FDA Public Hearing: Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds

Larry A. Walker, Director Emeritus
National Center for Natural Products Research

THE UNIVERSITY OF MISSISSIPPI
National Center for Natural Products Research

National Center for Natural Products Research
University of Mississippi

- **FDA/CFSAN CoE for Botanical Ingredients Research**
  [Ikhlas Khan, UM/NCNPR]
- **Cannabis/cannabinoids contractor for NIDA Drug Supply Program**
  [Mahmoud ElSohly, UM/NCNPR]
- **Partner in the Botanical Adulterants Prevention Program of American Botanical Council [Ikhlas Khan, UM/NCNPR]**
- **Current "Expanded Access" IND for CBD Extract Oral Solution in refractory childhood epilepsy [Brad Ingram, UMMC]**

THE UNIVERSITY OF MISSISSIPPI
National Center for Natural Products Research

Potential safety issues – Cannabis

- Risks in NASEM Assessment 2017: primarily THC and smoking related?
- Product authenticity/quality issues
- Potential CBD safety issues

CBD Content vs. Product Label Claim

Product	CBD Label Claim	Total CBD	% Label Claim	THC > 0.3%	Synthet. Cannab.
1	350 mg	417 mg	119%		
2	300 mg	0.2 mg	0.1%		
3	No claim	10 mg	???		
4	500 mg	521 mg	104%	+++	
5	4-5 mg	---	0%	+++ only THC	

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

molecules

MDPI

Article

Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model

Laura E. Ewing [1,2], Charles M. Skinner [1,3], Charles M. Quick [4], Stefanie Kennon-McGill [1], Mitchell R. McGill [1,2,3], Larry A. Walker [5,6], Mahmoud A. ElSohly [5,6,7], Bill J. Gurley [3,8] and Igor Koturbash [1,3,*]

CrossMark

Marijuana's Effects on Brain Structure and Function: What Do We Know and What Should We Do? A Brief Review and Commentary

Richard D. deShazo, MD, MACP,[a,b,e] Sara B. Parker, BA,[a] Daniel Williams, PhD,[c] John B. Ingram, MD,[b,d] Mahmoud Elsohly, PhD,[f] Kathryn Rodenmeyer, BA,[e] Kyle McCullouch, BBA[a]

[a]*Department of Medicine, University of Mississippi Medical Center, Jackson;* [b]*Department of Pediatrics, University of Mississippi Medical Center, Jackson;* [c]*Department of Psychiatry, University of Mississippi Medical Center, Jackson;* [d]*Department of Neurology, University of Mississippi Medical Center, Jackson;* [e]*Mississippi Public Broadcasting, Jackson;* [f]*The National Center for Natural Products Research, University of Mississippi, Oxford.*

Mississippi Program
CBD Extract Oral Solution in Childhood Epilepsy

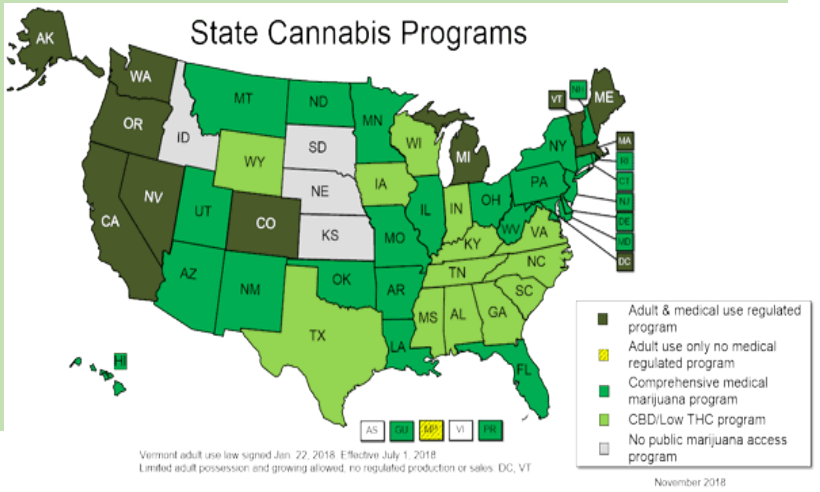
Harper Grace's Law
Mississippi Code § 41-29-136 (2017)
Expires July 1, 2021

Purpose:
- Needs of patients with refractory childhood epilepsy
  - Evaluate tolerability under guidance of UMMC physicians
  - Protect patient/family wrt state/federal Controlled Substance laws

Allows
- **CBD Extract** provided by NCNPR

- Only UMMC Pharmacy can dispense **CBD Solution** to patients
  - CBD/THC Ratio ≥ 20:1
  - CBD ≥ 50 mg/mL (5%)
  - THC ≤ 2.5 mg/mL (0.25%)

Does NOT Allow:
- CBD ⇨ non-DEA C-I registrant
- Sale of any CBD products



"Restricted THC" program, similar to 12 other states, but difficulty in implementation b/c of DEA restrictions

UM Program –
- **Small 'expanded access' IND**
- **Primary endpoint: tolerability**
- **Secondary endpoints: seizure control, QoL, drug interactions**

At 6 mo. all 10 pts enrolled continue in program
- **Low doses (2 increasing to avg 6 mg/kg/d)**
- **Most have reductions in seizure frequency**
- **Generally well tolerated, but some side effects**
- **Drowsiness, agitation, GI upset, skin rash**
- **Several patients w/ mild infections fall/winter**
- **Very mild elevations in liver enzymes**
- **Elevation in clobazam metabolite**
- **Increased perampanel toxicity**

Cannabis/Hemp/CBD Products – Possible Regulatory Approach

1. **GRAS – existing now for a few 'cannabinoid-free' hemp products**
   - Food ingredients fiber-type hemp, from certified seed

2. **Strict limits for CBD, hemp- derived supplements**
   - Derived from "Farm Bill" certified seed, THC-free, restricted CBD
   - GMPs; AE surveillance; SF claims only; adult only, limited dose
   - Special attention warranted, as for performance enhancer, weight loss, sexual enhancer products
   - Consider conditional registration for manufacturers participating in rigorous safety/quality stewardship programs?

Cannabis/Hemp/CBD Products – Possible Regulatory Approach

3. **Cannabis-derived botanical or "single chemical entity" drugs**
   - Developed under appropriate INDs, with adequate CMC package, trial design, etc.
   - With relaxed DEA restrictions on sourcing extracts for legitimate research programs

4. **What about state medical marijuana programs?**
   - Assuming these will continue in varied forms…
   - Need professional and coordinated national system for gathering identity, quality and safety surveillance data

Important National Needs/Recommendations:

1. Clinical research on controlled quality, well-defined Cannabis-derived products [whether CSA or not]
2. Necessitates relaxed DEA restrictions on producing Cannabis by appropriately licensed entities for legitimate clinical research
3. FDA-sponsored research – basic clinical safety and pharmacokinetic studies on representative products
4. Extend animal work to establish NOAEL on representative products
5. National testing program for cannabinoid quality and standardization methods for extracts and finished products [FDA, NIST?]
6. National AE reporting system for allowed CBD supplement products
7. Rapid response program for products involved in serious incidents
8. Research on safety outcomes in state medical Cannabis programs