University of Colorado **Anschutz Medical Campus**

Challenges in Conducting Academic Cannabis Research

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Colorado and Cannabis

November 2012 –

- Colorado Amendment 64 passed statewide by approximately 55 percent, making Colorado the first state to legalize the recreational use of cannabis.
- Allows adults aged 21 or older to grow cannabis plants privately in a locked space, and to purchase cannabis from a state licensed source.

- So why are academic institutions in Colorado not doing more clinical trials?

Federal Boundaries for Research with Cannabis

- **1961 International Single Convention on Narcotic Drugs** designated cannabis as a **Schedule I** substance; requires that participating countries restrict production, manufacture, possession and distribution of marijuana except for medical and scientific purposes; requires that "Only **cultivators licensed by the Agency** shall be authorized to engage in such cultivation."

- In the US, the **Drug Enforcement Administration (DEA)** regulates the cultivation of marijuana for research purposes through registration requirements and through establishing annual aggregate production quotas under the authority of the **1970 Controlled Substances Act (CSA).**

- Since 1968, DEA has issued only one license for cultivation of cannabis for research, to the **University of Mississippi (UM),** which is funded through a contract with the **National Institute on Drug Abuse (NIDA).** NIDA's contract with UM was renewed in 2015.

- **Racketeer Influenced and Corrupt Organizations Act (RICO).** Passed in **1970**, RICO is a federal law designed to combat organized crime in the United States. It **allows prosecution and civil penalties for racketeering activity performed as part of an ongoing criminal enterprise.** Such activity may include illegal gambling, bribery, kidnapping, murder, money laundering, counterfeiting, embezzlement, **drug trafficking**, slavery, and a host of other unsavory business practices.
- "Racketeering activity" means any act or threat involving murder, kidnapping, gambling, arson, robbery, bribery, extortion, dealing in obscene matter, **or dealing in a controlled substance** or listed chemical (**as defined in section 102 of the Controlled Substances Act)…**

Challenge #1 – Single Source for Research Cannabis

- NIDA
- Limited cannabis product options (type, strength, profile)
- Products provided in bulk, need to be compounded and packaged in appropriate dosage form by the research team
- Potential delays with study start up due to unavailable product
- Questions about comparability to effects with local products
- No dispensary products, no dispensary product gifts
- Note: in 2018, over 25 cultivators applied to DEA for license to provide cannabis for research. None has been approved as of today.

Challenge #2 - DEA Research C-I license

- DEA C-I application for license
- C-I storage and diversion control requirements
  Separation of C-I and C-II to V, placebo;
  Cabinets bolted to wall/floor; double-locks;
  Security camera
- Local DEA site visit at storage location
- Annual renewals to C-I license
- Submission when changes to protocol or new protocol

Challenge #3 – IND with FDA, clinicaltrials.gov posting

- NIDA requires that all human research with cannabis was reviewed through FDA's IND process
- Research IND application to FDA for all human research projects (even for non-medical endpoints, such as driving impairment)
- Annual Reports/ Final Reports to FDA
- Registration/annual updates on Clinicaltrials.gov

Challenge #4 –

A Plethora of Downstream Effects due to the Federal Schedule I Status

Operational Challenges

- Colorado's **State Board of Pharmacy** objects to the use of state licensed pharmacies to manage cannabis, even for investigations under IND with FDA and with DEA Schedule I Research license.

- Colorado **DEA field office** will not approve storage of research cannabis products in a state licensed pharmacy.

- CU investigators cannot utilize the existing **state-licensed investigational drug pharmacy** on its campus, even though this pharmacy is licensed, equipped and staffed to manage controlled substances (C-II to V).

- **SOLUTION ($)**: a specifically designated space had to be created for the storage of cannabis products outside the licensed pharmacy.

- **SOLUTION ($):** Research cannabis is managed by the research teams directly, primarily through pharmacists from the University of Colorado School of Pharmacy and Pharmaceutical Sciences.

- Cannabis products **cannot be provided to or administered to study participants within our affiliate state hospital.**

- **Nurses in the research suite** are employees of the state hospital; they cannot provide or administer the cannabis products.

- **SOLUTION**: patients seen and treated by our clinicians in the state hospital need to make separate appointments for the clinical research suite to receive cannabis products.

- **SOLUTION**: Only University employed research staff is allowed to provide and administer cannabis products to study participants.

- Cannabis product not approved under an IND cannot be brought onto campus for use in humans.

- **SOLUTION**: Research IND

Funding Challenges

- Money from the cannabis industry is considered money from racketeering activities (“drug trafficking”.

- Limited acceptable funding sources –
  - Federal grants (NIH etc)
  - State grants (e.g. CDPHE)
  - Non-profit organizations (e.g. patient advocacy groups)
  - Commercial IND holder (i.e. pharma company’s clinical trial)
  - Cannot accept gifts or funding from cannabis industry for investigator-initiated studies


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Most relevant current Initiatives

- **The Marijuana Opportunity, Reinvestment and Expungement (MORE) Act of 2019 (H.R. 3884)**
- **Scheduled for vote in US House of Representatives the week of November 30th, 2020**
- Would remove marijuana from the federal Controlled Substances Act and open up the industry to business opportunities and interstate commerce over time.
- Enable states to continue to regulate commercial marijuana markets as they see fit.
- Open access to traditional banking services for cannabis companies.
- End the federal 280E tax restrictions that prevent state-legal marijuana businesses from taking deductions that are available to ordinary businesses.
- Pave the way for interstate and international marijuana trade.

H.R.3797 - Medical Marijuana Research Act of 2019

Sponsor: Earl Blumenauer (D-OR)
Introduced to House: 7/17/2019
Latest Action: House - 09/09/2020 Ordered to be Reported (Amended) by Voice Vote.

Sec.3. FACILITATING MARIJUANA RESEARCH:

- **No DEA C-I license required:**
  - Anyone with a schedule II-V DEA license would be able to register for research with marijuana. For human studies, they need to provide a protocol to the FDA *__or__* NIH , for animal studies to NIH, AND they must demonstrate that they have proper diversion control measures in place.
  - **Clear criteria for DEA registration review process and feedback:**
    - The AG must grant the application, unless the registration is inconsistent with public interest (based in applicant's experience dispensing or doing research with controlled substances, the applicant's conviction record with controlled substances, and compliance with state or local laws).
    - The AG must either approve or deny a registration within 60 days of receipt, and if denied, must provide written explanation and describe curative steps that may be taken to be approved need to be provided. A submission is deemed complete when protocol and diversion control description was submitted to FDA or NIH.
- **Less stringent storage requirements:**

  Storage requirement limited to a securely locked, substantially constructed cabinet, otherwise the researchers would need to follow requirements consistent with schedule II storage requirements.

- **Fewer submissions to DEA once a research protocol changes, or a new protocol is approved to proceed; clear expectations on DEA review, approval timeline and process:**
  - The applicant may amend or supplement a research protocol without reapplying/submitting an amendment to the registration as long as the type of drug, source of drug, or storage conditions are not changed, or there is another reason for increased risk of diversion. Notice of these changes can be submitted to DEA with the registration renewal.

  - If there is a change in type or source of drug, or storage conditions, the researcher must notify the AG at last 30 days prior to implementing the study, and the AG has 30 days to review. If the AG does not object during that time, the researcher may proceed. The AG may only object based on the need for additional safe guards against diversion or abuse.

SEC.4. MANUFACTURING AND DISTRIBUTION

- **No limit on number of manufacturers and distributors, criteria for approval.**
  - Registration of Manufacturers:
    - AG must register an applicant to manufacture marijuana to be used by a qualified marijuana researcher for research unless the AG determines the registration is inconsistent with public interest. The criteria for that are again limited to diversion control, compliance with State and local laws, and prior conviction record of the applicant. No other factors may be considered.
  - Registration of Distributors:
    - AG must register an applicant to distribute marijuana for use by a qualified marijuana researcher for research unless the AG determines the registration is inconsistent with public interest. The criteria for that are limited to diversion control, compliance with State and local laws, prior conviction record of the applicant, and prior experience with distribution of controlled substances. No other factors may be considered.

  - **No limit is allowed on the number of persons eligible to register as manufacturers and distributors.**

- Verification of use of legitimate, medical research for any person to whom marijuana will be supplied is submitting a protocol and its review as described above to the AG.

- The AG must review all applications (manufacture and distribution) within 30 days of receipt of the registration, and either grant or deny the request. If denied, a written explanation, and a description of curative steps that may be taken to be approved need to be provided. If the AG fails to grant or deny within these 30 days, the application is deemed approved.

Sec.6. CONSIDERATION OF RESULTS OF RESEARCH

- As soon as FDA approves an IND for a marijuana study and within 5 years of the date of enactment of this Act, Secretary of HHS is required to **conduct a review of existing medical and other research with respect to marijuana, submit a report to Congress about it, and include in that report** (based on potential medical benefits, gaps in research, impacts on federal restrictions or policies on research) **whether marijuana should be rescheduled (if that has not already happened).**


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THANK YOU

Regulatory and Practical Research Limitations and Solutions for Cannabis-Derived Products

Wednesday, December 9, 2020

Evelina Norwinski

Arnold & Porter LLP

FDLI

Cannabis: Marijuana v. Hemp

Marijuana

- Federal: Schedule I
- Regulated by DEA
- Legalized in 45 states

Hemp

- Federal: legal
- Regulated by USDA
- Legal in most states

Cannabis Research: Sources

Marijuana

- Sole source

THE UNIVERSITY of MISSISSIPPI

Hemp

- Any state or USDA licensed grower
- Caution: THC ≤ .3%

Cannabis Researchers

Marijuana

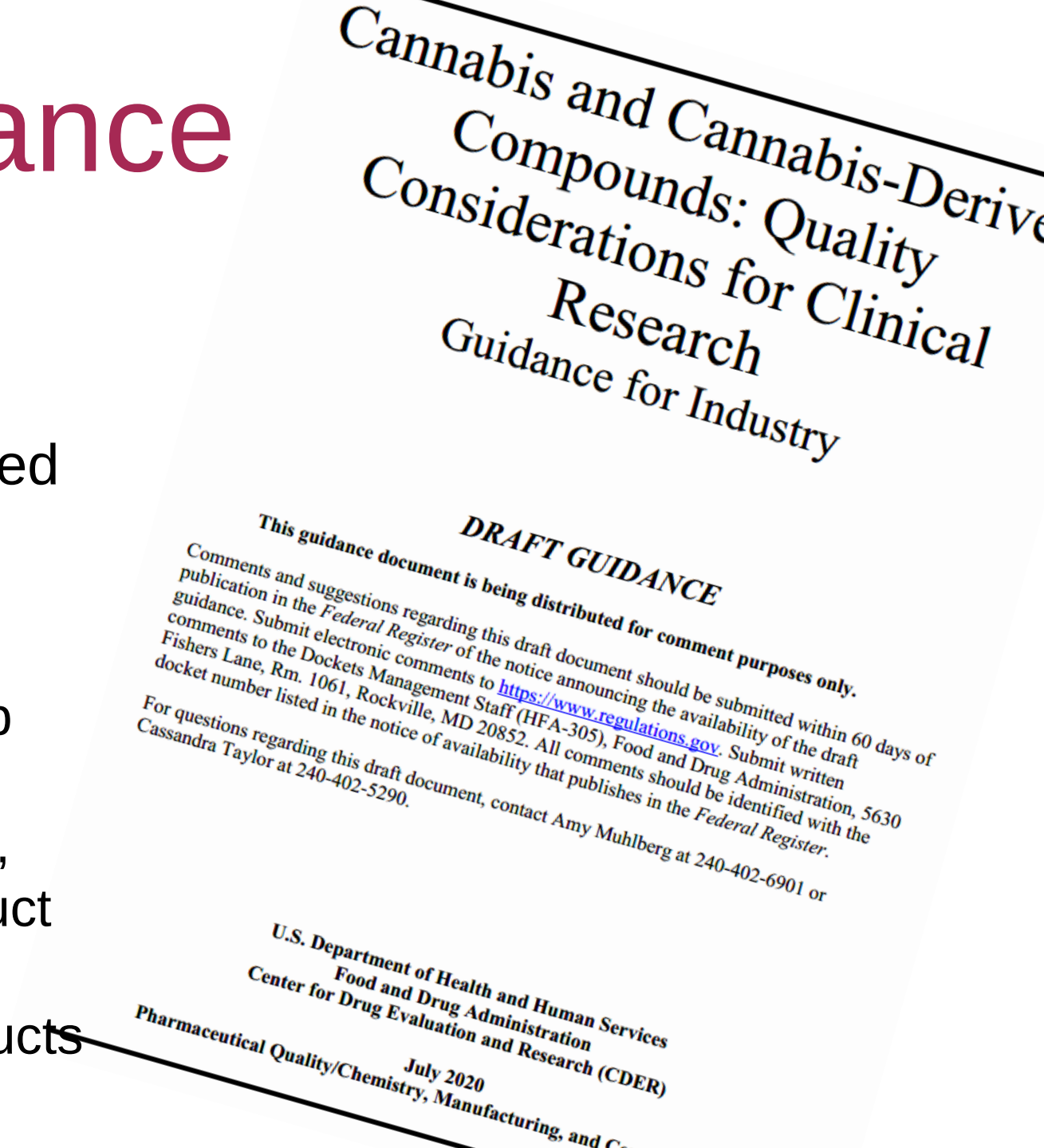
- DEA registration and regulation
  - 21 USC § 823; 21 CFR § 1301.18
- FDA regulation (clinical research)
- State license

Hemp

- Possibly state license
- If > .3% THC, then must have DEA license
- FDA regulation (clinical research)

FDA Draft Guidance

- Cannabis drugs subject to same rules as other drugs
- Only marijuana from NIDA allowed for clinical trials
- Hemp allowed – must be ≤ .3%
  - Analytical testing by reliable lab
  - USDA testing requirements
  - Test raw material, intermediate, drug substance and drug product
  - Special testing procedures for intermediate and finished products


Cannabis and Cannabis-Derive
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

Regulatory and Practical Research Limitations and Solutions for Cannabis-Derived Products State Research Programs

Wednesday, December 9, 2020

Debby Miran

Consultant and Former Commissioner MMCC

FDLI

The Challenge to State Medical Programs

- Still illegal for a state licensed cultivators to provide cannabis to scientists and physicians for research

- Illegal for researcher to purchase or receive donated study supplies as this is considered trafficking

Challenges with the Quality of Study Material

- NIDA cannabis does not resemble cannabinoid and terpene content of state regulated cannabis in dispensaries
- Purity tests required by state testing programs is stricter and more comprehensive
- No legal source for Phase III CTs

Pennsylvania Became First State-Authorized Medical Marijuana Research Program

- Authorized by law in 2014 but first program launched in May 2020 at Thomas Jefferson U in Philadelphia
- State law allows up to 8 Clinical Registrants (CRs)
- 7/8 CR licenses have been awarded to Penn, Drexel, Temple, TJU, Philadelphia College of Osteopathic Medicine, Penn State, and Lake Erie College of Osteopathic Medicine
- PA DOH Sec'y Rachel Levine- "we will be the epicenter for MM research in the US"

Basic Requirements

- CR must have proof of $15mm in capital
- Set dollar amount plus percentage of profit to be dedicated to research
- At least one IRB approved protocol required to achieve full state license

How This Works

- A CR partners with a licensed cultivator and licensed dispensary
- CR is funded by the revenue from cultivator/dispensary sales
- CR does NOT handle any of the cannabis medications
- Patients are recruited through dispensary
- CR has duty to report progress and results to DOH during regular meetings (scheduled for Dec. 8-10)

Program Launch Delayed in Courts

- CR program allowed up to 6 dispensaries whereas regular licensees were allowed 3
- Lawsuits by non CRs argued this was unfair and did not want competition that would dilute market share
- CR dispensaries could use published papers to “promote conditions to patients”
- Eventually, these cases were resolved with no material change to CR program

What are the CRs Doing?
Thomas Jefferson University

- Observational study to understand use and outcomes with the 23 qualifying conditions
- Focus groups and patient surveys to assess patient experiences at the dispensary
- Pre-clinical studies on allergy and inflammation

Research at Penn State

- Developing a database to compare patient responses among PA's list of approved conditions
- Pre-clinical research in cell lines and animal models studying dosing and cannabinoid combinations
- Eventually, plans to conduct DB randomized, placebo-controlled trials

Drexel University and Lake Erie

- Drexel- Observational study looking at effects of cannabis on serious medical conditions and symptoms
- Drexel- Plans pilot human trials on several of PA conditions
- Lake Erie- Plans to study how cannabis use changes patterns of opioid use

Temple University

- Temple is one of the oldest cannabis research programs in the US (pre-clinical studies for over 12 years)
- 6 researchers have been chosen to study a wide range of topics from best routes of administration using animal models to specific disease states and conditions
- Goal is to “conduct trials to inform clinical trials”

Other State Research Initiatives

- New Jersey law permits up to 4 vertically integrated CRs having a written contractual relationship with an academic medical center
- To date, no RFA (request for application) have been issued (Earliest could be June 2021)
- CRs would be allowed one extra dispensary
- West Virginia 2017 Medical Cannabis Act Ch.16A establishes a program to authorize the use of medical cannabis to conduct medical research

State Research Funding Challenges

- Tax revenues from adult use sales are not available in states with only medical programs
- Tax revenues are typically not available to private colleges and universities
- Private research funding is difficult to secure (eg. Maryland) unless there is a CR program