other claims may be difficult to assert FDA jurisdiction over

FDA Public Hearing

- FDA held a public hearing on May 31, 2019
  - Goal: Obtain scientific data and other information about products containing cannabis and cannabis-derived compounds to inform FDA regulatory oversight of these products
  - Over 100 speakers presented
  - Over 4500 comments submitted to the docket
  - More hearing information

- On March 11, 2020, FDA reopened the docket
  - FDA encourages stakeholders to submit comments, data, and information related to CBD to the public docket

FDA Work on Cannabis

Office of the Commissioner

FDA Cross-Agency team collaborates on cannabis issues

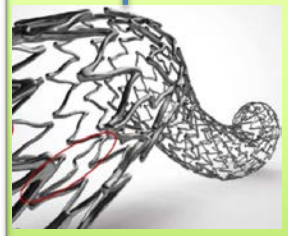
Office of Regulatory Affairs

Botanical Review Team (BRT)
Office of Pharmaceutical Quality (OPQ)

Center for Food Safety & Applied Nutrition

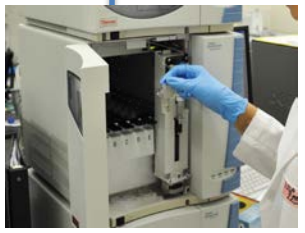
Center for Drug Evaluation & Research

Center for Biologics Evaluation & Research



Center for Devices & Radiological Health

Center for Veterinary Medicine

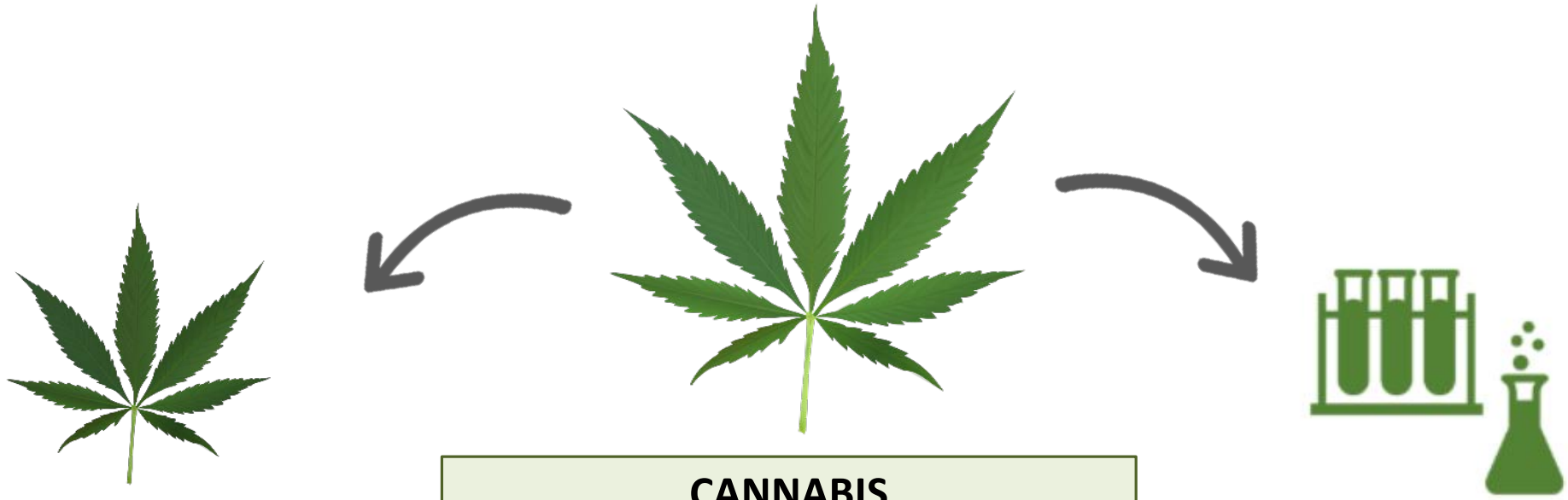


National Center for Toxicological Research

Center for Tobacco Products

Pictures: https://www.umassmed.edu/nutrition/Cardiovascular/ask-nutritionist/How-Can-I-Eat-More-Fruits-and-Veggies/ ; https://www.usatoday.com/story/news/nation/2018/07/25/prescription-drugs-industry-has-long-promised-cut-prices/830704002/ ; https://mymodernmet.com/fantastic-portraits-of-farm/ ; https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/RecentlyApprovedDevices/ucm624483.htm ; https://www.theatlantic.com/politics/archive/2016/05/low-tar-cigarettes/481116/ ; https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM611463.pdf ; https://www.fda.gov/aboutfda/centersoffices/oc/officeofscientificandmedicalprograms/nctr/whatwedo/researchdivisions/ucm078482.htm ; https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm234680.htm

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)

FDA and Cannabis: Research and Drug Approval Process

Cannabis – Derived Compounds

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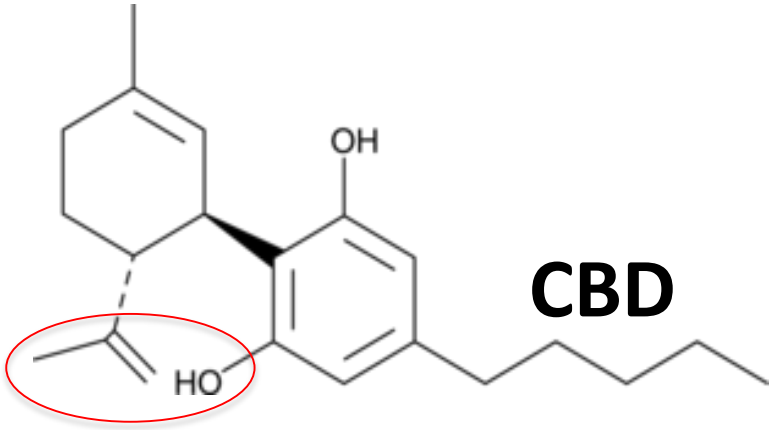
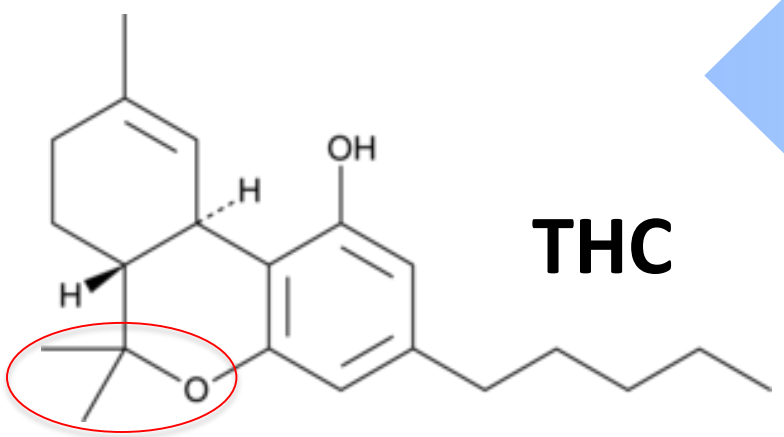


CBD



THC

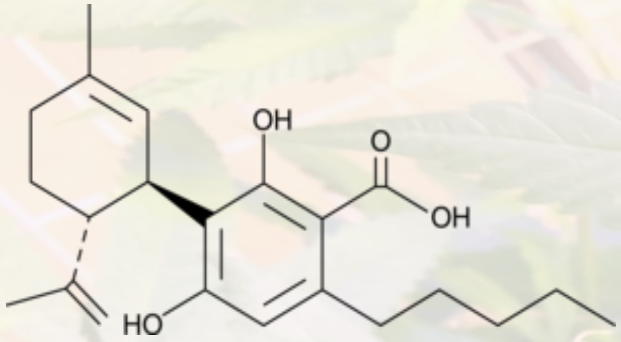
Examples of other cannabis-derived compounds

- **Other Cannabinoids**: CBDA, THCA, CBN, CBDV, CBC, CBG, CBGA, THCV, etc.
- **Terpenes**: Myrcene, Limonene, Linalool, Caryophyllene, Pinene, etc.

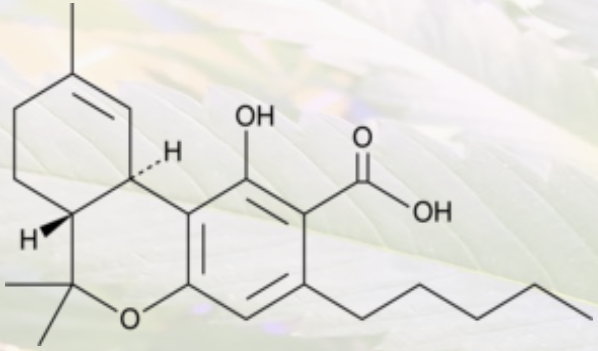
[FDA and Cannabis: Research and Drug Approval Process]

Cannabis – Derived Compounds: Cannabinoids

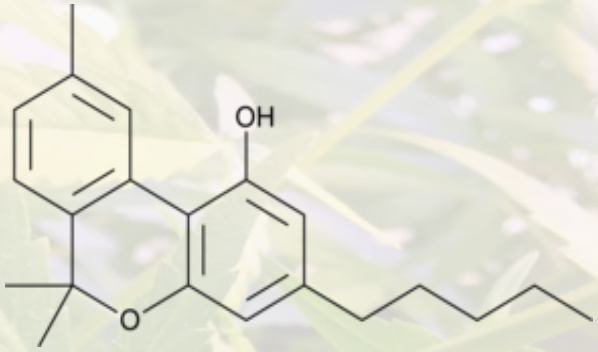
Cannabidiolic Acid (CBDA)



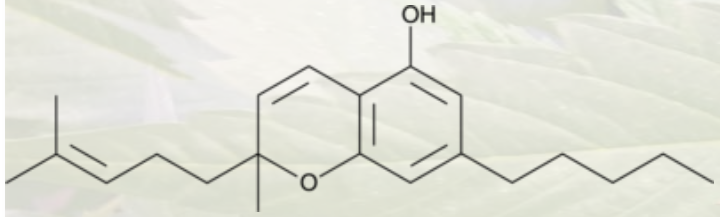
Tetrahydrocannabinolic Acid (THCA)



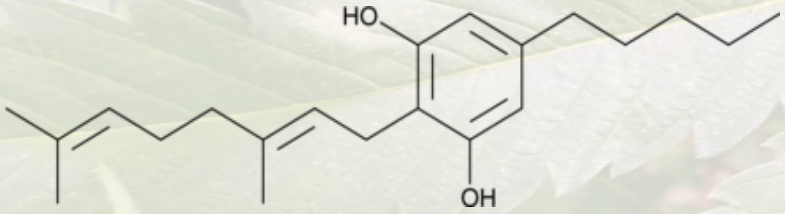
Cannabinol (CBN)



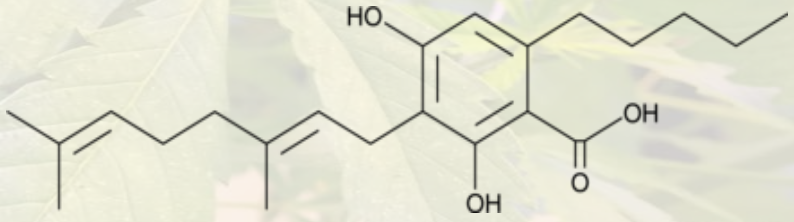
Cannabichromene (CBC)



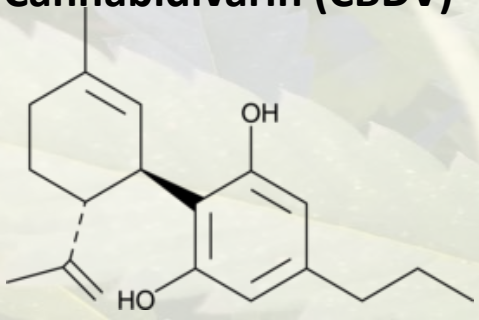
Cannabigerol (CBG)



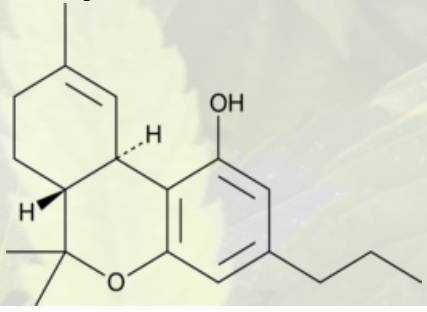
Cannabigerolic Acid (CBGA)



Cannabidivarin (CBDV)



Tetrahydrocannabivarin (THCV)



>100 different cannabinoids naturally occur in cannabis

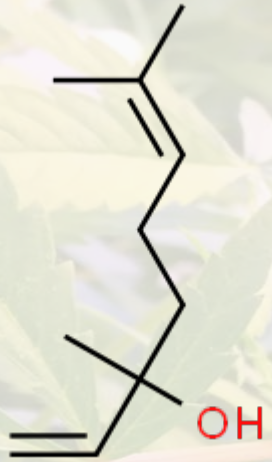
Chemical structures from: https://www.caymanchem.com/product/90080/cannabidiol; https://www.caymanchem.com/product/12068/%CE%B49-thc; https://www.caymanchem.com/product/18090/cannabidiolic-acid-(crm); https://www.caymanchem.com/product/ISO60175/thca-a-(crm); https://www.caymanchem.com/product/25495/cannabinol; https://www.caymanchem.com/product/ISO60163/(%C2%B1)-cannabichromene-(crm) ; https://www.caymanchem.com/product/15293/cannabigerol ; https://www.caymanchem.com/product/9001572/cannabigerolic-acid ; https://www.caymanchem.com/product/20165/cannabidivarin-(crm); https://www.caymanchem.com/product/18091/tetrahydrocannabivarin-(crm)

Cannabis – Derived Compounds: Terpenes

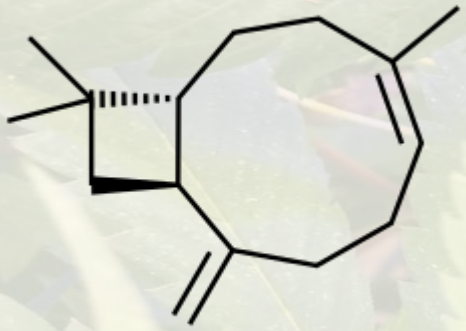
Myrcene

Limonene

Linalool



Caryophyllene



Pinene

- **At least 20,000 different terpenes exist in nature**
- **>100 different terpenes naturally occur in cannabis**

Chemical structures from: http://www.chemspider.com/Chemical-Structure.28993.html ; http://www.chemspider.com/Chemical-Structure.388386.html?rid=92f338e2-4be3-45d9-98ba-b0a485adb345 ; http://www.chemspider.com/Chemical-Structure.13849981.html?rid=e442d668-4833-47b0-bb73-6e9005eb035f&page_num=0 ; http://www.chemspider.com/Chemical-Structure.4444855.html?rid=2ed455f9-002e-498e-98c9-4b7aa557aabf&page_num=0 ; http://www.chemspider.com/Chemical-Structure.74205.html?rid=315cfc32-16fd-4ec1-af7a-8811c4c5eeba&page_num=0

Cannabis Drug Development

- Cannabis products intended for use under clinical trial with a claim of therapeutic benefit or with any other disease claim **are drugs**
  - Submit an Investigational New Drug Application (IND) or request Pre-IND meeting with clinical division
  - Drug sponsors formally propose that FDA approve a new pharmaceutical via the New Drug Application (NDA)

- We treat products containing cannabis or cannabis-derived compounds as we do any other FDA-regulated products
  - Meaning they're subject to same authorities and requirements as FDA-regulated products containing any other substance

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

- 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. The amount of information appropriate to meet this expectation **will increase with successive stages of drug development**

- ***Botanical Drug Development Guidance for Industry***
  - Provides Agency's current thinking on botanical drug development
  - Focuses on quality controls
  - Botanical raw material growing conditions

Botanical Raw Material Controls

Harvest
- GPS location

Testing Facility
- Pesticide residues

FDA
- Team-based review

Plant Species
- Varieties and cultivars
- Botanical ID, macro and microscopic

Geographic Location
- GPS location of the farms or indoor growing facilities

Cultivation and Harvesting
- Growth conditions (RH, temp, light)
- Stage of plant growth at harvest
- Harvest time/season

Processing
- Washing, drying, grinding BRM
- Control of foreign matter
- Preservation procedures
- Transportation

Storage Condition
- Preservation procedures
- Temperature, relative humidity %, light conditions
- Long-term vs. short-term storage

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indoor growing facilities

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Tracing Good Agriculture and Collection Practices (GACP)

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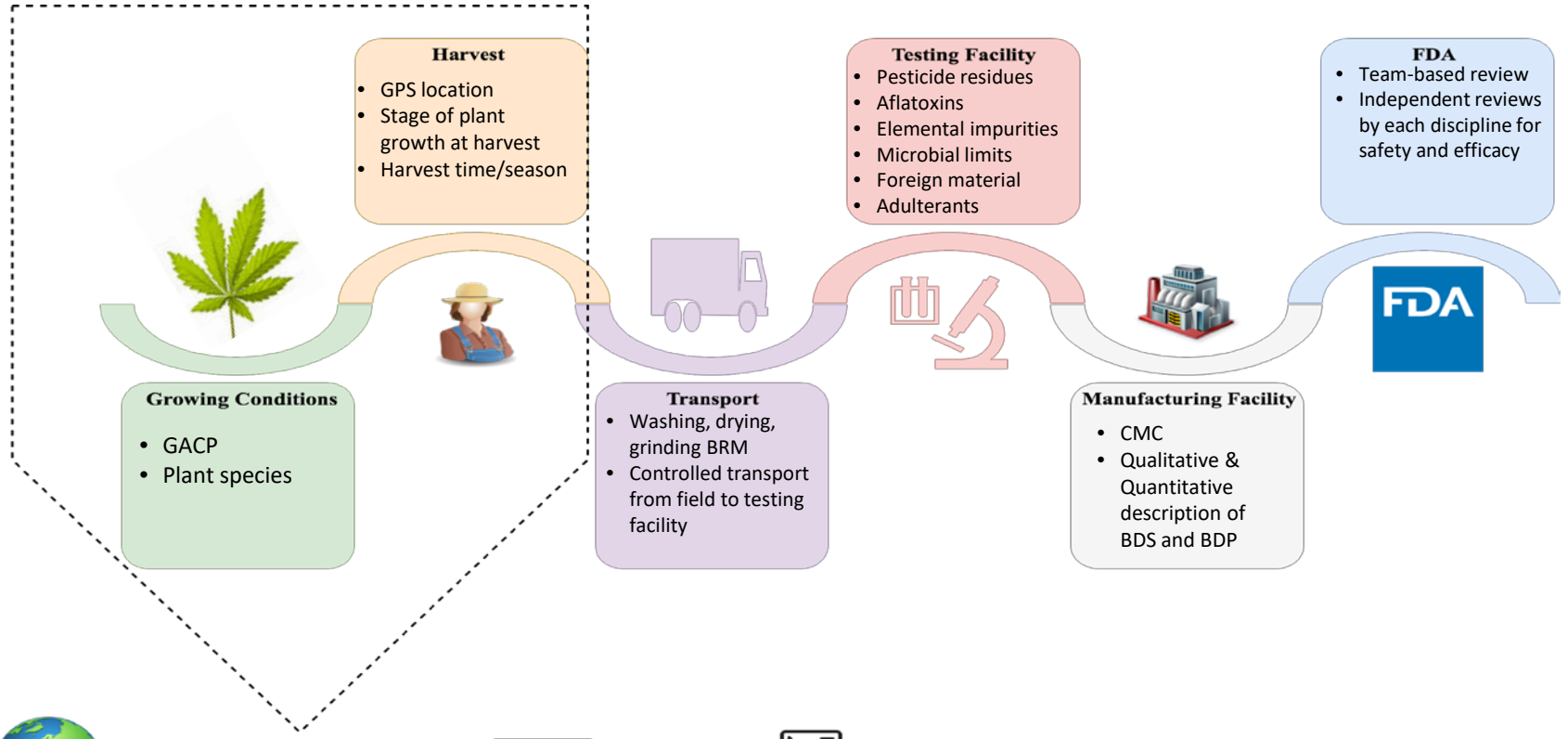
Botanical Raw Material Controls



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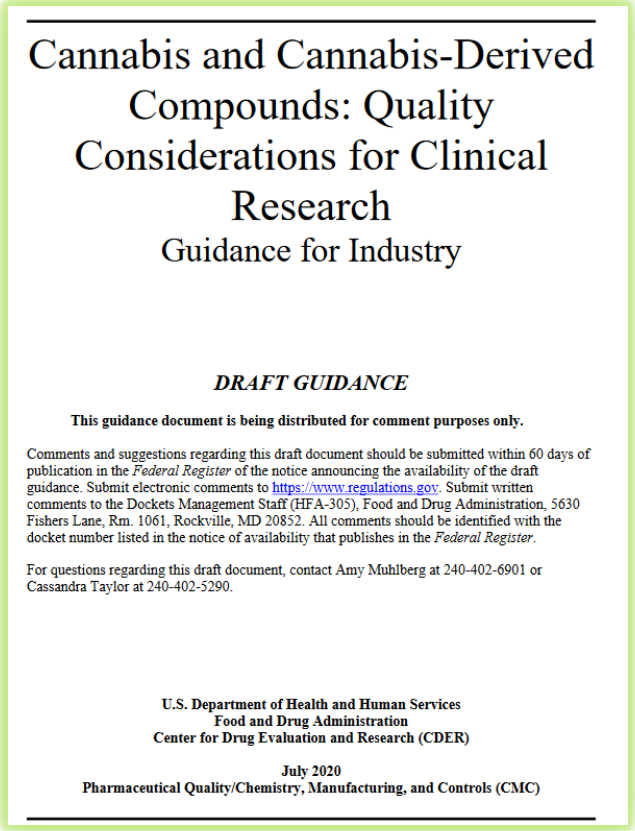
Tracing Good Agriculture and Collection Practices (GACP)

Cannabis Drug Development Draft Guidance

- On July 21st, 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

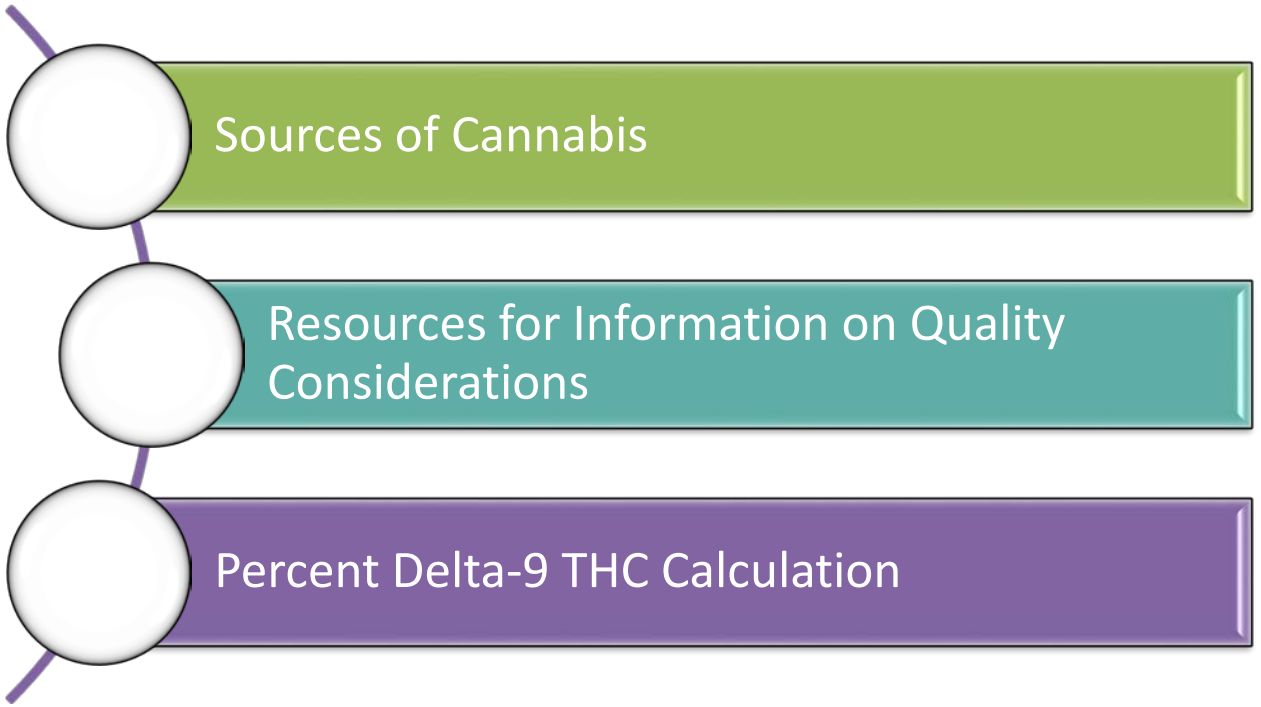
This guidance document is being distributed for comment purposes only.

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)



Sources of Cannabis

- Botanical Raw Materials (BRMs)
  - Sponsors **must meet all FDA requirements** to conduct human clinical trials, **regardless of the source** of cannabis or any other botanical products under study in the trial (21 CFR part 312)

- National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP)
  - For many years, NIDA DSP provided the only domestic federally legal source of cannabis for clinical research
  - Cannabis DSP is grown under contract by the University of Mississippi at the National Center for Natural Products Research (NCNPR)

Sources of Cannabis

- 2018 Farm Bill
  - Changes made by 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**
  - The 2018 Farm Bill gives sponsors and investigators of clinical studies new options that do not involve the NIDA Drug Supply Program

Sources of Cannabis

- Sources of cannabis
  - Sponsors **must meet all FDA requirements** to conduct human clinical trials, regardless of the source of cannabis or any other botanical products under study in the trial.

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
- Cannabis **at or 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 Controlled Substances Act (CSA)

Resources for Information on Quality Considerations

- In all INDs, sponsors are expected to show they can consistently manufacture a quality product
- Sponsors must submit sufficient information to ensure identity, quality, purity, and potency or strength of the investigational drug (21 CFR 312.23)
- Sponsors should provide quantitative data of phytochemicals such as cannabinoids, terpenes, flavonoids, etc.
- Sponsors should refer to FDA and ICH guidance to assist with their analytical method validation
- Guidance documents on pharmaceutical quality are available at:
  - Pharmaceutical Quality Resources
  - Guidances and Manuals on Pharmaceutical Quality

Resources for Information on Quality Considerations

- Consider following these principles and documents:

Adequate Characterization via chemical fingerprint	USP <563> Identification of *Articles of Botanical Origin*	USP <561> *Articles of Botanical Origin*	USP <61> & <62> Microbiological Info for nonsterile products
USP <232> *Elemental Impurities - Limits*	Drug scheduling consideration; abuse potential assessment	FDA does not recommend pursuing approval of NDA relying on published literature	Human metabolite 7-COOH-CBD, is expressed disproportionately in humans compare to animals
If device used in combination with drug, product is considered a combination product and must comply with CGMP	Choose container closure systems carefully	Quality tests, including dosage form, can be found in ICH Guidance Q4B	Impurity profiles expected to differ between synthetic and botanically isolated compound

Percent Delta-9 THC Calculation

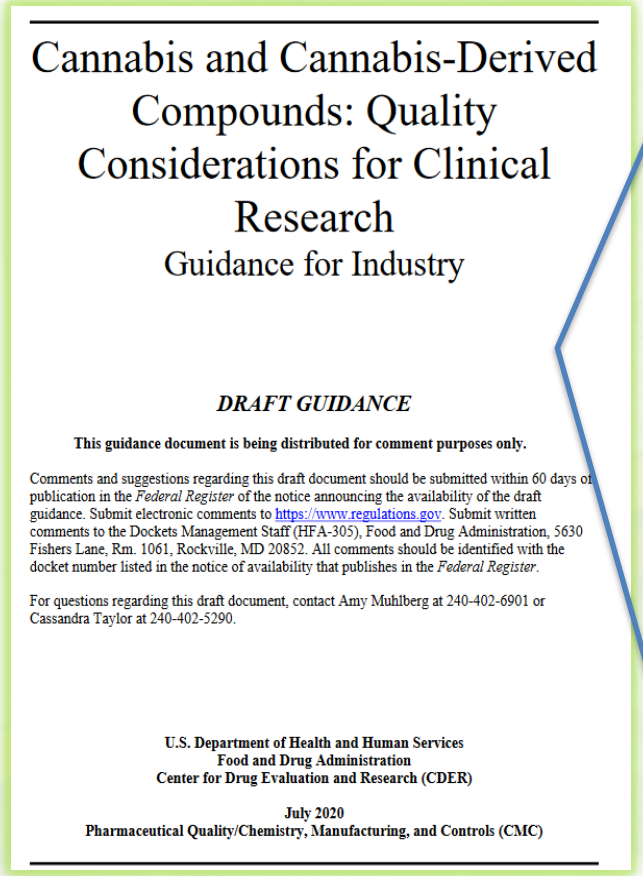
- Growing and manufacturing cannabis for use in research must comply with CSA and DEA requirements if cannabis is >0.3% Δ-9 THC by dry wt.
- Consult DEA if proposing clinical trials with controlled substances
- Useful to calculate level of Δ-9 THC in proposed investigational drug early in development process to gain insights on potential control status
- Work with reliable labs for analytical testing → FDA may request additional CMC info during development and submission processes
- Calculation of tetrahydrocannabinols may provide info about composition of the proposed raw material, intermediate, drug substance, or drug product
  - The 0.3% Δ-9 THC by dry wt. is not appropriate as a limit for tetrahydrocannabinols as impurities for quality control purposes and application submission (i.e., CMC)
  - Quality-related calculations for these compounds will be evaluated during IND review process

Percent Delta-9 THC Calculation

- Reference the USDA interim final rule or any superseding rule for sampling and testing methods for evaluating Δ-9 THC in a cannabis BRM
- Provide quantitative data, like a certificate of analysis, indicating Δ-9 THC by dry wt. in your BRM
- Provide detailed testing methods to evaluate Δ-9 THC for phase 2 and 3 studies and marketing applications
- Consider section 7.20 Rounding Rules, in the USP *General Notices and Requirements* when calculating and reporting Δ-9 THC levels to FDA
- BRM composition = $\frac{\text{amount of compound(s) interest naturally present}}{\text{dry wt. of the BRM prior to extraction}}$

Percent Delta-9 THC Calculation

- For intermediates or finished products, calculate Δ-9 THC based on composition of the formulation with the **amount of water removed**, including any water in excipients
- This calculation should not be used for other purposes, such as CMC



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- 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.

Percent Delta-9 THC Calculation

- Specific recommendations are provided to calculate:
  - Solution-based material (intermediate, in-process material, or final drug products)
  - Solid oral dosage form (e.g., tablet, capsule)

- Intermediates or by-products created during manufacturing may exceed the Δ-9 THC dry wt. threshold, even if starting with materials meeting definition of *hemp*, and may be considered Schedule 1 controlled substances
  - Contact DEA for recommendations if you anticipate generating such intermediates or by-products

Cannabis Drug Development Draft Guidance

- FDA draft guidance is available for public comments via the Federal Register [Public Docket]
- We welcome comments until 11:59PM on 09/21/20
- Possible comments might include:
  - Potential challenges
  - Topics that are useful/not useful
  - Suggestions for improvement
  - Additional topics for consideration in guidance
  - Data or information related to guidance you want to share with FDA

- We encourage you share the draft guidance with your staff, colleagues, coworkers and networks who operate in the cannabis space

How to protect proprietary info?

- During our May 31st, 2019 public hearing on cannabis and cannabis-derived compounds we heard concerns from stakeholders about their ability to protect proprietary information while participating in drug development

- Stakeholders may want to consider utilizing our well-established Drug Master File (DMF) pathway

What are Drug Master Files (DMFs)?

- DMFs are submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products
  - Info only shared between **FDA and the DMF Holder**
- 4 types → will focus on most common Type II: drug substance, drug substance intermediate, material used in their preparation or drug product

Can share sensitive data confidentially with FDA

Allows parties to reference your DMF without disclosing contents to those parties

Electronic submission platform

Can be updated at anytime

Neither approved nor disapproved

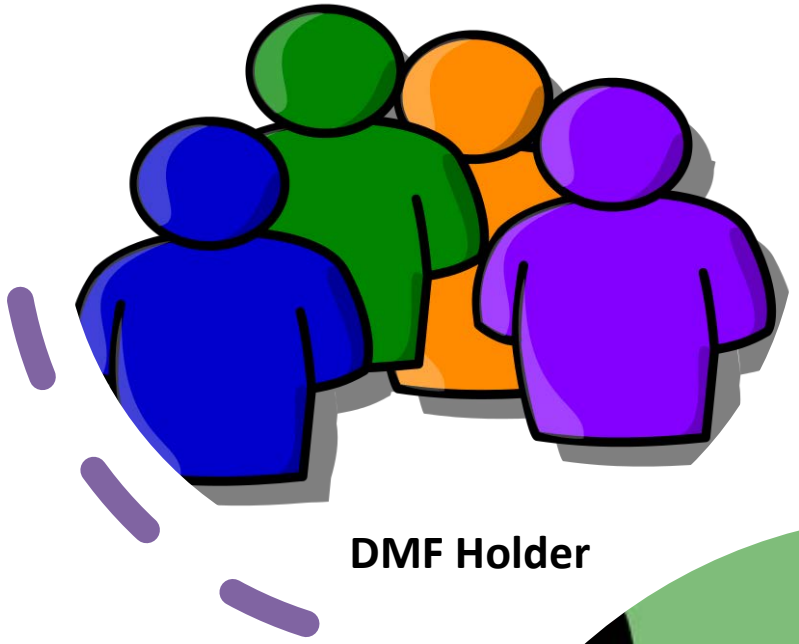
No cost when submitted to support INDs or NDAs*

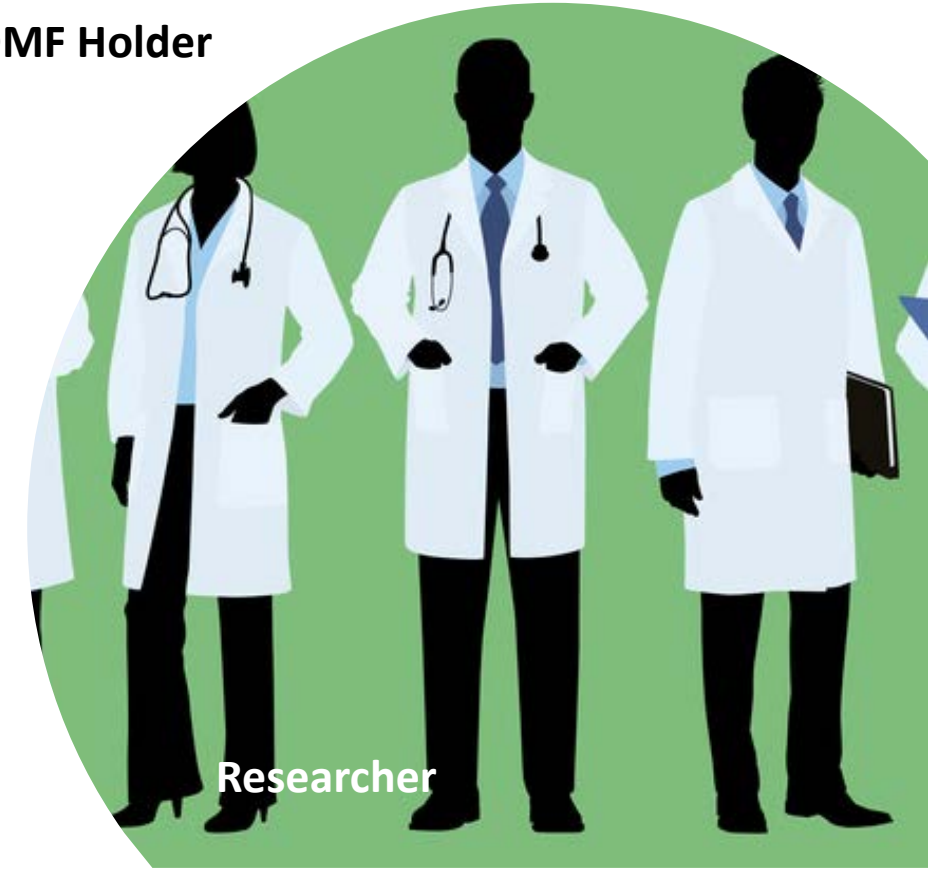
*fees apply when submitted to support ANDA

Who can submit and use DMFs?

- **Anyone** can submit a DMF who is wishing to communicate information to FDA about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products
  - The entity who submits the DMF is called a **DMF Holder**
  - FDA will only discuss contents of the DMF with the DMF Holder

- **Anyone** conducting clinical research under an IND or NDA can use information in a DMF with permission from the DMF Holder
  - DMF Holders provide permission for FDA to conduct a **technical review** of the contents of their DMF via a **Letter of Authorization (LOA)**





What is the DMF process?

Obtain pre-assigned number before DMF submitted electronically to FDA

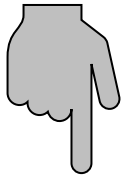
DMF is submitted & undergoes administrative review

If accepted, FDA confirms acceptance with DMF Holder

LOA to DMF is submitted to support drug application under IND/NDA

FDA will technically review contents of DMF to support clinical trial or application

FDA will find DMF Adequate or Inadequate in support of clinical trial or application



Click HERE for detailed info on this process

When are DMFs reviewed?

- FDA performs a **cursory administrative review** of a DMF upon submission
  - Checks for required FDA information
- When a Letter of Authorization (LOA) for a DMF is submitted to support an IND or an NDA, FDA will conduct a **technical review** of the DMF contents to support the clinical trial
  - The DMF is deemed **Adequate** or **Inadequate**
  - DMF Holder only will be alerted of Adequate/Inadequate status
  - There are no approvals of DMFs
- DMF Holder is required to submit annual reports and any updates/changes to the DMF regularly

When are DMFs reviewed?

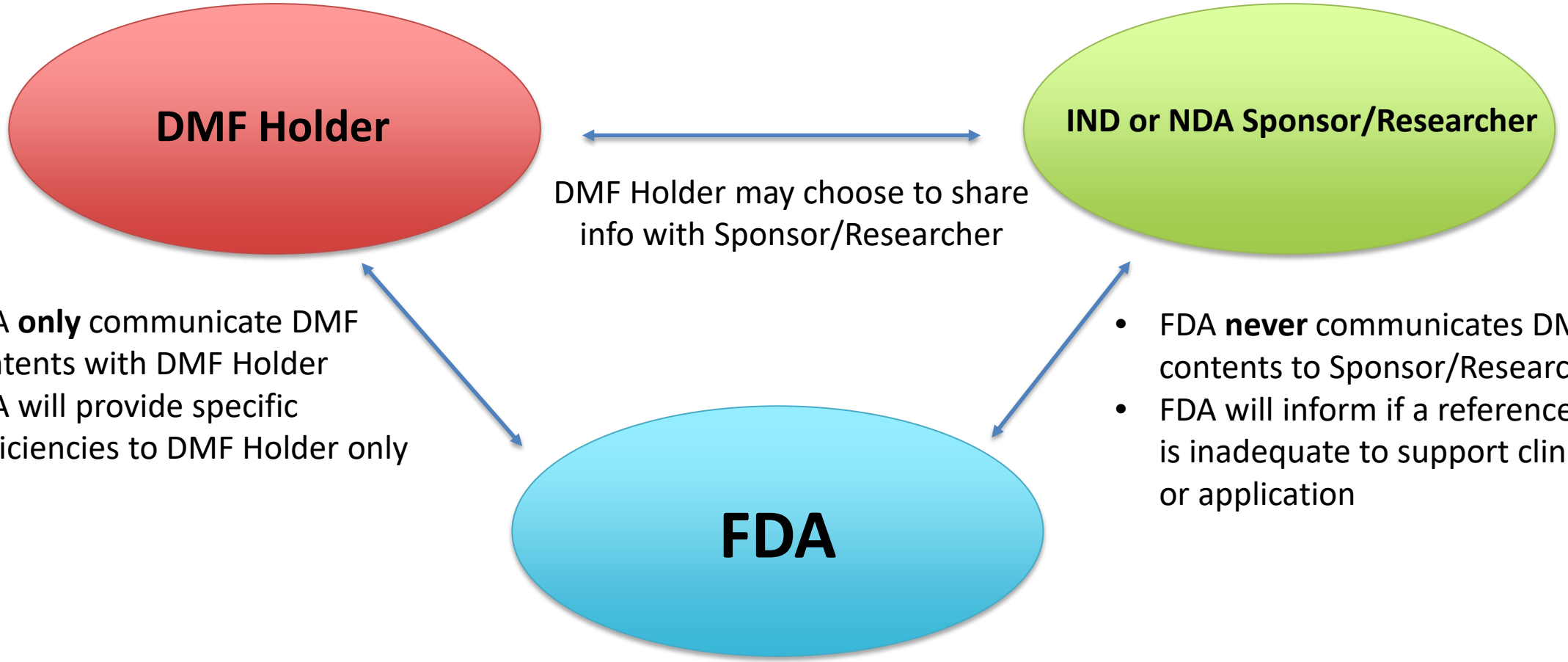
- The LOA is provided by the DMF Holder to the researcher wishing to use the contents in the DMF to help support the proposed clinical research

- FDA will not technically review a DMF in support of a clinical trial without an LOA
  - **LOA is required** to reference a DMF and trigger FDA technical review of DMF contents

- What happens when DMF is Inadequate to support the clinical trial?
  - FDA will reach out to the DMF Holder with the deficiencies and request DMF Holder to provide information to address those deficiencies
  - FDA will inform the IND sponsor/researcher the DMF referenced is Inadequate to support their clinical trial and they need to speak to the DMF Holder
  - FDA will never share DMF contents with anyone but the DMF Holder

How is DMF content shared?

- DMF content is only shared between the **DMF Holder and the FDA**
- FDA **never shares** contents of a DMF with a sponsor/researcher who provides an LOA in support of clinical research
- If a DMF is found Inadequate to support a clinical trial, FDA will provide deficiencies to **DMF Holder only**
  - **DMF Holder** will reply to those deficiencies and send back all the information to FDA for review



Dr. Kathy Smith

Dr. Tonya Rhodes

Bob's CBD Emporium

How do DMFs work?

Hypothetical Examples:

- **Bob's CBD Emporium** extracts CBD from industrial hemp using a proprietary process.
- Bob has been contacted by two different researchers (**Dr. Smith** and **Dr. Rhodes**) asking if they can use his CBD extract in two different clinical trials.
- Bob decides to submit a DMF to FDA so his confidential processing and manufacturing information does not have to be given to researchers wishing to use his CBD extract under clinical trials.
- Bob's DMF is electronically submitted, goes under administrative review, and **FDA waits until an LOA is provided to support a clinical trial (e.g., IND or NDA) before initiating a technical review.**
- Bob is notified by FDA his DMF has been accepted and receives the DMF #123456.

Dr. Kathy Smith

Dr. Tonya Rhodes

Bob's CBD Emporium

How do DMFs work?

Hypothetical Examples:

- **Dr. Kathy Smith** would like to use Bob's CBD extract under her clinical trial to study how it may affect participants suffering from anxiety.
- Bob and Dr. Smith agree that he will provide her with CBD extract for her clinical study.
- Bob provides Dr. Smith with an LOA to his DMF #123456.
- Dr. Smith submits her IND to FDA and **includes the LOA for DMF #123456** from Bob's CBD Emporium giving FDA permission to conduct a **technical review of the DMF** contents in support of Dr. Smith's research.

Dr. Kathy Smith

Dr. Tonya Rhodes

Bob's CBD Emporium

How do DMFs work?

Hypothetical Examples:

- **Dr. Tonya Rhodes** learns about Bob's CBD Emporium and their CBD extract from industrial hemp.
- She would like to use it for her clinical research to study how the CBD may effect children with autism.
- She contact's Bob and asks if he is willing to supply her team with the CBD extract for her clinical research and Bob agrees.
- Bob sends the Dr. Rhodes an LOA to his DMF, which is already at FDA.
- Dr. Rhodes submits her IND and includes the LOA from Bob's CBD Emporium giving FDA permission to conduct a **technical review of the DMF** contents in support of Dr. Rhodes' research.

Benefits of using DMFs

- Proprietary and confidential information (e.g., CMC, cultivation) is protected
- DMF Holder does not have to disclose confidential information to researchers/collaborators
- FDA will never share the contents with anyone
  - DMF Holder is only entity FDA will discuss DMF contents with
- Can be used by many researchers at one time
  - LOA is required with IND for FDA to conduct technical review in support of each clinical trial
  - Multiple INDs may reference the same DMF at the same time
- No cost if submitted in support of IND or NDA
- Provides researchers with more options to conduct clinical trials using human drug products with cannabis and cannabis-derived compounds

DMF Resources

- Draft Drug Master Files Guidance for Industry provides more detailed information about preparing and submitting DMFs
- DMF web page provides additional information about DMFs and their submission, such as:
  - List of DMFs is updated quarterly by FDA
    - Sponsor/Researcher can go to this list to seek out DMF Holders they may want to collaborate with
  - Types of DMFs :Type II, Type III, Type IV and Type V
  - DMF Submission Resources
  - DMF Templates
  - DMF Related Information

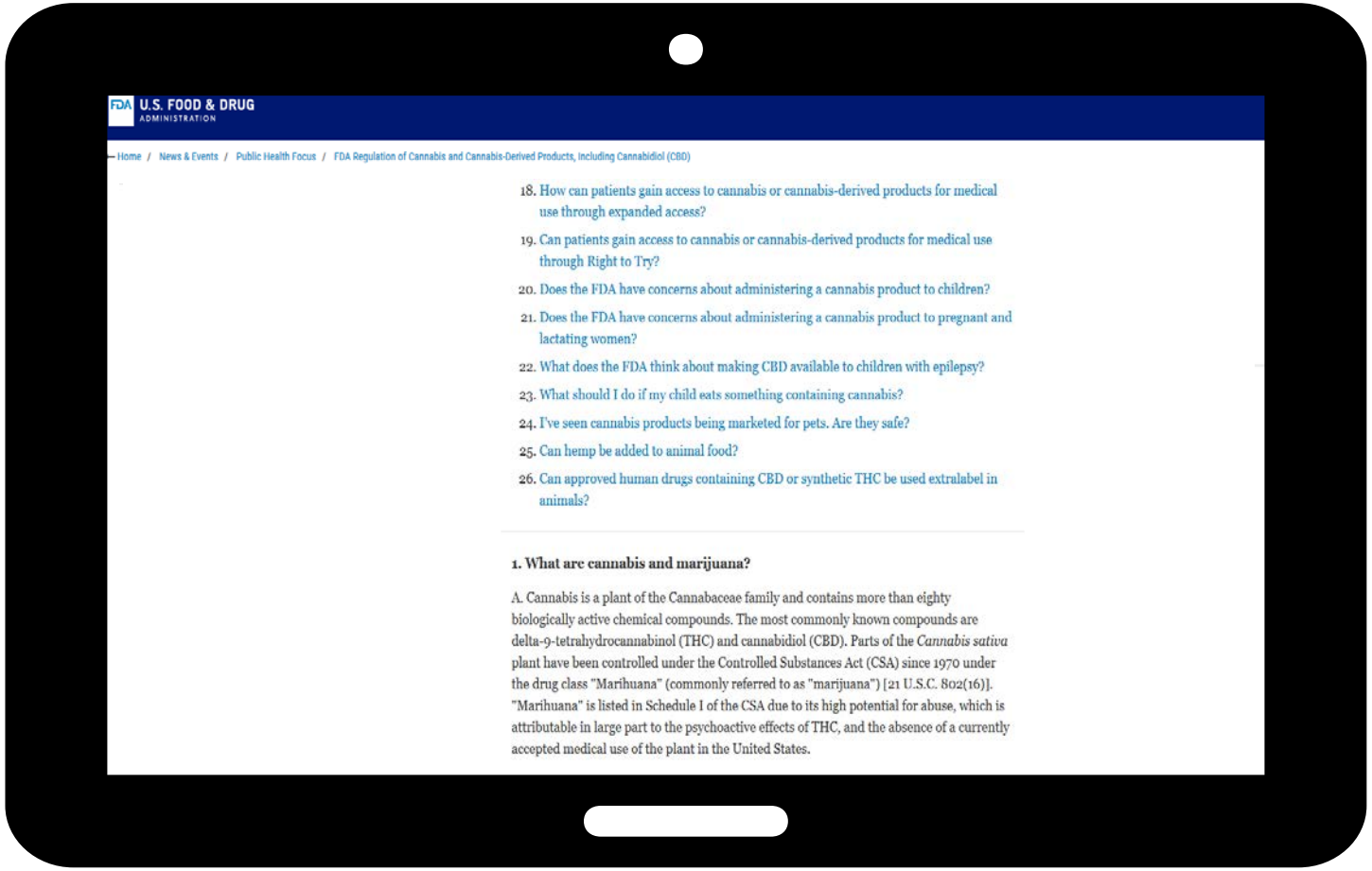
Additional Resources

FDA Resources

FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)

On this page:

- Consumer Information
- FDA Communications
- Regulatory Resources
- Questions and Answers



FDA Support for Botanical Drug Development

- CDER Botanical Review Team (BRT) serves as an expert resource for CDER on all botanical issues
- Provides a stand-alone pharmacognosy review for all original botanical INDs and NDAs (MaPP 5210.9)
- General inquiries: CDER-OPQ-Inquiries@fda.hhs.gov
- Get more information, FAQ's and related links at the BRT webpage

FDA Support for Drug Development – CSS

- Controlled Substance Staff (CSS) is available to help with FDA-DEA interactions
  - Example: issues around abuse potential assessment requirements to an NDA submission
  - CSS performs specific functional roles, including providing consultation services to CDER Review Divisions and acting as the CDER FDA liaison to other government organizations

- Get more information at the CSS webpage

FDA Cannabis Resources

- Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research Guidance for Industry (Draft Guidance issued July 21, 2020)
  - Public Docket is accepting comments until 11:59PM on 09/21/20
- FDA in Brief: FDA Issues Draft Guidance to Encourage Cannabis-Related Clinical Research
- FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD) – this is our Q&A page and has lots of resources
- What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD
- FDA Statement from Commissioner Stephen M. Hahn, M.D. (March 5, 2020) – FDA Advances Work Related to Cannabidiol Products with Focus on Protecting Public Health, Providing Market Clarity
- Botanical Drug Development: Guidance for Industry (Final Guidance issued Dec 2016)

FDA Support for Drug Development – SBIA

- CDER Small Business & Industry Assistance (SBIA)
  - Mission: engage with small pharmaceutical business and industry by providing timely and accurate information on human drug development and regulation
  - Who they serve: focus on small businesses, all regulated pharmaceutical industry, both domestically and internationally
  - Goals: help small pharmaceutical business and industry navigate the wealth of information that FDA offers and provide assistance in understanding regulation of human drug products
  - Outreach Services and more information
- Get more information at the SBIA webpage and follow them on LinkedIn

Summary

- FDA authorities were specifically preserved by the 2018 Farm Bill
- FDA supports and encourages strong science-based research for all botanical human drugs, including those with cannabis and cannabis-derived compounds
- Quality considerations for cannabis and cannabis-derived compounds in human drugs are in the draft guidance
  - Comments on Public Docket before it closes on 09/21/20 are appreciated!
- Stakeholder can protect proprietary information using DMFs
- A DMF may be referenced by multiple INDs at same time
- No cost for DMF if submitted in support of IND or NDA
- DMFs may provide researchers with more options to conduct clinical trials using human drug products with cannabis and cannabis-derived compounds

Point of Contact

- Can’t find what you are looking for? Contact the CDER SBIA staff:
  - Phone:
    - (866) 405-5367
    - (301) 796-6707
  - Email:
    - CDERSBIA@fda.hhs.gov
  - Mail:
    - **CDER SBIA**
      Office of Communications
      10001 New Hampshire Avenue
      Hillandale Building, 4th Floor
      Silver Spring, MD 20993

Thank you!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