Applied Cannabis Research within VA: An Overview & Successful Example

Clinical Science Research & Development Service

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Introduction

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Overview of Webinar

• Office of Research & Development and Cannabis Research
• Mechanisms of Support
• Design Considerations
• Procedures
• Q&A
Veterans and Cannabis
1. **YES, it’s allowed!** Under the Controlled Substance Act, research with cannabis is permissible with regulatory approvals.

2. Currently funded by VA Office of ORD:
   - Clinicaltrials.gov Registration# NCT03518801
Mechanisms of Support

1. VA CSR&D Merit
2. VA PTSD Psychopharmacology Initiative
1. **Aims**
   - Determine how Veterans currently use cannabis
     - Does it help or hurt?
   - Develop cannabinoid-based pharmacotherapy

2. **Study Drug**
   - Whole plant cannabis versus single molecule formulation
   - Plant-derived versus synthetic

3. **Formulation**
   - Method of administration
     - Oral, sublingual, smoked/vaporized, topical
An Example: CBD-PE Study

- **Design:** Prospective, randomized controlled investigation testing CBD as adjunctive pharmacotherapy
- **Methods:**
  - N = 136 military veterans
  - 16 weeks drug or placebo
    - dose: 600mg CBD daily, oral
    - 12 sessions PE therapy
Sources of Drug

1. NIDA Drug Supply
2. Traditional Drug Development Process
3. FDA-approved Medications
NIDA Drug Supply Program

Bulk Marijuana

Bulk marijuana is currently available in the following general categories, and due to recent interest its strength is being provided for both THC and CBD as Low (<1%), Medium (1-5%), High (5-10%), and Very High (>10%). Bulk marijuana has small amounts of other cannabinoids (CBC, CBG, CBN, and THCV) which are reported in the batch specific details.

- **Placebo marijuana (produced by solvent extraction)**
  - THC (0%) / CBD (0%)

- **Low THC varieties**
  - Low THC (<1%) / Medium CBD (1-5%)
  - Low THC (<1%) / High CBD (5-10%)
  - Low THC (<1%) / Very High CBD (>10%)

- **Medium THC varieties**
  - Medium THC (1-5%) / Low CBD (<1%)
  - Medium THC (1-5%) / Medium CBD (1-5%)
  - Medium THC (1-5%) / High CBD (5-10%)
  - Medium THC (1-5%) / Very High CB(>10%)

- **High THC varieties**
  - High THC (5-10%) / Low CBD (<1%)
  - High THC (5-10%) / High CBD (5-10%)
  - High THC (5-10%) / Very High CB (>10%)

- **Very high THC varieties**
  - Very High THC (>10%) / Low CBD (<1%)

Marijuana cigarettes

The following represents the existing stocks of manufactured marijuana cigarettes, which will be made available to the research community until depleted. Please note that NIDA does not plan to manufacture marijuana cigarettes in the near future. Only bulk marijuana will generally be available for research.

**Table 1 - Marijuana Cigarettes (RTI)**

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>THC</th>
<th>CBD</th>
<th>%THC</th>
<th>%CBD</th>
<th>%CBC</th>
<th>%CBG</th>
<th>%CBN</th>
<th>%THCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>12792-1208-77</td>
<td>Medium</td>
<td>Low</td>
<td>2.000</td>
<td>0.020</td>
<td>N/A</td>
<td>N/A</td>
<td>0.470</td>
<td>N/A</td>
</tr>
<tr>
<td>10074-0301-97</td>
<td>Medium</td>
<td>Low</td>
<td>2.800</td>
<td>0.080</td>
<td>N/A</td>
<td>N/A</td>
<td>0.220</td>
<td>N/A</td>
</tr>
<tr>
<td>12792-0109-120</td>
<td>Medium</td>
<td>ND</td>
<td>3.600</td>
<td>ND</td>
<td>N/A</td>
<td>N/A</td>
<td>0.270</td>
<td>N/A</td>
</tr>
<tr>
<td>12792-0109-146</td>
<td>High</td>
<td>ND</td>
<td>5.600</td>
<td>ND</td>
<td>N/A</td>
<td>N/A</td>
<td>0.400</td>
<td>N/A</td>
</tr>
<tr>
<td>10604-0203-95</td>
<td>High</td>
<td>ND</td>
<td>6.700</td>
<td>ND</td>
<td>N/A</td>
<td>N/A</td>
<td>0.490</td>
<td>N/A</td>
</tr>
<tr>
<td>12944-0509-105</td>
<td>Placebo</td>
<td>Placebo</td>
<td>0.002</td>
<td>0.001</td>
<td>N/A</td>
<td>N/A</td>
<td>0.004</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Legend - Low = <1%; Medium = 1-5%; High =5-10%; ND = Not detected, N/A = Not available
Note: %THC contents may vary with time and storage conditions. Therefore researchers should inquire about latest THC strength before submitting their request.

NIDA Drug Supply Program Director, Dr Rik Kline at rkline@nida.nih.gov
Traditional Drug Development Process

Developing a new medicine takes an average of 10-15 years.

- **Drug Discovery**: 5,000 – 10,000 compounds
- **Preclinical**: 250
- **Clinical Trials**: 5
  - Phase 1: 20 - 100
  - Phase 2: 100 - 500
  - Phase 3: 1,000 - 5,000
- **FDA Review**: 6 - 7 years
- **Scale-Up to Manufacturing**: 0.5 - 2 years
- **Post-Marketing Monitoring and Research**: Indefinite

**Pre-Discovery**

3 - 6 years
Traditional Drug Development Process

• Must have sufficient data in Drug Master File (DMF) for FDA to approve Investigational New Drug (IND)
  – In-vivo
  – Preclinical
  – Safety & Dosing

• Company/Manufacturer must have DEA Schedule-1 license to manufacture and transport
FDA Approved Cannabinoids

• Epidiolex – botanically derived CBD extract
• Marinol & syndros (dronabinol) – synthetic functional analogue of THC
• Cesamet (nabilone) – synthetic functional analogue of THC
Other Options?
Process of Approval ~ 6-12 mo.

1. State DOJ/DEA
   - Site Inspection
   - DEA Local
     - DEA HQ
       - DEA HQ Approves
         - Begin Study

2. Local IRB
   - IND
   - FDA
     - Provides DMF

3. NIDA or other source

4. Begin Study
Process of Approval ~ 6-12 mo.

1. State DOJ/DEA
2. Local IRB
3. NIDA or other source

- 4. Provides DMF

- 5. DEA Local
- 6. DEA HQ

- Site Inspection
- DEA HQ Approves
- Begin Study

FDA
IND
Research Advisory Panel

California law, pursuant to Health & Safety Code Sections 511480 & 511481, requires proposed research projects using certain opioid, stimulant, and hallucinogenic drugs classified as Schedule I and Schedule II Controlled Substances as their main study drugs, to be reviewed and authorized by the Research Advisory Panel of California in the Attorney General’s Office. See the Guidelines page for specific criteria.

The Research Advisory Panel primarily seeks to ensure the safety and protection of participating human research subjects and adequate security of the controlled substances used in the study. The Panel Members evaluate the scientific validity of each proposed project, and may reject proposals where the research is poorly conceived, would produce conclusions of little scientific value, or would not justify the exposure of California subjects to the risk of research.

During 2018 the Panel reviewed forty-four research study submissions. Thirty-nine were approved by the Panel. Among the approved studies, twenty-four studies were Academic research studies, fifteen studies were Multi-Center Clinical Drug Trial research studies.

At the end of 2018 the Panel was monitoring one hundred and twenty research projects.

In California, there is not a separate controlled substance license requirement. When the researchers
Process of Approval ~ 6-12 mo.

1. State DOJ/DEA

2. Local IRB

3. NIDA or other source

4. Provides DMF

5. DEA HQ

Notice of Funding

DEA HQ Approves

Begin Study

Site Inspection

DEA Local

FDA

IND
INSTRUCTIONS

This form is for new applicants. Any person who does not currently possess a DEA registration to conduct business with controlled substances in the following categories may access the application form. The categories of applicant who can apply using this form are manufacturers, distributors, researchers, canine handlers, analytical laboratories, importers, and exporters.

Complete DEA Form 225 Online (If possible, you are encouraged to use the online forms system to apply for your registration.)

Download DEA Form 225 (PDF) to apply via U.S. Postal Service.

Before you enter the form, you may wish to print the instruction pages (recommended) which will assist in completing the form. After completing the form, print, sign and mail to DEA.

INSTRUCTIONS

SECTION 1. APPLICANT IDENTIFICATION
Process of Approval ~ 6-12 mo.

1. State DOJ/DEA
2. Local IRB
3. NIDA or other source
4. FDA

- IND

3. DEA HQ
4. Provides DMF
5. Site Inspection

- DEA HQ Approves
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Process of Approval ~ 6-12 mo.

1. State DOJ/DEA
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5. DEA Local
6. Site Inspection
7. DEA HQ
8. DEA HQ Approves
9. Begin Study
10. Provides DMF

Notice of Funding
Questions?
Contact for Research Questions from this Webinar

Please email questions to:

VHABLRD-CSRD@va.gov
Additional Resources

• DMF List & Search:
  https://www.pharmacompass.com/us-drug-master-files-dmfs
  https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/drugmasterfilesdmfs/default.htm

• NIDA Drug Supply Program:
  https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program

• FDA IND Application Information:
  https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsarededevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

• DEA Schedule 1 Registration:
Acknowledgements

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  – National Center for PTSD (NCPTSD) Executive Division