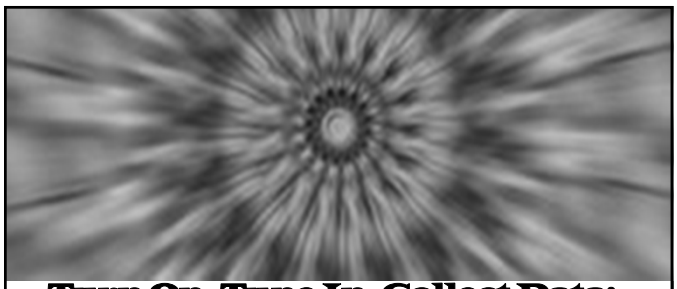


Turn On, Tune In, Collect Data: Conducting Clinical Investigations with Controlled Substances

Kris West, Chief Compliance Officer, Emory University, Atlanta, GA

Presentation Overview

- Background of Controlled Substances Regulations
- Current Controlled Substances Research
- Site Preparation for a Clinical Investigation Involving a Schedule I Controlled Substance as a Test Article
- Pitfalls to Avoid

Background of Controlled Substances Regulations

Regulatory Timeline

Late 1800s to Early 1900s – No federal regulation

Harrison Narcotics Act 1914 – Registration of manuf., distrib., & prescribers; tax; records.

Marihuana Tax Act of 1937 – Unofficial federal ban of marijuana via high transfer tax; all states made possession illegal.

Regulatory Timeline

1956 Narcotic Control Act – death penalty for selling heroin to minors.

1963 Bureau of Drug Abuse Control in Dept. of Health, Education & Welfare – shift to medical approach to drug abuse.

1970s War on Drugs and Controlled Substances Act; Establishment of DEA

Controlled Substances Act

- Drugs are scheduled based on medicinal value and potential for abuse.
- Schedule I = No medicinal value & high potential for abuse.
  - Examples: Marijuana, Ectasy (MDMA), LSD, Heroin.
- Schedule II – V = Medicinal value and lessening potential for abuse as Schedule number increases.

Current Controlled Substances Research

Controlled Substance Research Then . ..

Harvard Crimson

CAMBRIDGE, MASS., TUESDAY, MAY 28, 1963 TEN CENTS

Corporation Fires Richard Alpert For Giving Undergraduates Drugs

First Dismissal Under Pusey

By JOSEPH H. RUBIN and ANDREW T. WEIL

The Corporation has terminated the appointment of Richard Alpert as assistant professor of Clinical Psychology and of Education for violating a University agreement by giving consciousness-expanding drugs to an undergraduate, Pusey said. Pusey told the Crimson yesterday.

Pusey also said that Timothy F. Leary, Lecturer on Clinical Psychology, will be relieved of his teaching duties and lose his salary terminated on April 30 for leaving Cambridge and his classes without permission.

In his statement to the Crimson, Pusey said Alpert had violated an agreement with the University not to give consciousness-expanding drugs such as psilocybin and mescaline to undergraduates. The statement also implied that Alpert had lied to an officer of the University last November when he "assured" the Administration that "he had not given drugs to any undergraduate."

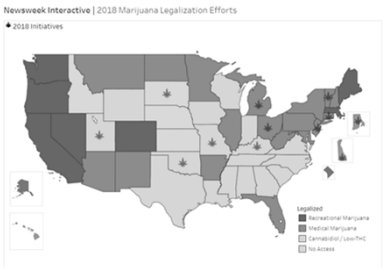
Alpert's appointment as assistant professor of Clinical Psychology was to have expired June 30, but he also held an appointment through next year at the [illegible] action terminated both of these appointments effective immediately.

PRESIDENT PUSEY RICHARD ALPERT

. . .and NOW !

http://www.mapn.org/participate/participate-in-research

What Changed?



2018 Legislative Initiatives

Recreational Marijuana: NJ, MI, DE, RI, CN, OH, VT (passed)

Medical Marijuana: OK, KY, SD, UT, MO

http://www.newsweek.com/marijuana-legalization-2018-which-states-will-consider-cannabis-laws-year-755282

Hot Trials

CNBC

Cannabis-derived drug clears hurdle on path to FDA approval

- Epidiolex would be the first drug on the U.S. market derived from the cannabis plant.
- An outside panel of advisors to the FDA gave a unanimous vote of approval.
- The medication, which is manufactured by GW Pharmaceuticals, is used in the treatment of seizures associated with childhood epilepsy.

https://www.cnbc.com/2018/04/19/cannabis-derived-drug-clears-hurdle-on-path-to-fda-approval.html

Hot Trials

Science By Kai Kupferschmidt | Aug. 26, 2017 , 6:30 PM

That an illegal dancefloor drug could become a promising pharmaceutical is another indication that the **efforts of a dedicated group of researchers interested in the medicinal properties of mind-altering drugs** is paying dividends. Stringent drug laws have stymied research on these compounds for decades. "This is not a big scientific step," says David Nutt, a neuropsychopharmacologist at Imperial College London. "It's been obvious for 40 years that these drugs are medicines. But it's a huge step in acceptance."

MDMA is better known as the party drug ecstasy. DEA

All clear for the decisive trial of ecstasy in PTSD patients

http://www.sciencemag.org/news/2017/08/all-clear-decisive-trial-ecstasy-ptsd-patients

So you have a PI who wants to do an Ecstasy Trial with Human Subjects…

What could go wrong?

Site Preparation for a Clinical Investigation Involving Controlled Substances as a Test Article

Meet the Regulators You'll Be Working With

- Food & Drug Administration
  - IND required
  - IRB approval
- Drug Enforcement Agency
  - Registration & Inspection Required
- State Regulators (e.g., State Board of Pharmacy, State Drugs & Narcotics Enforcement Agency)
  - Registration & Inspection may be required

Step 1: Review & Get Approval for Your Protocol & IND Application

- Is there a sponsor, or will researcher be serving as a sponsor-investigator?
- Where will researcher be obtaining drug?
  - Chemistry information required for IND – Typically requires a Letter of Authorization from manufacturer.
    - IND and LOA must be provided to FDA and DEA
  - Will compounding be necessary?
  - Using marijuana . . . .

Single Marijuana Supplier – U. of Miss.

Is the University of Mississippi the only legal marijuana grower in the U.S.?

Answer:

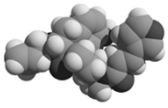
Under the 1961 international Single Convention on Narcotic Drugs and the 1970 Controlled Substances Act (CSA), the federal government is the single "agent" allowed to provide marijuana for research. As of now, the DEA has only authorized one grower, the University of Mississippi, which grows marijuana under contract with the National Institute on Drug Abuse (NIDA). As part of this contract, UM holds a DEA Schedule-I Bulk Manufacturer registration to cultivate plants for this purpose. However, in 2016 DEA announced a **new interpretation** of the Single Convention to allow other growers to cultivate marijuana to supply researchers. As of July 2017, UM is unaware of any growers who have been approved under this new program.

DEA has accepted applications from other suppliers, but has not yet approved any.

https://pharmacy.olemiss.edu/marijuana/

Possible Source for Other Controlled Substances

NIH National Institute on Drug Abuse



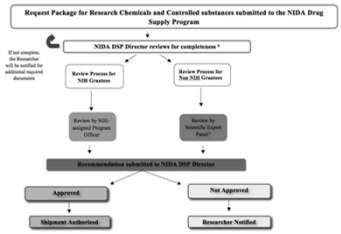
RESEARCH RESOURCES

DRUG SUPPLY PROGRAM CATALOG

- Yes, there is a Catalog, but you need permission to look at the marijuana page.
- Available for grantees and non-grantees.
- Must have IND and DEA registration to order.

https://www.drugabuse.gov/sites/default/files/indocat24thedmarch2015.pdf

NIDA Review Process



https://www.drugabuse.gov/ordering-guidelines-research-chemicals-controlled-substances

Human Subjects Considerations

- IRB approval must be obtained before DEA approval can be obtained for a Schedule-I drug study.
- Certificates of Confidentiality
  - Available for non-federally funded studies
- Medical care for emergencies
  - Who will be on hand?
  - Transportation to hospital if needed
  - Subjects going to emergency room on their own

Human Subjects Considerations

- Informed consent issue
  - Risks:
    - Failing drug tests
    - How to quantify health risks?
    - Payment for subject injury
- Where/how will subjects be recruited?
  - Will students be recruited? What age?
  - Will school administrators be informed?
  - Communication plan is vital!
    - "Mom, guess what I did at school this past semester!"

Step 2: Get Your Registrations in Order

- Determine if your state requires registration with state authorities. Consult counsel and/or the compliance office on what needs to be done.
- State registration typically requires full protocol to be submitted for Schedule I study.
- State regulators will typically perform inspection of site, including security, procurement, record-keeping and disposal.
- Process may take several weeks/months.
  - PLAN AHEAD!!!!!

DEA Registration

- Principal Investigator must apply for DEA Registration using DEA Form 225 (Researcher).
  - Practitioner Registration is not enough for Schedule I Studies.
- Requires submission of IND, LOA, IRB approval and full protocol.
- DEA will inspect site.
- More than one research site?
  - Each site will require a separate registration and inspection.
  - Drugs may only be delivered to site listed on registration.

Step 3: Prepare for your Inspections – Security

- Security – Personnel
  - Criminal background checks
  - Signed certification of no felony conviction, drug use. [21 CFR 1301.90]
  - Access log.
- Security – Physical
  - Drug Safe or Locked Cabinet securely fastened to wall or floor or weigh more than 750 lbs.
  - Key or combination lock. Forced entry must be easily detectable.
  - Located in locked room accessible only by research personnel.
  - Located where drug will be dispensed.
  - Schedule I and II drugs must be kept separately from other higher scheduled drugs.

Prepare for Inspections – Records

- Paperwork re. ordering
  - Electronic – DEA CSOS system
  - DEA 222 Forms for Schedule I & II Substances
  - Order Receipt Log
  - DEA Power of Attorney Form for ordering
- Inventory
  - Initial inventory
  - Biennial inventory
- Current Use and Disposition Log
- Discrepancy Report Form
- Separate records should be kept for Schedule I-II drugs and Schedule III – V drugs.

Pitfalls to Avoid

Take Inspections Seriously!

- Have your paperwork in order.
- Do not argue with the DEA inspector.
- Do not have controlled substances in your safe before the inspection.
- Be prepared for post-registration visits
- You might think these things are obvious …

Co-Investigators

- Investigator is the person authorized to dispense.
- Will there be a co-investigator?
  - Check with DEA and State regulatory authorities as to whether co-investigator must also have a registration.
  - Remember to have a DEA Power of Attorney if Co-investigator will be ordering study drug.

Drug Accountabiltiy

- Monitoring processes for detecting loss and diversion
- Any theft must be reported to DEA, state authorities and police.
  - DEA Form 106
- Loss of significant amount must be reported.

Disposal of Left Over Controlled Substance

- Return to sponsor
- Reverse distribution
- What happens if the investigator retires or moves to another site?

Forms & References

- See link below for sample DEA forms.
  - http://compliance.emory.edu/controlled-substances/forms.html
- Other references
  - https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research
  - https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program
  - https://www.drugabuse.gov/nida-drug-supply-program-dsp-ordering-guidelines

Questions?

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