University of Colorado **Anschutz Medical Campus**

So you want to do research with cannabis – How difficult can it be?

12/3/2021

Regulatory frame work

- 1961 - international Single Convention on Narcotic Drugs - cannabis is designated a Schedule I substance, and participating countries are required to restrict production, manufacture, possession and distribution of marijuana except for medical and scientific purposes.
  - The Drug Enforcement Administration (DEA) regulates the cultivation of marijuana for research purposes. Since 1961, the DEA had only issued a single registration for the cultivation of marijuana for research, to the University of Mississippi, which is funded through a contract with the National Institute in Drug Abuse (NIDA). For many years, academic researchers voiced concerns about being limited to a single source for research marijuana.
- 2016 - DEA solicited proposals for additional suppliers. More than 20 applications were submitted within the first year, more followed.
- March 2020 - the DEA posted a proposed rule in the Federal Register to facilitate registration of additional growers (85 FR 16292; Controls To Enhance the Cultivation of Marihuana for Research in the United States).
- December 18, 2020 - Final rule was published and became effective January 19, 2021.
- May 2021 - DEA starts approving additional suppliers for research marijuana (3 at this time).

May 14, 2021

DEA Continues to Prioritize Efforts to Expand Access to Marijuana for Research in the United States

On May 14, 2021, the Drug Enforcement Administration took an important step to increase opportunities for medical and scientific research. DEA is nearing the end of its review of certain marijuana grower applications, thereby allowing it to soon register additional entities authorized to produce marijuana for research purposes. Currently, the National Center for the Development of Natural Products at the University of Mississippi is the only approved supplier of marijuana for research purposes in the United States, and that production has been exclusively for the National Institute on Drug Abuse.

Pending final approval, DEA has determined, based on currently available information, that a number of manufacturers' applications to cultivate marijuana for research needs in the United States appears to be consistent with applicable legal standards and relevant laws. DEA has, therefore, provided a Memorandum of Agreement (MOA) to these manufacturers as the next step in the approval process.

On December 18, 2020, DEA finalized new regulations pertaining to applications by entities seeking to become registered with DEA to grow marijuana as bulk manufacturers for research purposes. Under these and other applicable regulations, applicants are responsible for demonstrating they have met various requirements, including requirements to possess appropriate state authority, document that their customers are licensed to perform research, and employ adequate safeguards to prevent diversion.

At this time, DEA has presented those manufacturers referenced above, who appear to meet the legal requirements, with an MOA outlining the means by which the applicant and DEA will work together to facilitate the production, storage, packaging, and distribution of marijuana under the new regulations as well as other applicable legal standards and relevant laws.

To the extent these MOAs are finalized, DEA anticipates issuing DEA registrations to these manufacturers. Each applicant will then be authorized to cultivate marijuana – up to its allotted quota – in support of the more than 575 DEA-licensed researchers across the nation. As individual manufacturers are granted DEA registrations, that information will be made available on DEA's Diversion Control website.

DEA will continue to prioritize efforts to evaluate the remaining applications for registration and expects additional approvals in the future.

Source: https://www.dea.gov/stories/2021/2021-05/2021-05-14/dea-continues-prioritize-efforts-expand-access-marijuana-research

DEA's Diversion Control website

BULK MANUFACTURERS

Effective November 4, 2019, the Importers and Bulk Manufacturer Notices of Registration (NORs) will no longer be published in the Federal Register.

View Previously Published Federal Register Notices

File	Registrant	FR Docket	Date
DRG-21-0055	Patheon Pharmaceuticals Inc.	86 FR 13586	9/28/2021
DRGR-17-0182	Biopharmaceutical Research Company, LLC (Correction)	84 FR 44920 84 FR 54926	9/28/2021
DRG-21-0094	Chemic Laboratories	86 FR 34045	9/28/2021
DRG-20-0147	Scottsdale Research Institute	85 FR 10462	9/28/2021
DRG-21-0092	Organix Inc.	86 FR 32279	9/28/2021
DRGR-17-0175	Scottsdale Research Institute	84 FR 44920 84 FR 54926	9/28/2021
DRG-21-0191/DRG-21-0065	Groff NA Hemplex LLC	86 FR 13587	9/14/2021
DRGR-17-0182/DRG-19-0034	Biopharmaceutical Research Company, LLC	86 FR 44920	9/14/2021
DRG-21-0084	American Radiolabeled Chem	86 FR 28152	9/14/2021
DRG-21-0058	Stepan Company	86 FR 13586	6/28/2021
DRG-21-0007	Sterling Wisconsin, LLC	85 FR 81220	6/28/2021
DRG-21-0038	Noramco Coventry, LLC	86 FR 14767	6/28/2021
DRG-21-0034	Synthcon LLC	86 FR 11330	6/7/2021
DRG-20-0253	Chattem Chemicals	86 FR 11557	6/7/2021
DRG-21-0024	S&B Pharma, Inc.	86 FR 11558	6/7/2021
DRG-21-0030	Sigma Aldrich Research Biochemicals, Inc.	86 FR 11329	6/7/2021
DRG-21-0021	IsoScience, LLC	86 FR 3197	4/29/2021
DRG-20-0273	Sterling Pharma USA, LLC	85 FR 80159	4/1/2021
DRG-20-0283	Organix, Inc.	86 FR 2457	4/1/2021
DRG-21-0028	Siemens Healthcare Diagnostics Inc.	86 FR 3197	4/1/2021
DRG-21-0009	Cedarburg Pharmaceuticals	86 FR 2457	4/1/2021
DRG-20-0168	Patheon Pharmaceuticals, Inc.	85 FR 10471	4/1/2021
DRG-21-0015	Johnson Matthey Pharmaceutical Materials, Inc.	85 FR 74765	2/26/2021
DRG-21-0001	Kinetochem, LLC	85 FR 67375	2/26/2021
DRG-20-0284	Navinta, LLC	85 FR 70190	2/26/2021
DRG-21-0022	Janssen Pharmaceuticals Inc.	85 FR 78149	2/26/2021
DRG-21-0013	Johnson Matthey, Inc.	85 FR 80159	2/26/2021
DRG-21-0016	Novitium Pharma, LLC	85 FR 76108	2/26/2021
DRG-20-0277	S & B Pharma, LLC	85 FR 63141	1/26/2021
DRG-20-0241	Synthcon, LLC	85 FR 65074	1/26/2021
DRG-20-0274	Eli Elsohly Laboratories	85 FR 63142	1/26/2021
DRG-20-0282	Halo Pharmaceutical	85 FR 63141	1/26/2021
DRG-20-0266	Cerilliant Corporation	85 FR 70190	1/26/2021

Applications
Tools
Resources
CMEA Required Training & Self-Certification
Quota Applications
Marihuana Growers Information
Notice of Registration

Source : https://www.deadiversion.usdoj.gov/drugreg/nor/manufacturers/index.htm

BULK MANUFACTURERS

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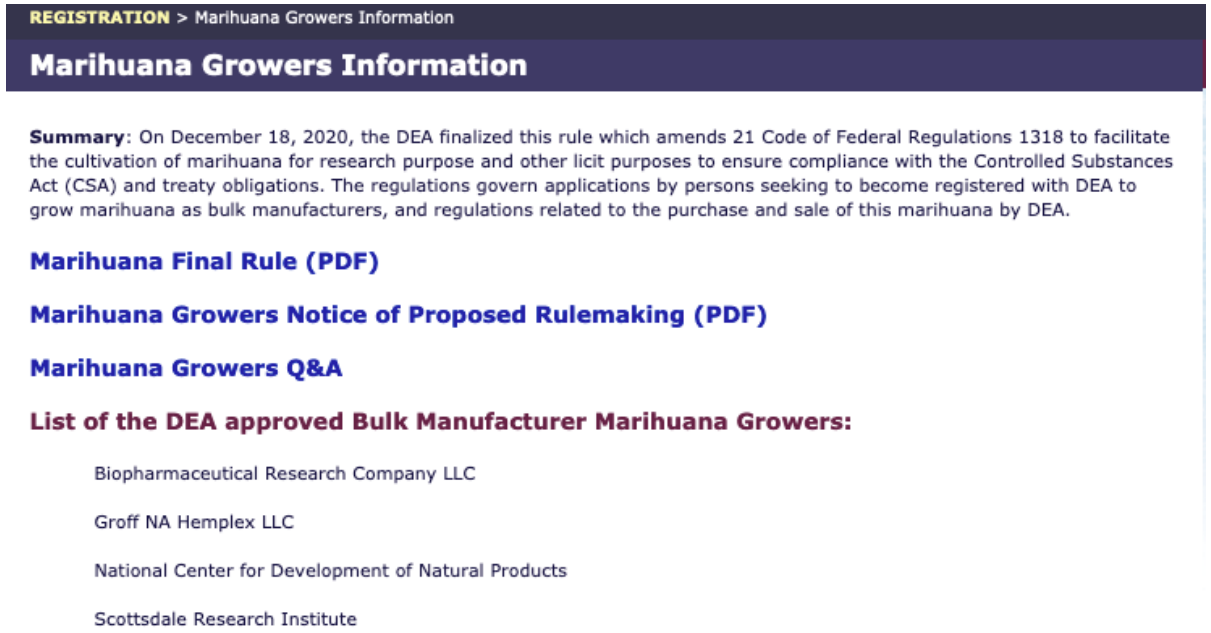

REGISTRATION > Marihuana Growers Information

Marihuana Growers Information

Summary: On December 18, 2020, the DEA finalized this rule which amends 21 Code of Federal Regulations 1318 to facilitate the cultivation of marihuana for research purpose and other licit purposes to ensure compliance with the Controlled Substances Act (CSA) and treaty obligations. The regulations govern applications by persons seeking to become registered with DEA to grow marihuana as bulk manufacturers, and regulations related to the purchase and sale of this marihuana by DEA.

Marihuana Final Rule (PDF)

Marihuana Growers Notice of Proposed Rulemaking (PDF)

Marihuana Growers Q&A

List of the DEA approved Bulk Manufacturer Marihuana Growers:

Biopharmaceutical Research Company LLC

Groff NA Hemplex LLC

National Center for Development of Natural Products

Scottsdale Research Institute

Source: https://www.deadiversion.usdoj.gov/drugreg/marihuana.htm

Questions about additional suppliers

- Which products can be obtained from them?
  - Products they purchase from another supplier?
  - Imported products?
  - Hemp-derived products?
  - Matching placebos for final active formulations?
  - Any final formulation?
- Process for requesting products?
  - Order product directly through supplier? DEA? Depends?
- Cost of product(s)?
- How is DEA involved, beyond approving the DEA CS-1 RESEARCH license application?
- At what point is the DEA-CS 1 license required?
  - Placing an order?
  - Prior to shipment?
- What limitations do researcher be aware of?

What to expect from FDA ?

A Randomized Double-Blind Placebo Controlled Crossover Study of Tolerability and Efficacy of CBD on Tremor in Parkinson Disease

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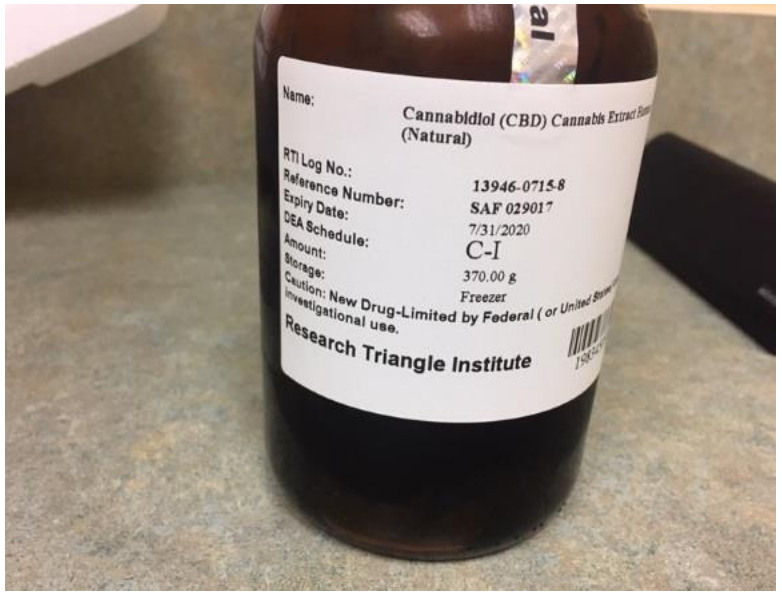
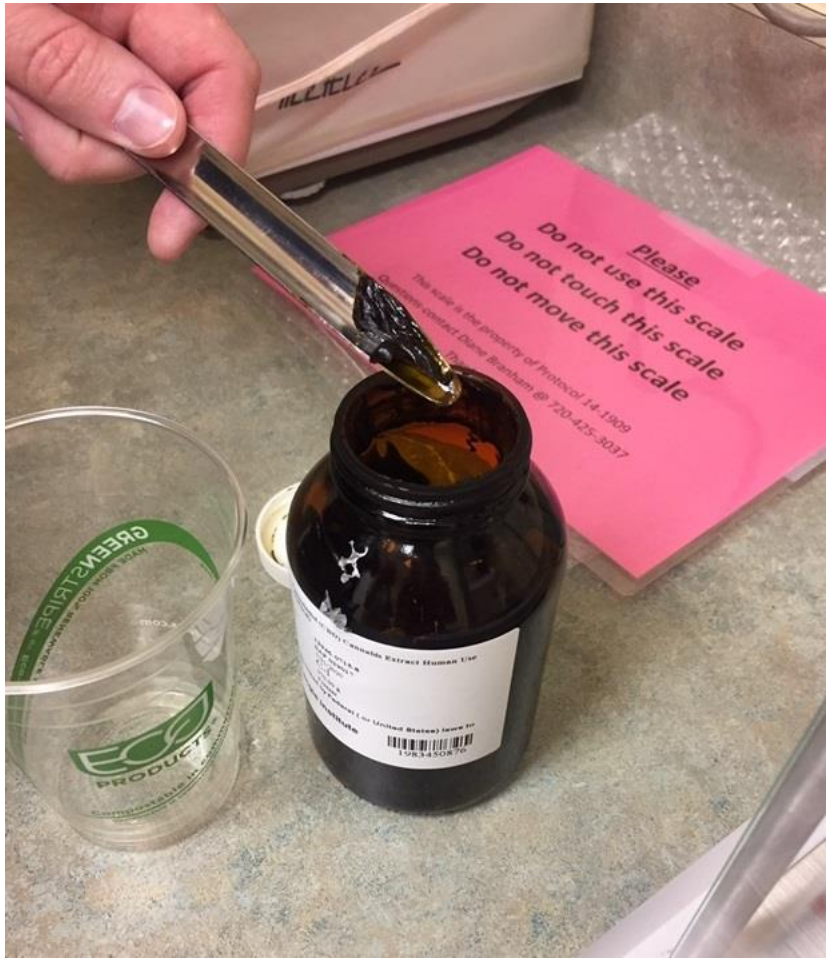
CBD FROM The National Institute of Drug Abuse (NIDA)



CBD GOO



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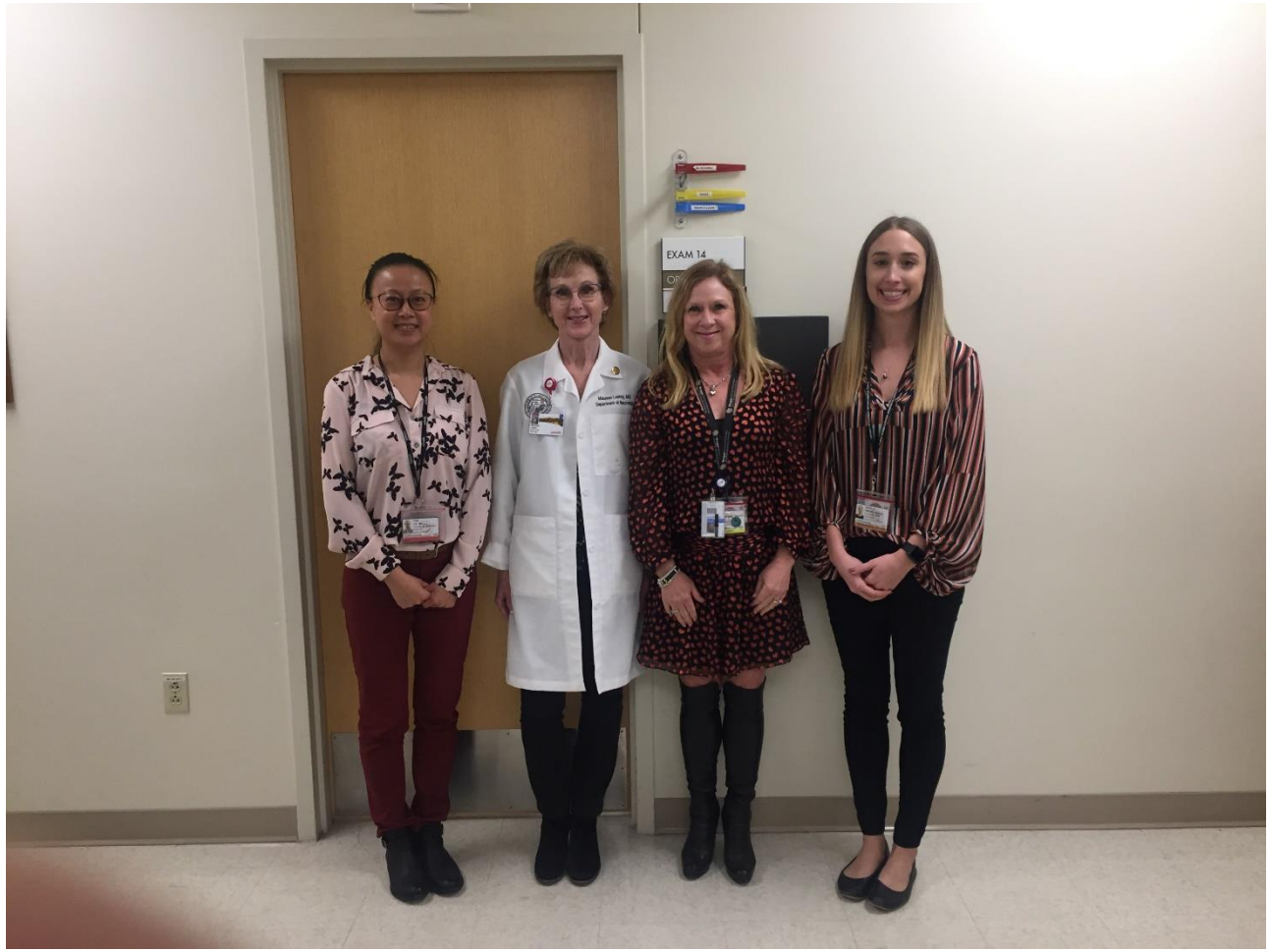

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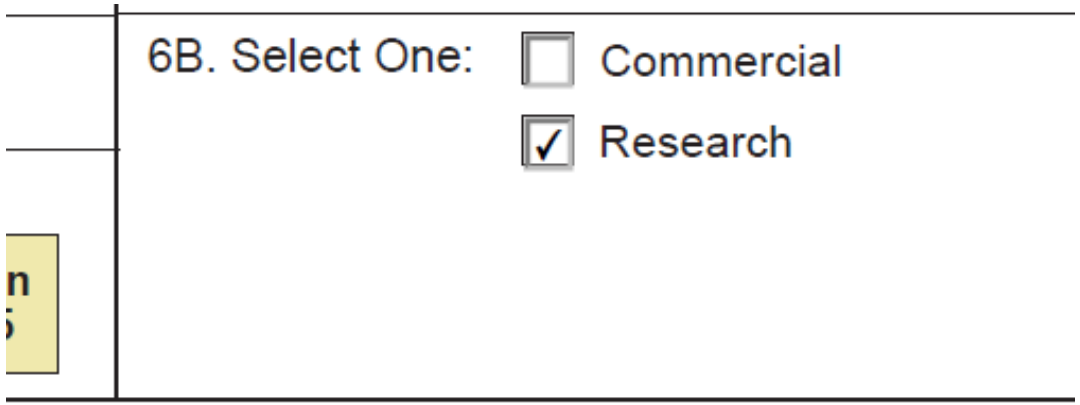
Clinical Hold Deficiencies/Recommendations to a recently submitted Research IND with NIDA's whole plant extract

Form FDA 1571



8. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☑ Phase 3 ☐ Other *(Specify)*: _____

Clinical Hold Deficiencies

Nonclinical Pharmacology/Toxicology

2. There is inadequate information to evaluate the safety of tangerine food flavoring, yellow food color powder, and brown food color powder, which are excipients that either are not in approved drugs as listed in the FDA Inactive Ingredients Database (IID) or are associated with higher daily intake levels compared to levels found in the IID.

   Information to resolve deficiency

   Provide safety justifications for the maximum daily intake of tangerine food flavoring, yellow food color powder, and brown food color powder associated with your proposed dosing schedule that includes the quantitative composition of each excipient or provide a letter of authorization to a Drug Master File (DMF) that contains the safety justification for an individual excipient. Reference exclusively to FEMA numbers or GRAS designation that is not listed in the CFR should be accompanied by underlying data to support the conclusion that the compound is GRAS at the levels proposed in the drug product. Copies of all references should be included in the submission to permit independent evaluation.

CMC (Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP))

3. There is not sufficient chemistry, manufacturing, and controls information to assure proper identification, quality, purity, and strength of the investigational drug substance and product.

   Information to resolve deficiency

   a. Provide quantitative composition for the brown and yellow food color and tangerine food flavor. Alternatively, if any of these excipients are GRAS, then provide the CFR citation, or if under a DMF, provide a letter of authorization allowing the Agency to review the DMF in support of your IND.

   b. Provide a certificate of analysis for each strength drug product to be used. This should include assay determination of all cannabinoids demonstrating mass balance to 100% as well as an impurity profile.

   c. It appears the drug product will be compounded and stored. Provide stability data to support the storage and in-use time of the drug product. Provide stability data to support the storage and in-use time of the drug product.

Non-Hold Recommendations

Botanical Review Team

2. Refer to the Guidance for Industry: *Botanical Drug Development*[1] for further discussion and guidance about late phase trials (i.e., Phase 3), particularly Section VI.

3. To assess batch-to-batch consistency, the botanical raw material (BRM) source should be confirmed and representative BRM sample batches should be selected (i.e., raw material from 3 or more representative cultivation sites or farms) for the manufacturing of the clinical drug substance from multiple batch Phase 3 studies.

4. Growing of the BRM should adhere to the principles outlined in the Good Agricultural and Collection Practices (GACP), which will help reduce the likelihood of insufficient supply of the BRM post-NDA approval.

5. Provide additional characterization of the BRM (e.g., chemical identification of each BRM by spectroscopic or chromatographic method, and authentication of each BRM by a DNA fingerprinting method as necessary), updates on the quality control tests and analytical procedures applied by the BRM supplier, and the proposed acceptance criteria, with the goal of work toward final development in preparation for an NDA submission.

6. Provide prior human experience using the two proposed botanical drug products (BDPs):
    a. CBD/THC oral solution (5 mg THC/50mg CBD per mL, ~34:1 CBD:THC ratio in extract)
    b. THC oral solution (5 mg THC/mL, ~70% THC extract)

Contact Info

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THANK YOU

Questions

Cannabis for Academic Research

Why is cannabis research different from conventional pharma research using experimental products?

FDLI

Jargon – *Let's get this out of the way*

- What we are talking about:

  Academic research with unapproved products, not new research on marketed drugs.

- What the products are called by Regulators / Industry:

  Investigational Product or Test Article

  - **Drug Substance**:
    - Starting materials
    - API – active pharmaceutical product
  - **Drug Product**
    - Formulation development
    - Excipients

Conventional Drug Development

10 -15 yrs

Receptor / Targets

Candidate Screening

Manufacturing

Test article evaluation

Non-clinical

Human

Phase III

NDA

Therapeutic gap

Unmet medical need

Controlled Data:

- Formulation,
- In vitro characteristics,
- Drug-drug interactions,
- In vivo characteristics,
- Safety profile,
- Efficacy profile

FDA Guidance

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.

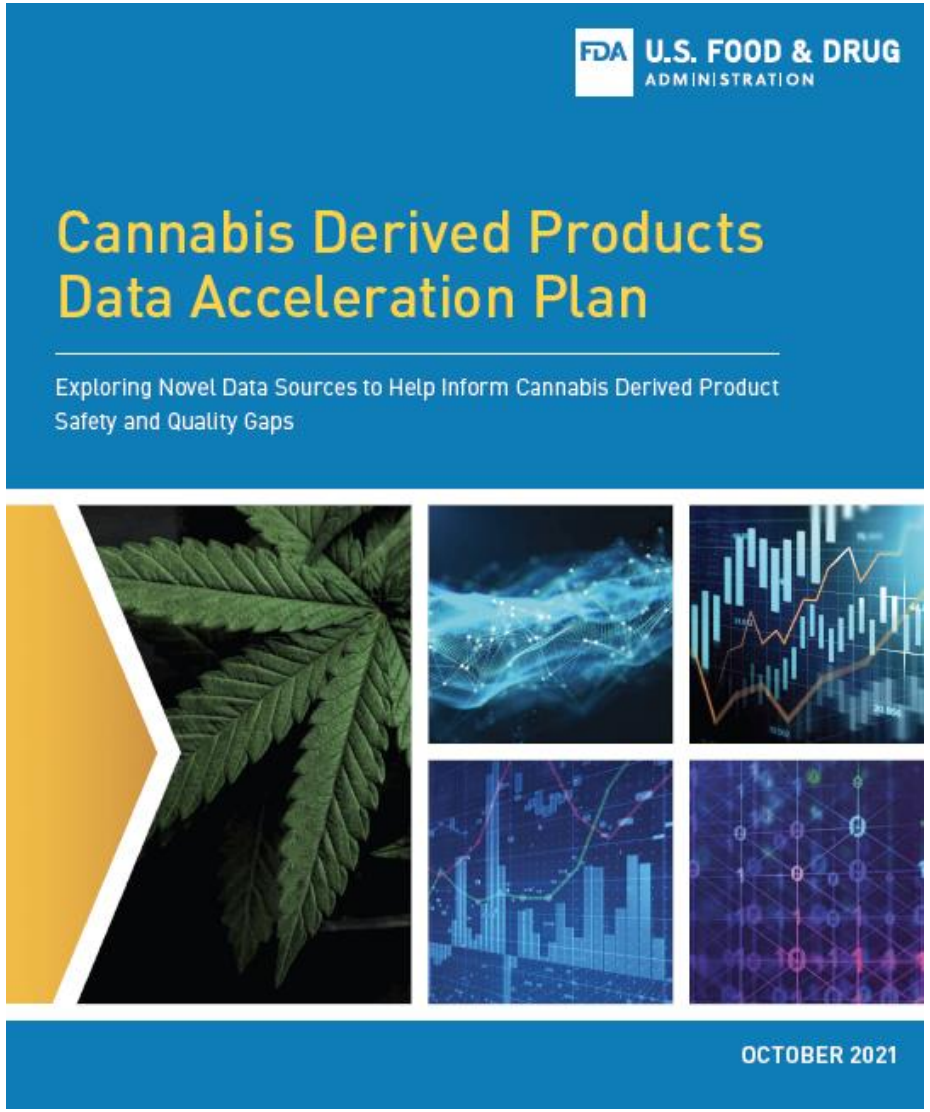
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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

https://www.fda.gov/media/140319/download

SAFETY

QUALITY



https://www.fda.gov/media/153183/download

“Medical Grade Cannabis” - Definitions Matter

cGMP

Sample Pilot Projects[5]	Overview
Analyze Online Certificates of Analysis (COA) to Evaluate Quality Communication vs. Actual Ingredients	*COAs are used by product manufacturers as a tool to communicate product quality to consumers and communicate that the product's THC levels are below the 0.3% threshold set in the Farm Bill.* Primary Objective: Map product COA data to the data collected via the FDA's CBD product sampling project[6], which is testing hundreds of hemp products for cannabinoids, toxic elements, pesticides, residual solvents, and microbial pathogens. Compare product COA data with the FDA analytical data on the product sold in-market to identify inconsistencies and quality issues.

21 CFR Part 111

EudraLex *The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* (“EU-GMP”). ***EU-GMP of Annex 7*** *– Manufacture of Herbal Medicinal Products.*

Enhanced Research – Pharma / Academia

Academic Research

Explore new potential applications

Manufacturing

Formulation development

Test article evaluation

What Phase is this?
Who cares?

Potential new indication

ICH harmonisation for better health

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Controlled Data:

- Drug Quality,
- Formulation development,
- In vitro characteristics,
- Drug-drug interactions,
- In vivo characteristics,
- Safety profile,
- Efficacy profile

21 CFR Part 111 vs. Part 211

Raw Materials

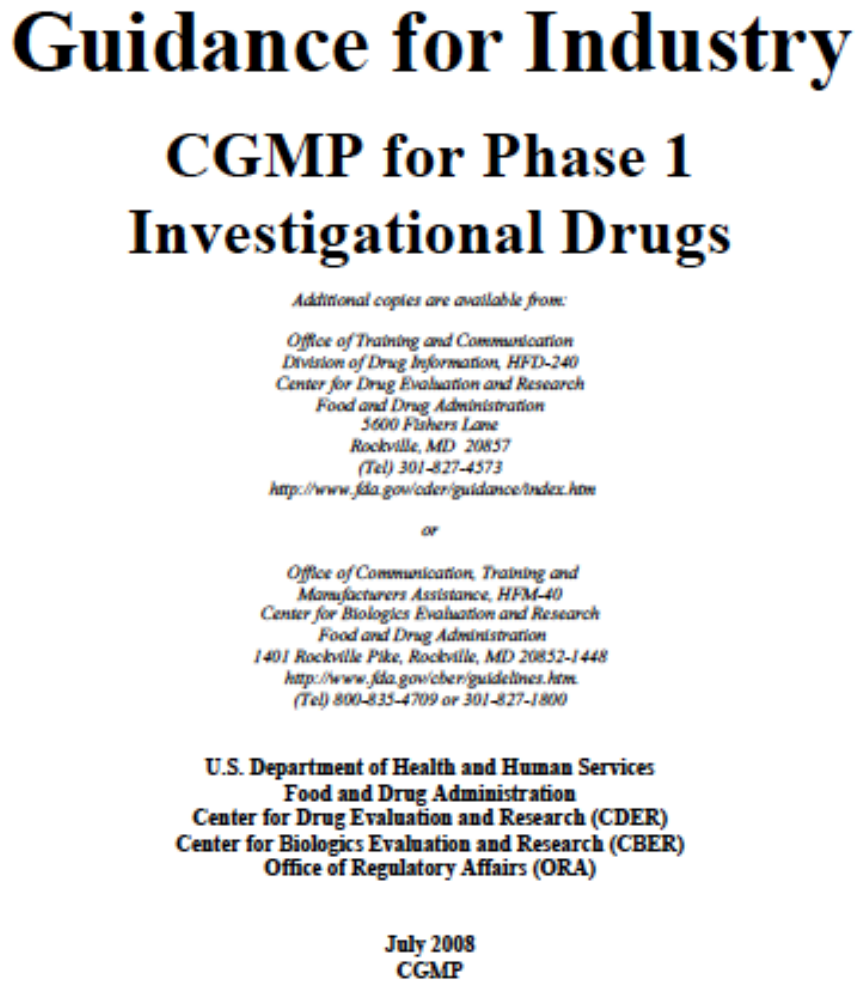
[111.75(a)(2)] There is no requirement for the dietary supplement manufacturer to confirm the identity of non-dietary ingredients used in the finished dietary supplement product if the supplier has been previously qualified by the manufacturer.

vs.

[211.84(d)(1)] There is a requirement that at least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

21 CFR Part 211 – Phase I vs Phase III

Academic trials are routinely “One off” and not part of a drug development plan targeted at an NDA



Guidance for Industry

CGMP for Phase 1 Investigational Drugs

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
(Tel) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

July 2008
CGMP

This guidance does ***not*** apply to the following phase 1 investigational products:

- Human cell or tissue products regulated solely under § 361 of the Public Health Service Act
- Clinical trials for products subject to the device approval or clearance provisions of the FD&C Act
- Investigational products manufactured for phase 2 and phase 3 clinical trials[7]
- Already approved products that are being used during phase 1 clinical trials (e.g., for a new indication)[6]
- Positron Emission Topography (PET) drugs that are subject to § 501(a)(2)(C) of the FD&C Act and/or the new PET CGMP in 21 CFR part 212 when finalized