National Center for Natural Products Research

Research Institute of Pharmaceutical Sciences
School of Pharmacy, The University of Mississippi

Hemp Cultivation Task Force Meeting

July 8, 2019

Larry Walker, Director Emeritus, NCNPR

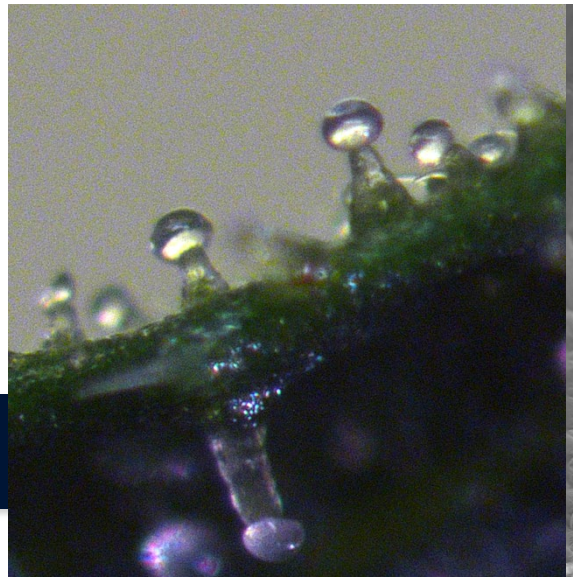
1. *Univ. of Mississippi Cannabis Research Program*
2. *NIDA Drug Supply Contract*
3. *Harper Grace's Law and the UMMC epilepsy trial*
4. *Farm Bill 2018 - impact on UM program*
5. *FDA regulation of CBD supplements – impact on markets*

THE UNIVERSITY OF MISSISSIPPI
National Center for Natural Products Research

University of Mississippi's NIDA Cannabis Project
Mahmoud ElSohly, PhD

- **50 years as sole contractor for Cannabis production for NIDA**
- **Competitively bid contract, recompeted every 5 yrs**
- **Contract executed according to detailed specifications by NIDA**
- **Develop and maintain genetic stocks of cultivars of varied cannabinoid profiles (14)**
- **Grow, harvest, and process cannabis plant material to produce standardized marijuana of different potencies for research**
- **Isolate and characterize different cannabis components for pharmacological studies**
- **Prepare bulk quantities of extracts and specific purified cannabinoids (for example, THC, CBD, CBN, CBC, and CBG)**
- **GMP preparation of materials for clinical trials**
- **Analysis of confiscated Cannabis materials**
- **All of this under Schedule I DEA registrations**
- **Only as directed by NIDA– for National Drug Supply Program**

NIDA Cannabis Contract



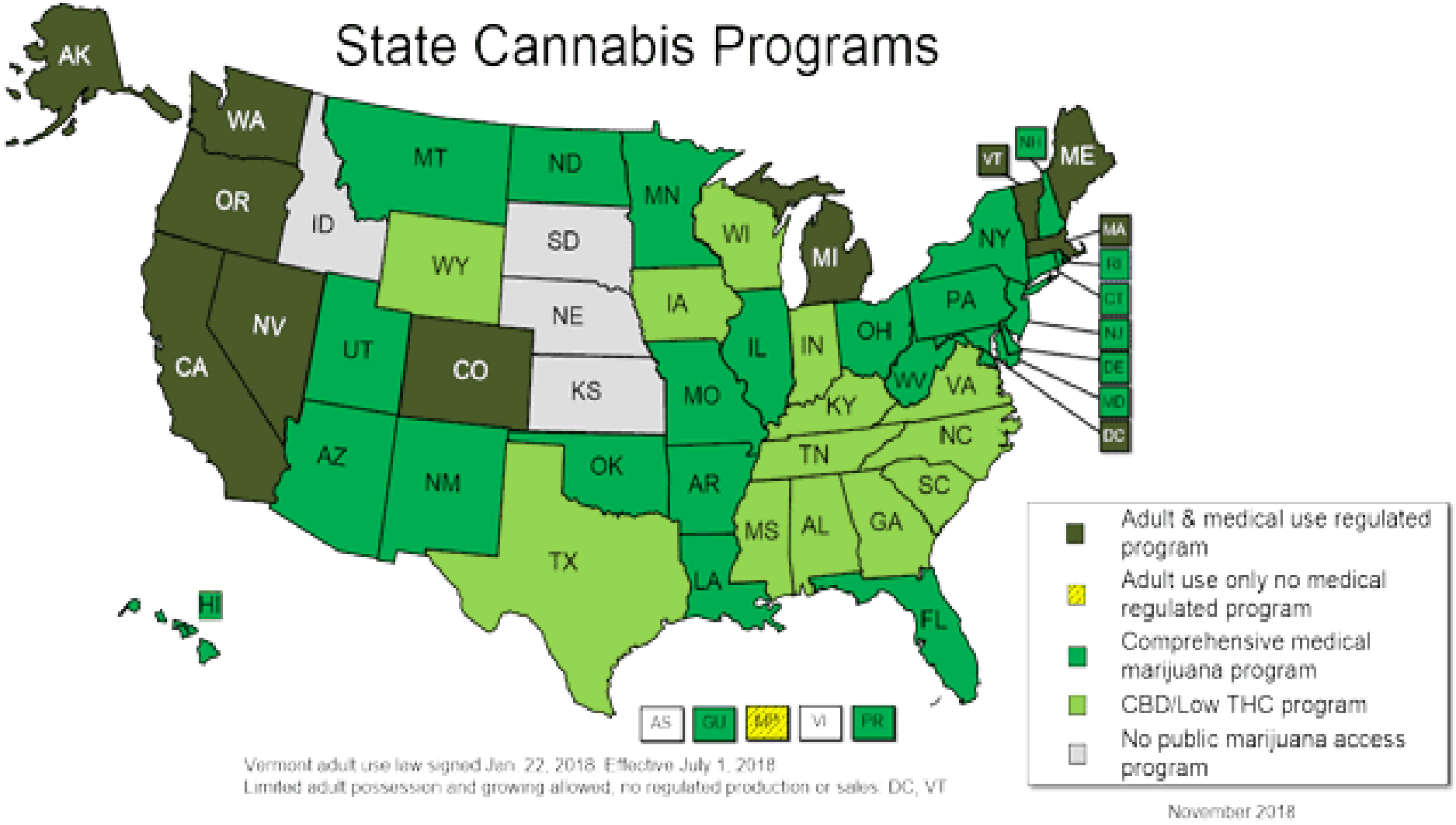
Constituents of *Cannabis sativa* L.

Chemical Class	
Δ^9-THC type	18
Δ^8-THC type	2
CBG type	17
CBC type	9
CBD type	7
CBND type	2
CBE type	5
CBL type	3
CBN type	10
CBT type	9
Misc type	23
Total Cannabinoids	**105**
Total non-cannabinoids	**441**
Total	**546**

Cannabinoid Analysis –
GC, GC/MS, LC/MS

Non-normalized Cannabinoid Averages of Illicit Cannabis Samples by Year Seized from January 1, 1994 to December 31, 2004

		# of seizures	% Delta-9 THC	% CBD	% CBC	% CBN
Year	1994	3282	3.48	.34	.21	.20
	1995	4759	3.75	.31	.20	.31
	1996	2435	4.07	.42	.23	.23
	1997	2454	4.53	.40	.25	.20
	1998	2263	4.43	.41	.22	.23
	1999	2655	4.55	.43	.21	.38
	2000	3117	4.86	.45	.21	.34
	2001	2693	5.31	.47	.23	.28
	2002	2389	6.35	.42	.24	.22
	2003	2475	6.29	.45	.24	.23
	2004	1362	7.08	.47	.24	.22
Total		29884	4.76	.40	.22	.27


State Cannabis Programs
AK
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
DC
HI
AS
GU
MP
VI
PR
Adult & medical use regulated program
Adult use only no medical regulated program
Comprehensive medical marijuana program
CBD/Low THC program
No public marijuana access program
Vermont adult use law signed Jan. 22, 2018. Effective July 1, 2018
Limited adult possession and growing allowed, no regulated production or sales. DC, VT
November 2018

NCSL.com

Harper Grace's Law

Mississippi Code § 41-29-136 (2017)

Expires July 1, 2021

Purpose:

- Needs of young patients with epilepsy
  - Evaluate safety under guidance of UMMC physicians
  - *Possibly* expand to statewide treatments
    - Protects patients from state/federal Controlled Substance laws

Other states enacted similar laws, but only MS has capability to carry out study!

Allows:

•Clinical studies by physicians at UMMC

•**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

GMP Production of Cannabis Extract

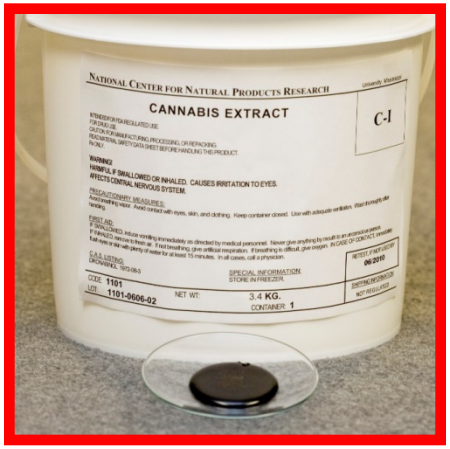
Clones of Mother Plants

Cultivation

Processed Plant Material "Intermediate Product"

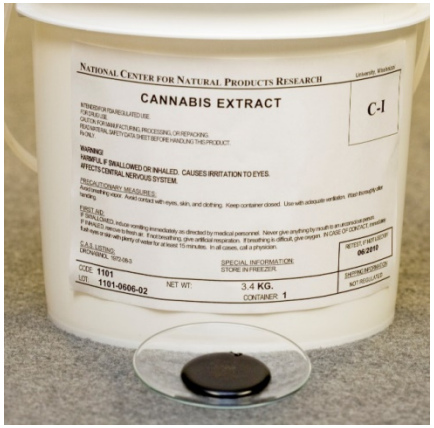
Solvent Extraction

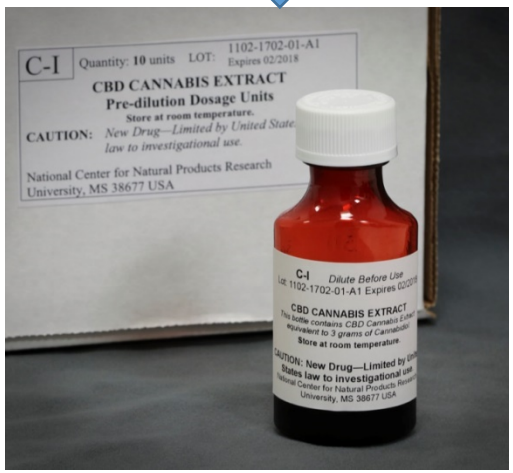
Package & Label



Finished Product

Preparation of CBD Solution
at UMMC Pharmacy





“Prepare” = Formulate for Patients

Dissolve Extract in Sesame Seed Oil

Extract ⇨ Solution

Trial design

- 10 patients
  - Medically refractory epilepsy
  - Nonverbal, Nonambulatory
  - 5-19 years of age
  - "Compassionate use"

  - Primary endpoint is tolerability
  - Secondary endpoints
    - Seizure control efficacy
    - QOL information from the familes
    - Drug/Drug interactions

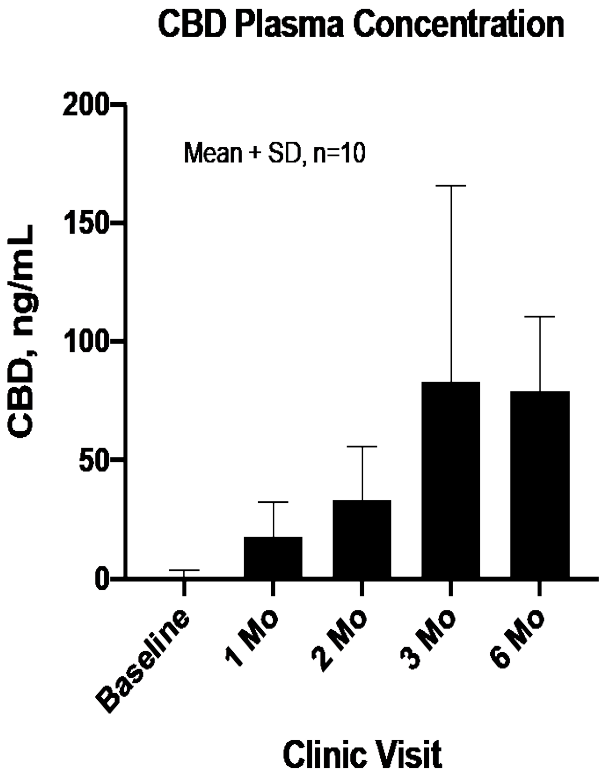
- 6 visits
  - Escalating dose visit 1,2,3. 3 month extension if family feels there is a reason to continue
  - Labs at each visit. CBC, CMP (that liver is a booger), AED levels, CBD/THC
    - Pregnancy test at first visit
  - EEG at onset, 3, 6 months
  - Seizure Calendar
  - QOE questionaire

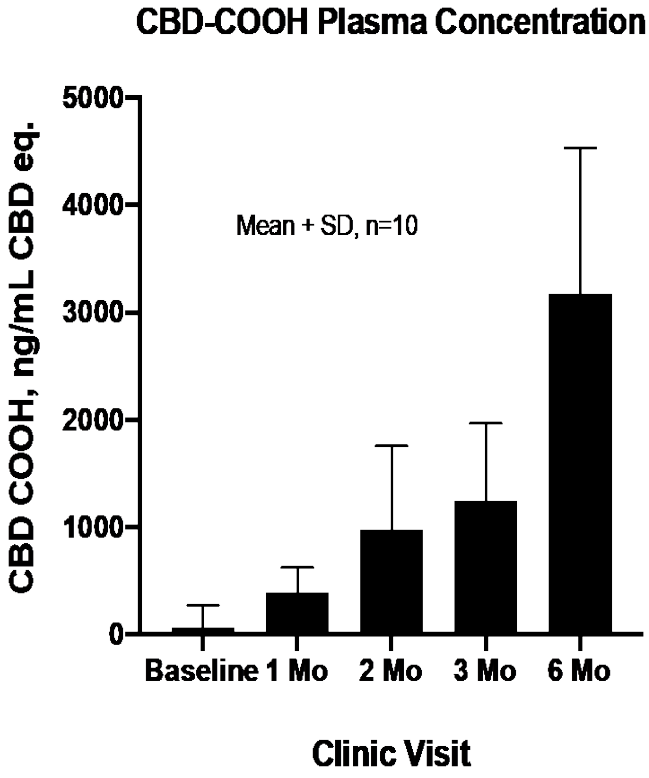
Status of Trial

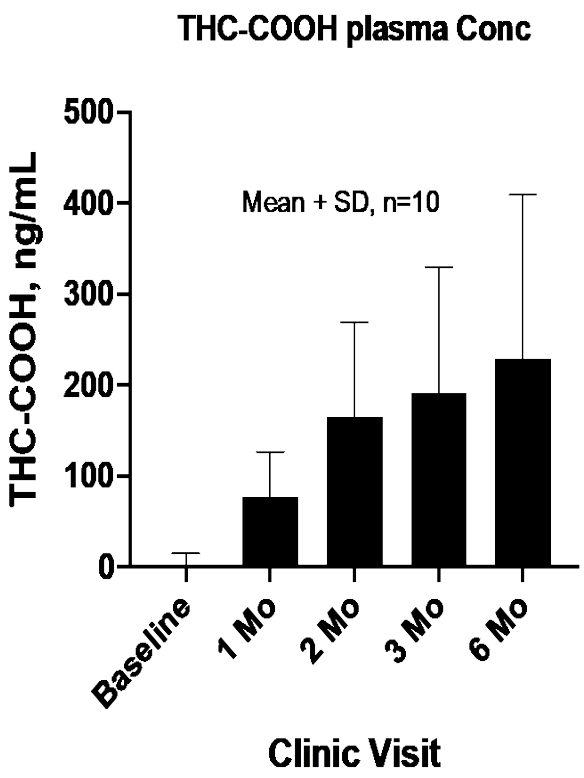
- All 10 patients still enrolled; families desire to continue
- Seizure frequency improvement in most subjects
- No severe adverse effects observed, but some side effects such as sedation in a few patients
- Interactions with other anti-epileptic drugs

- FDA approval for 1 yr extension of trial
- Dr. ElSohly secured NIDA permission secured to use additional extract for this

- Possibly add 10 or more this summer…


CBD Plasma Concentration
CBD, ng/mL
200
150
100
50
0
Mean + SD, n=10
Baseline
1 Mo
2 Mo
3 Mo
6 Mo
Clinic Visit


CBD-COOH Plasma Concentration
CBD COOH, ng/mL CBD eq.
5000
4000
3000
2000
1000
0
Mean + SD, n=10
Baseline 1 Mo
2 Mo
3 Mo
6 Mo
Clinic Visit


THC-COOH plasma Conc
THC-COOH, ng/mL
500
400
300
200
100
0
Mean + SD, n=10
Baseline
1 Mo
2 Mo
3 Mo
6 Mo
Clinic Visit

Farm Bill 2018
Amendments to The Agricultural Marketing Act of 1946
17 USC 1621

The term 'hemp' means the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.

State, Tribal, or USDA plan required. State plan to include:

- Designated areas
- THC level testing
- Disposal of plants >0.3% THC
- Annual inspections
- Licensed producers

Farm Bill 2018
Amendments to Controlled Substance Act

21 USC 802 *(Definition of Marihuana)*

(16)(A) Subject to subparagraph (B), the term "marihuana" means all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.

(B) The term 'marihuana' does not include:

– (i) hemp, as defined in section 297A of the Agricultural Marketing Act of 1946; or

– (ii) …

21 USC 812 *(List of Schedule-1 Controlled Substances)*

(c)(17) Tetrahydrocannabinols, except for tetrahydrocannabinols in hemp (as defined under section 297A of the Agricultural Marketing Act of 1946).

Federal Law

Food & Drugs

U.S. FOOD & DRUG ADMINISTRATION

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FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds

12. Can products that contain THC or cannabidiol (CBD) be sold as dietary supplements?

A. No. Based on available evidence, FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under sections 201(ff)(3)(B)(i) and (ii) of the FD&C Act, respectively. Under those provisions, if a substance (such as THC or CBD) is an active ingredient in a drug product that has been approved under 21 U.S.C. § 355 (section 505 of the FD&C Act), or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are outside the definition of a dietary supplement. FDA considers a substance to be "authorized for investigation as a new drug" if it is the subject of an Investigational New Drug application (IND) that has gone into effect. Under FDA's regulations (21 CFR 312.2), unless a clinical investigation meets the limited criteria in that regulation, an IND is required for all clinical investigations of products that are subject to section 505 of the FD&C Act.

HEALTH AND SCIENCE

FDA sets first hearing on CBD in May as the agency looks at legalizing the cannabis compound in food and drinks

PUBLISHED TUE, APR 2 2019 • 8:53 AM EDT | UPDATED TUE, APR 2 2019 • 6:52 PM EDT

CNBC

13. Is it legal, in interstate commerce, to sell a food to which THC or CBD has been added?

A. No. Under section 301(ll) of the FD&C Act, it is prohibited to introduce or deliver for introduction into interstate commerce any food (including any animal food or feed) to which has been added a substance which is an active ingredient in a drug product that has been approved under 21 U.S.C. § 355 (section 505 of the Act) or a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public. There are exceptions, including when the drug was marketed in food before the drug was approved or before the substantial clinical investigations involving the drug had been instituted or, in the case of animal feed, that the drug is a new animal drug approved for use in feed and used according to the approved labeling. However, based on available evidence, FDA has concluded that none of these is the case for THC or CBD. FDA has therefore concluded that it is a prohibited act to introduce or deliver for introduction into interstate commerce any food (including any animal food or feed) to which THC or CBD has been added. FDA is not aware of any evidence that would call into question these conclusions. Interested parties may present the agency with any evidence that they think has bearing on this issue. Our continuing review of information that has been submitted thus far has not called our conclusions into question.

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	1%		
3	No claim	10 mg	???		
4	500 mg	521 mg	104%	+++ (0.35%)	
5	4-5 mg	---	0%	+++ (45%) only THC	
6	75 mg	22 mg	30%		
7	200 mg	44 mg	22%		
8	50 mg	114 mg	2280%	+++ (0.6%)	
9	No claim	134 mg	???		
10	25 mg	42 mg	168%		
11	No claim	0.02 mg	???		4-F-MDMB-Butinaca
12	100 mg	40 mg	40%		
13	500 mg	433	87%		

CBD Content vs. Product Label Claim

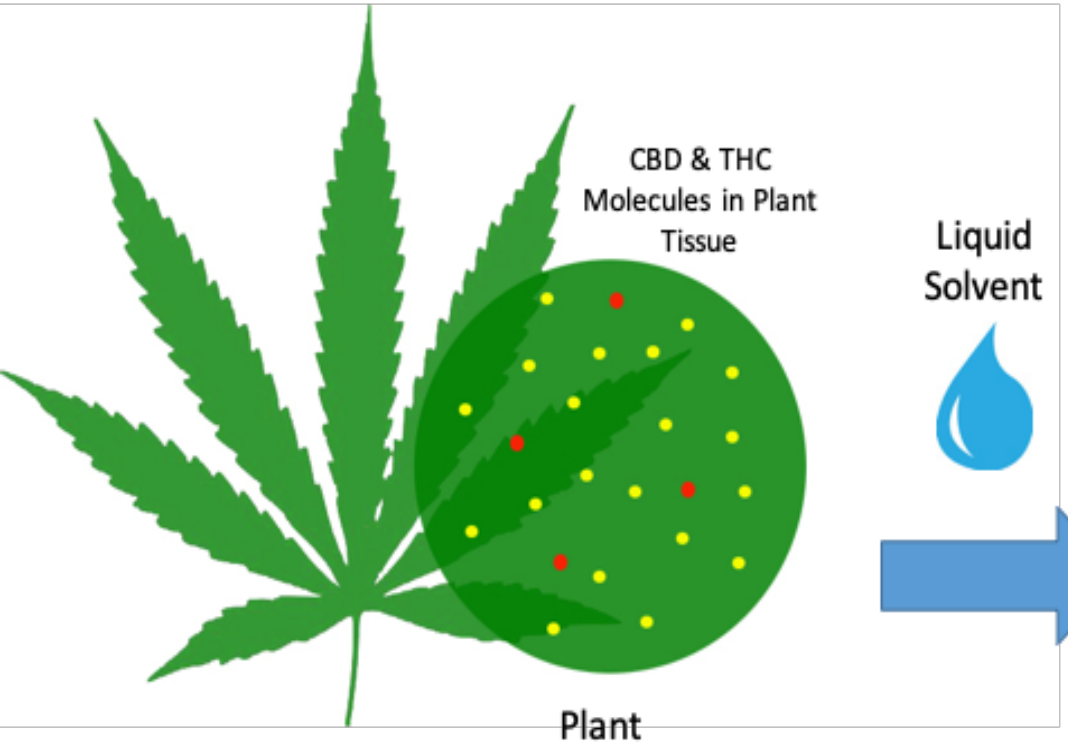
Product	CBD Label Claim	Total CBD	% Label Claim	Synthet. Cannab.
14	75 mg	45 mg	60%	
15	75 mg	19 mg	25%	
16	75 mg	10 mg	13%	
17	No claim	---	???	
18	25 mg	9 mg	32%	
19	100 mg	0.6 mg	0.006%	5-fluoro MDMB-PICA
20	500 mg	500 mg	100%	
21	200 mg	10 mg	0.05%	
22	No claim	10 mg	???	
23	No claim	17 mg/g	???	
24	No claim	---	???	5-fluoro-ADB
25	No claim	---	???	5-fluoro-ADB

FDA and CBD Supplements

Expecting some regulatory decision late summer

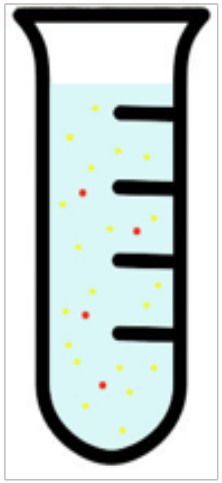
1. **Ignore current law and allow CBD in dietary supplements**
2. **Enforce current law/policy and prohibit CBD in supplements**
3. **Create some room for supplements with a limit on CBD**

Plant Extraction Process

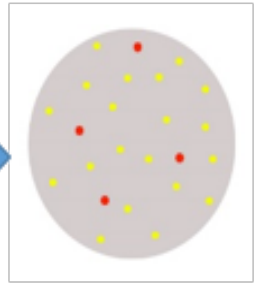


Plant
2% CBD
0.2% THC

Liquid
Solvent



Evaporate
Solvent



Cannabis Extract
20% CBD
2% THC

2019 Season

UM Hemp Production Pilot Program Plan

Farm Bill Requirement	UM Plan
Designated growing areas	**Field and Greenhouse** **(SEPARATE FROM NIDA FACILITIES)** GPS coordinates, acreage/dimensions, map, address
THC level testing	**Pre-Harvest & Post Harvest** Sampling/Testing Protocol
Disposal of plants >0.3% THC	1. THC test results report to MDAC 2. Failed THC test cause for destruction of plants on site with chipper/shredder followed by turning under 3. Destruction reports to MDAC
Inspections	1. Internal audits/reports by NCNPR QAU 2. Unannounced inspections by MDAC
Licensed producers approved by State	Annual Approval by MDAC for NCNPR pilot production only
Approved by USDA	Submit detailed plan and protocols to USDA

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