

The CBD Summit:

*A National Dialogue on Public
Safety, Research and Policy*

Wednesday, January 15, 2020

9:00am – 5:00pm

Hyatt Regency, Washington DC

#CBDPolicySummit



Introduction & Welcome

Monica Weldon

President and CEO

Bridge the Gap – SYNGAP Education and Research Foundation

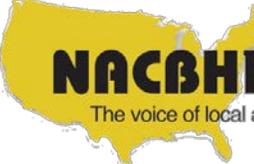
Summit Co-Hosts:  **AIMED ALLIANCE**

 **Council for Responsible Nutrition**
The Science Behind the Supplements®

 **LegitScript**

 **FDLI**
Food and Drug Law Institute

MENTAL HEALTH FIRST AID
NATIONAL COUNCIL
FOR BEHAVIORAL HEALTH

 **NACBHDD**
National Association of County Behavioral Health & Developmental Disability Directors
The voice of local authorities in the nation's capital

Healthy Minds. Strong Communities.
 **GREENWICH™**
BIOSCIENCES

#CBDPolicySummit

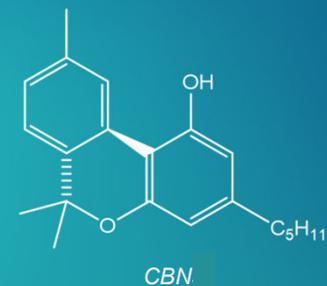
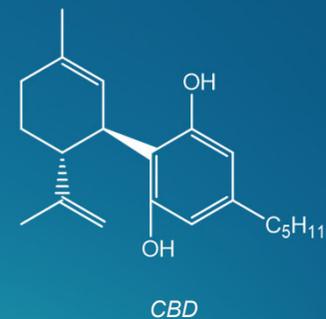
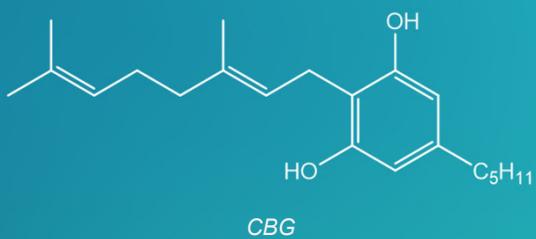
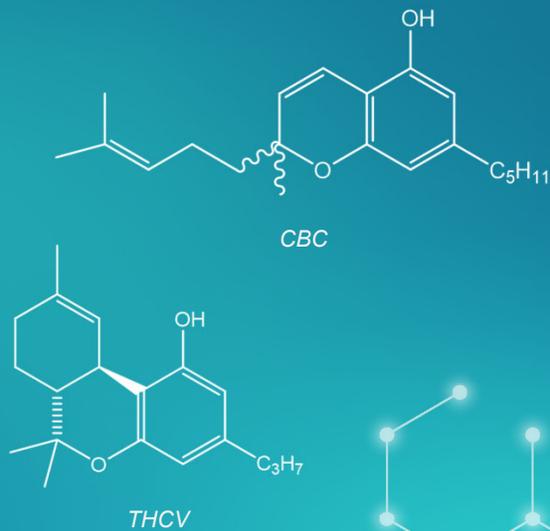
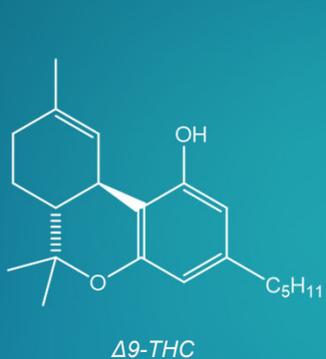
A large, dark blue ink splatter graphic is centered on a white background. The splatter has irregular, feathered edges and contains several smaller, lighter blue splatters and dots scattered around it.

GET SMART
Words Matter: Definitions to
Enable a Common Discussion

Jennifer Marlo-Triemstra, MS, PhD

Senior Manager, Cannabinoid Education

Greenwich Biosciences



Cannabinoid Science and Medicine

Dr. Jennifer L. Triemstra, MS, PhD

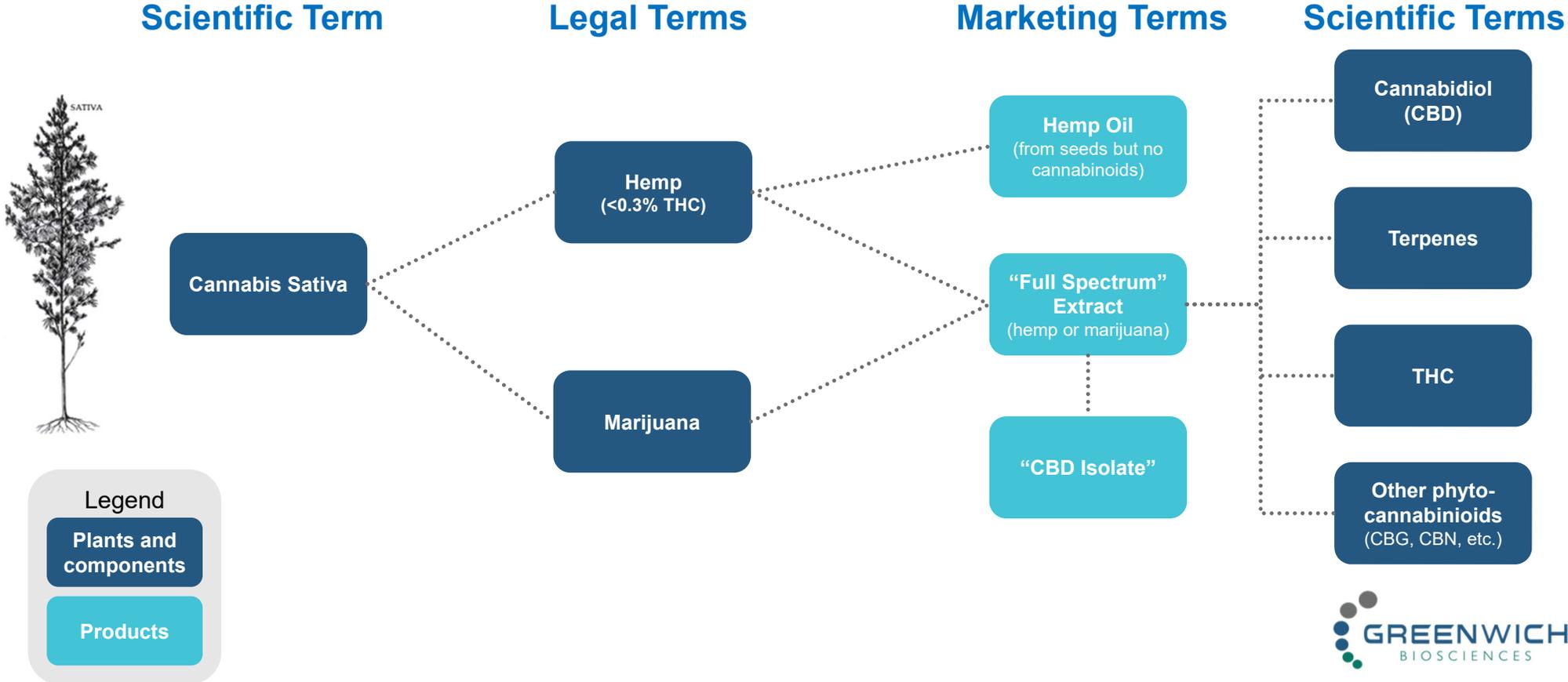


Disclaimer

- The accompanying slides are intended to be shown in their entirety.
- If you choose to use some or all of these slides in an independent presentation, then you must clearly communicate to your audience or reader that the presentation is independent, so that it is clear you are not presenting or writing on behalf of Greenwich Biosciences, and that any thoughts or opinions on might be included in your presentation are your own and may differ from those of Greenwich Biosciences.

Cannabis & Cannabinoids

Terminology



Cannabinoids Fall Into 3 Primary Classes^{1,2}



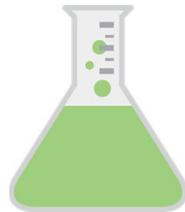
Phytocannabinoids

Plant-based compounds found in *Cannabis sativa L.* as well as other plants that may or may not function through the cannabinoids receptors



Endocannabinoids

Endogenous ligands to the cannabinoid receptors that have neuromodulatory effects in the body



Synthetic Cannabinoids

Compounds artificially synthesized to mimic the structure and/or function of endocannabinoids or phytocannabinoids

Cannabinoid Distribution in Cannabis Plant Varies¹



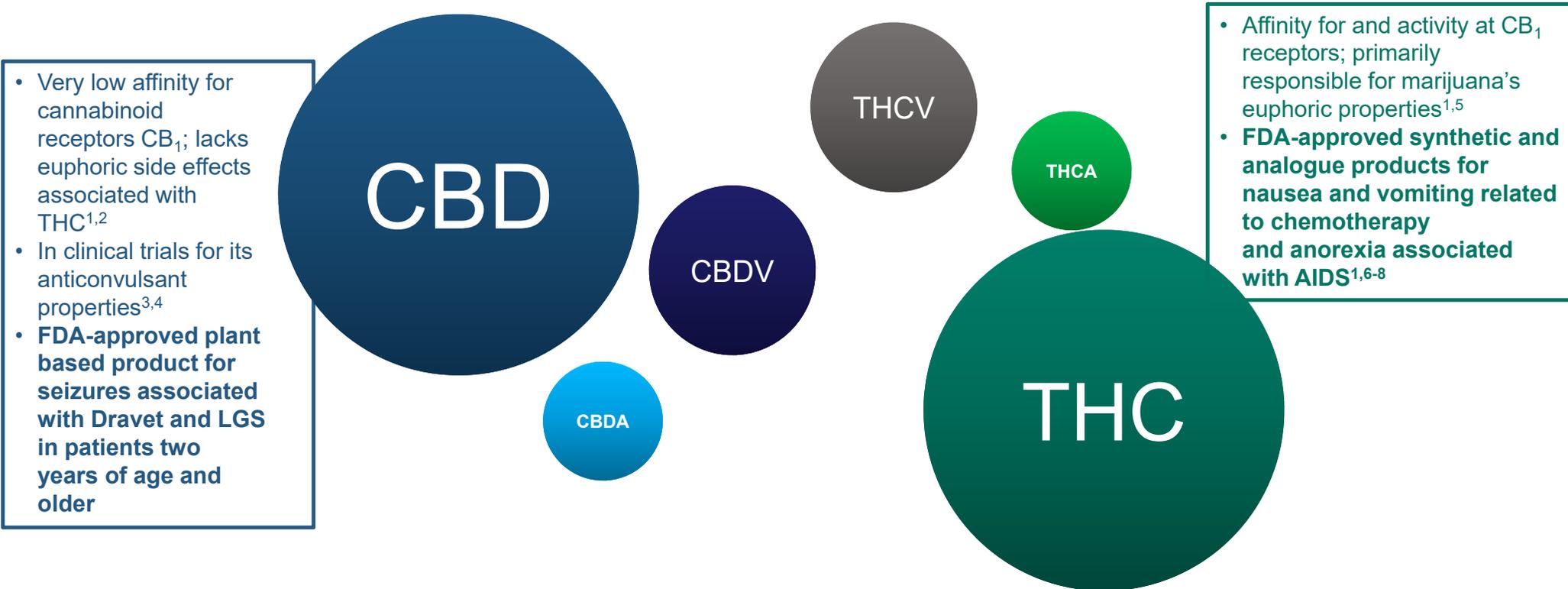
Cannabinoid Distribution in Cannabis ^{1,2}	
Seeds	0%
Roots	0%
Stems	≤0.3%
Lower leaves	<1%
Seeded Female Flowers "Buds"	6%
Unseeded Female Flowers "Buds"	15%
Male Inflorescence	<2%

Unseeded female flowers are the predominant source for extracting cannabinoids^{1,2}



1. Potter DJ. Cannabis horticulture. In: Pertwee RG, Ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:65-88.
 2. Small E et al. *Trends in new crops and new uses*. Alexandria, VA: ASHS Press; 2002: 284-326.

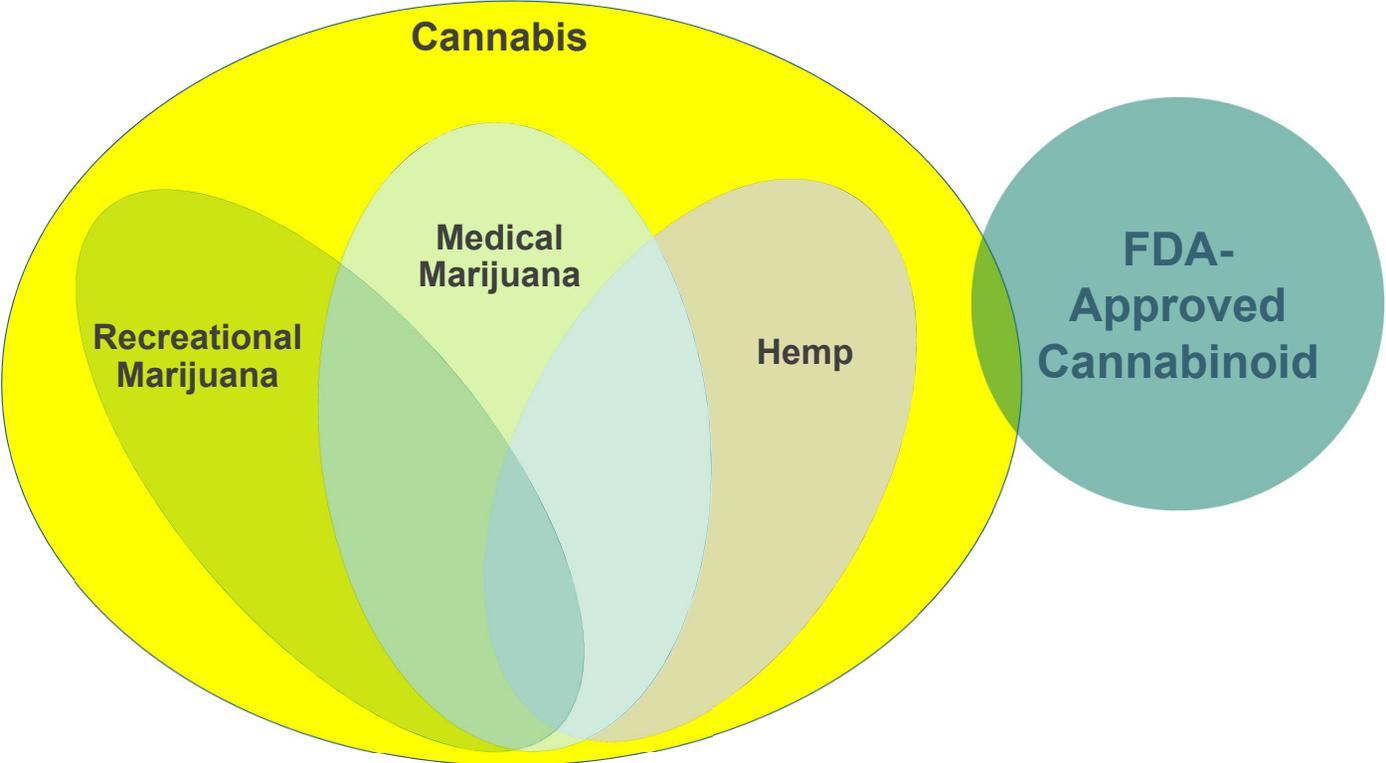
Over 100 identified cannabinoids in *Cannabis sativa L*



1. Pertwee RG. *Br J Pharmacol*. 2006;147:S163-S171. 2. EPIDIOLEX [package insert]. Carlsbad, CA: Greenwich Biosciences; 2018. 3. Devinsky O, et al. *N Engl J Med*. 2017;376:2011-2020. 4. Devinsky O et al. *Lancet Neurol*. 2016;15:270-278. 5. Pertwee RG, Cascio MG. Known pharmacological actions of delta-9-tetrahydrocannabinol and of four other chemical constituents of cannabis that activate cannabinoid receptors. In: Pertwee RG, ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:115-136. 6. Marinol [package insert]. North Chicago, IL: AbbVie Inc; 2017. 7. Cesamet [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2013. 8. Syndros [package insert]. Chandler, AZ: Insys Therapeutics; 2018.

Cannabis-Based Products

Cannabis Product Categories



1. Hall W. Recreational cannabis: sought-after effects, adverse effects, designer drugs, and harm minimization. In: Pertwee RG, ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:645-646. 2. Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. *Epilepsy Behav.* 2017 May;70(Pt B):288-291. 3. Small E, Marcus D. Hemp: a new crop with new uses for North America. In: Janick J, Whipkey A, eds. *Trends in New Crops and New Uses*. Alexandria, VA: ASHS Press; 2002:284-326. 4. Chandra S et al. Cannabis cultivation: Methodological issues for obtaining medical-grade product. *Epilepsy Behav.* 2017 May;70(Pt B):302-312. 5. DEA Eases Requirements for FDA-Approved Clinical Trials on Cannabidiol [news release]. Washington, DC: DEA; 2015. <https://www.dea.gov/divisions/hq/2015/hq122315.shtml>. Accessed May 31, 2017. 6. Hazekamp A, Pappas G. Self-Medication with Cannabis. In: Pertwee RG, ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:319-338. 7. Guidelines for the Use of Non-Pharmaceutical Grade Compounds in Laboratory Animals. NIH website. https://oacu.oir.nih.gov/sites/default/files/uploads/arac-guidelines/pharmaceutical_compounds.pdf. Accessed June 1, 2017. 8. Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. FDA website. <https://www.fda.gov/oc/oc/compliancemanuals/compliancepolicyguidancemanual/ucm200364.htm>. Accessed June 1, 2017.

Cannabis-Based Product Categories

Pharmaceutical Formulations

- Can be plant-derived or synthetic^{6,7}
- Controlled preparations that meet Food and Drug Administration standards of purity, consistency, stability, safety, and efficacy

Medical Marijuana*

- Cannabis or cannabis products used to treat disease or alleviate symptoms by patient choice, in absence of clinical evidence to support claim
- Healthcare providers can “recommend” but not prescribe hemp-derived dispensary products or marijuana, as they are illegal at the federal level.
- Lack of placebo-controlled trials supporting efficacy and safety of these products⁵

Recreational Marijuana

- Cannabis or cannabis products used to induce pleasure, euphoria, relaxation, and to enhance sociability¹
- Classified by intended use not by chemical, botanical, or formulation-based differences²

Hemp

- Historically grown for fibrous materials found in stalks and seeds
- Used industrially for items, such as clothing fiber³
- Generally also low in CBD (0.5–4%)⁸
- If NMT 0.3 % THC, federally legal to grow⁹

* There is no scientifically accepted definition for this term

1. Hall W. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:645-646.
2. Mead A. *Epilepsy Behav.* 2017 May;70(Pt B):288-291.
3. Small E, Marcus D. *Trends in New Crops and New Uses*. Alexandria, VA: ASHS Press; 2002:284-326.
4. DEA; 2015. <https://www.dea.gov/divisions/hq/2015/hq122315>. Accessed May 31, 2017.
5. Hazekamp A, Pappas G. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:319-338.
6. NIH website. https://oacu.oir.nih.gov/sites/default/files/uploads/armac-guidelines/pharmaceutical_compounds.pdf. Accessed June 1, 2017.
7. FDA website. <https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm200364.htm>. Accessed June 1, 2017.
8. Health Canada. About hemp & Canada's hemp industry. In. Ottawa, Ontario, Canada: Health Canada; 2017.
9. <https://www.agriculture.senate.gov/imo/media/doc/Agriculture%20Improvement%20Act%20of%202018.pdf> (1/7/2019)

What Is Hemp? Do We Care?

Hemp is a “bioaccumulator” or “bioremediator” that absorbs heavy metals and other chemical waste from the soil

HEMP

An inefficient source of CBD²

- As defined in Canada, Europe, and now in US, hemp has **no more than 0.2-0.3% THC**; it is also low in CBD (1-2%)^{1,2}
- CBD is not present in stalk, fiber nor seeds
- New “hemp” varieties are hybrids

1. Congressional Research Service bulletin RL3272.5.
2. Hemp Industries Association position statement, 2014. <http://www.thehia.org/HIAhempnewsreleases/3346474>.

How Much is 0.3% THC?

According to a recent study from Johns Hopkins University, marijuana-infused brownies containing **10 mg of THC** result in a psychoactive effect in adults¹

Vandrey R et al, *J Analytical Tox*, 2017: 1-17.

Rx

Starting dose for prescription THC (synthetic) is **2.5mg**

81mg = 32 doses



DISPENSARY

State recreational marijuana laws (OR):
5mg THC/serving; 50mg THC/product



RETAIL

30mL bottle of CBD oil could contain **81mg of THC** & ***still fall below 0.3%***



Single, 4-gram CBD gummy can have **12mg of THC**



Contamination

- **47 states** have some law allowing for use of medical cannabis; **only 23** have testing requirements
 - Only 20 test for content beyond cannabinoids
 - It is not clear whether states truly have the resources to conduct and enforce testing
 - Many states exclude “hemp” products from testing completely
- CBD products may be produced using sub-standard manufacturing and can be contaminated with heavy metals, mold and bacteria, or dioxins

HEMP SUCKS*
PHYTO-REMEDIATION
**absorbs*



HEMP CLEANS
FILTER ✪ FOOD ✪ FIBER ✪ FUEL

Types of Cannabis Testing^{1,2,3}

Potency Testing

Microbial Testing

Lack of Standardized Testing Labs

Heavy Metal Testing

Pesticide Testing

Lack of Standardized Testing Processes

Residual Solvent Testing

Aflatoxin Testing

Lack of Federal Testing Regulations for Cannabis Companies

General Lack of Understanding

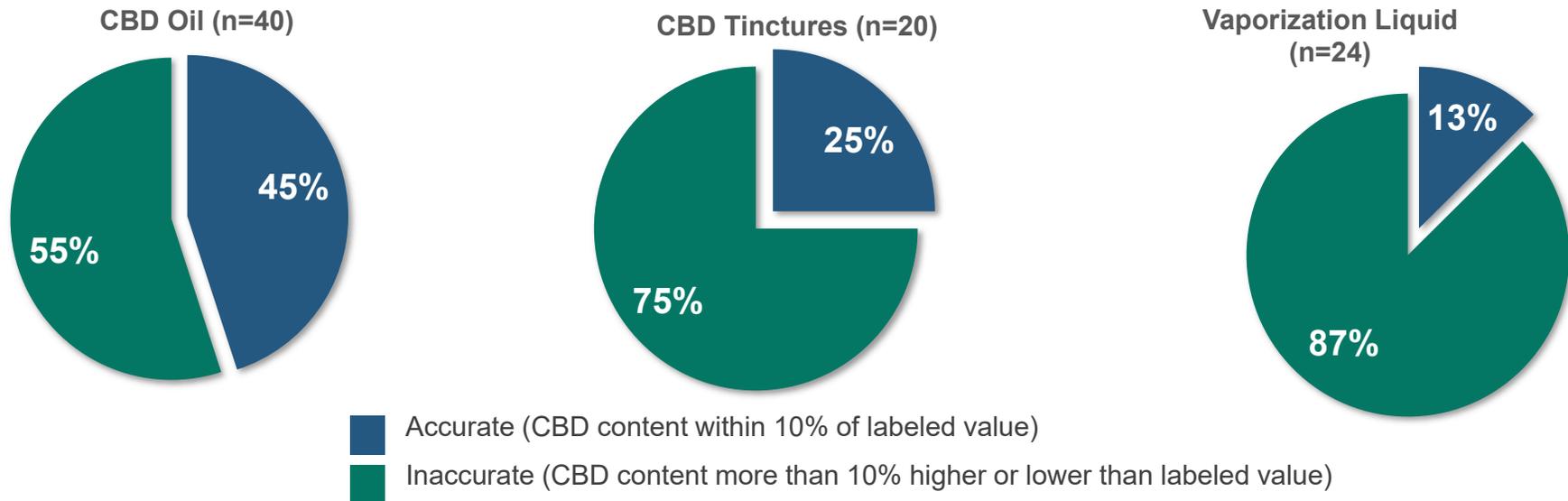
*Testing listed above is not mandatory.

1. Testing. CannLabs website. <http://cannlabs.com/testing/>. Accessed January 4, 2016.
2. <https://lcb.wa.gov/publications/Marijuana/BOTEC%20reports/1a-Testing-for-Contaminants-Final-Revised.pdf> (1/27/2019).
3. <https://www.labmanager.com/ask-the-expert/2016/09/challenges-in-medical-cannabis-analysis#.XE5oslxKjD4> (1/27/2019)



Cannabidiol Extracts May Be Inaccurately Labeled

Label Accuracy for CBD Extract Products by Category (n=84) ^{1,*}



- Of 84 products analyzed, nearly 70% were inaccurately labeled with respect to CBD and 21.4% contained THC¹
- Due to variable CBD and THC content, the authors conclude that these products should be avoided for pediatric patients²

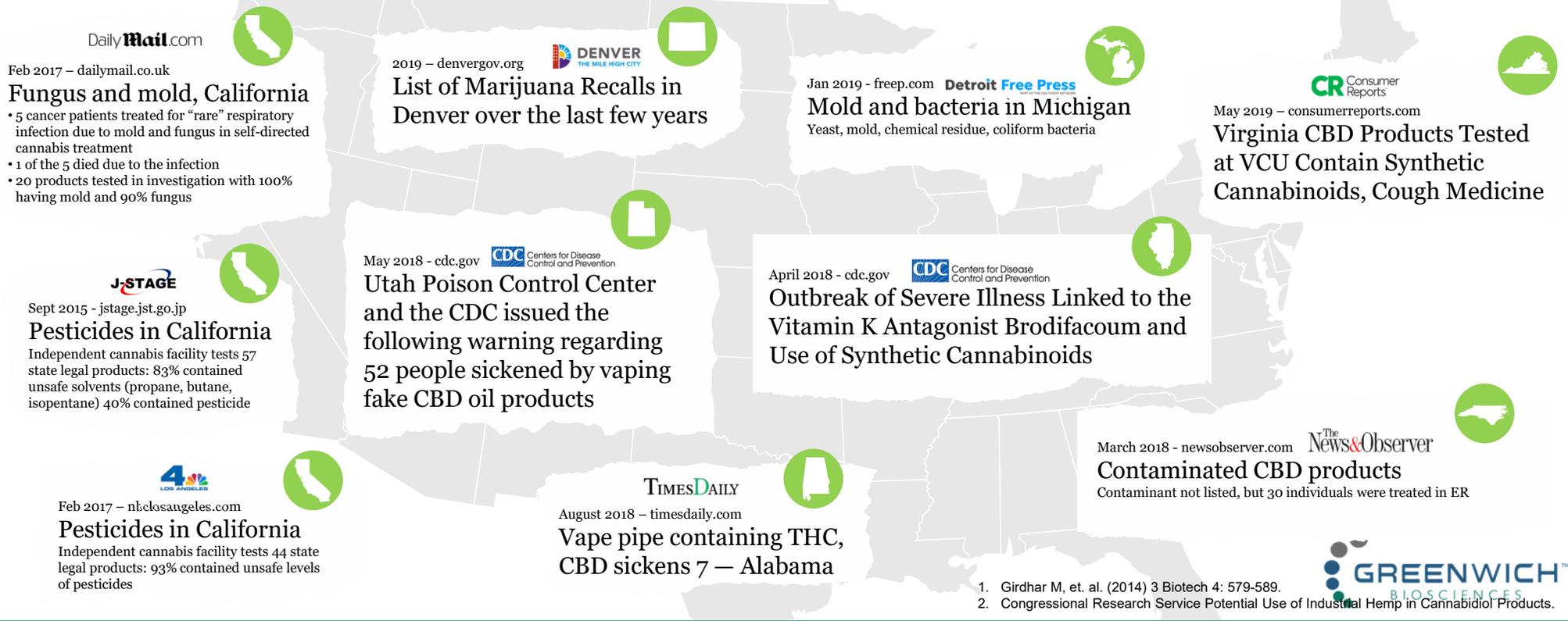
*Cannabinoid products from 31 companies were purchased and analyzed for CBD content by high-performance liquid chromatography.
1. Bonn-Miller MO, et al. *JAMA*. 2017;318(17):1708-1709. 2. Freedman DA, Patel AD. *Pediatric Neurology Briefs*. 2018;32:3.

What's in the Bottle?

Many commercially available CBD products are contaminated

Hemp is a bio-accumulator, meaning the plant draws toxins from the soil;²

Cannabis also naturally draws toxins from soil, so it can become contaminated with heavy metals, including lead, arsenic, mercury and cadmium¹



1. Girdhar M, et. al. (2014) 3 Biotech 4: 579-589.
2. Congressional Research Service Potential Use of Industrial Hemp in Cannabidiol Products.

FDA-Approved versus Non-FDA Approved Cannabinoid Products

Food & Drug Administration (FDA)-Approved Cannabinoid Products^{1,2} *Plant-Based and Synthetic Medicines*

Non-FDA Approved Cannabinoid Products³ *Hemp-Derived Dispensary Products and Medical Marijuana*

Study Evidence & Requirements

✓ Studied in placebo-controlled, clinical trials

Randomized clinical studies have not been conducted. Public disclosure of smaller, informal studies not required

Manufacturing

✓ Produced and federally inspected to ensure good manufacturing practices (cGMP) while adhering to strict specifications that ensure batch consistency and stable shelf life

Testing standards vary from state to state, and some states require no testing. There are no federal standards; FDA does not inspect the manufacturing sites for adherence to cGMP

Quality Standards

✓ Meets FDA standards for quality, stability, consistency

Non-prescription, non-FDA approved cannabinoid products are subject to inconsistent regulation at the state level. There are no federal standards for testing to ensure accuracy and consistency⁴

Legality

✓ Federally legal as prescribed; similar to other DEA-controlled prescription medicines

Restrictions to access vary by state.⁵ Healthcare providers can “recommend” but not prescribe hemp-derived dispensary products or marijuana, as they are illegal at the federal level. Interstate transportation of these products is federally illegal

Coverage

✓ Eligible for insurance coverage

Insurance coverage is non-existent



1. <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm>. Accessed October 31, 2017. 2. <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>. Accessed October 30, 2017. 3. https://oacu.oir.nih.gov/sites/default/files/uploads/attach/guidelines/pharmaceutical_compounds.pdf. Accessed October 30, 2017. 4. <https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm>. Accessed January 23, 2018. 5. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>. Accessed October 31, 2017.

Your knowledge Matters...Keep Learning!

Web-based Resources: **CannabinoidClinical.com**

CANNABINOID
CLINICAL

CANNABINOID SCIENCE | THC VS CBD | FDA DIFFERENCE | RESOURCES | COVERING CANNABINOIDS

 SIGN UP



From Medscape Education Neurology & Neurosurgery

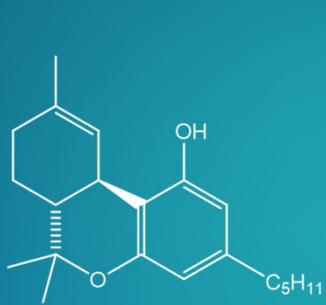
CME / CE

The Basis of Cannabinoid Therapeutics: What You Need to Know

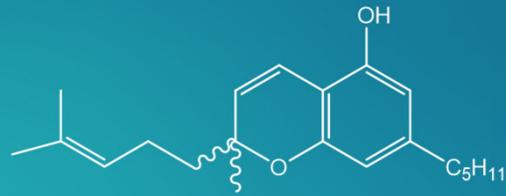
Authors: Ethan Russo, MD; Barry Gidal, PharmD **Faculty and Disclosures**

CME / CE Released: 10/31/2017, Reviewed and Renewed: 10/31/2018 Valid for credit through: 10/31/2019

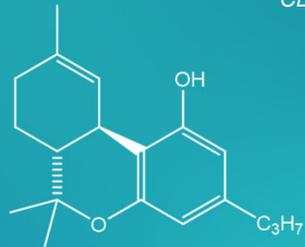




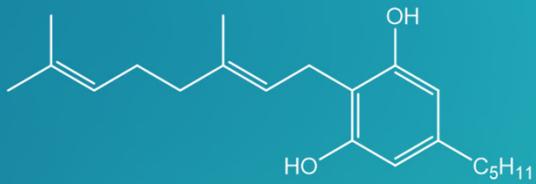
Δ9-THC



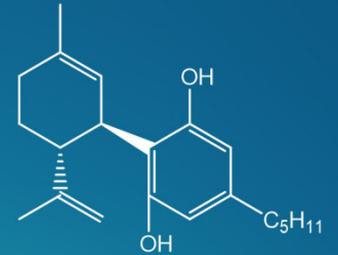
CBC



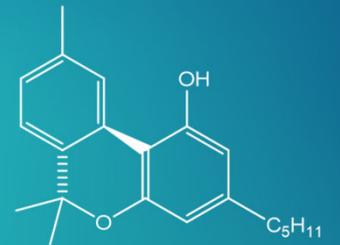
THCV



CBG



CBD



CBN3

Thank You!





GET SMART
Different Products, Different
Regulatory Frameworks

Heili Kim, JD, MPH

Partner, Faegre Baker Daniels LLP

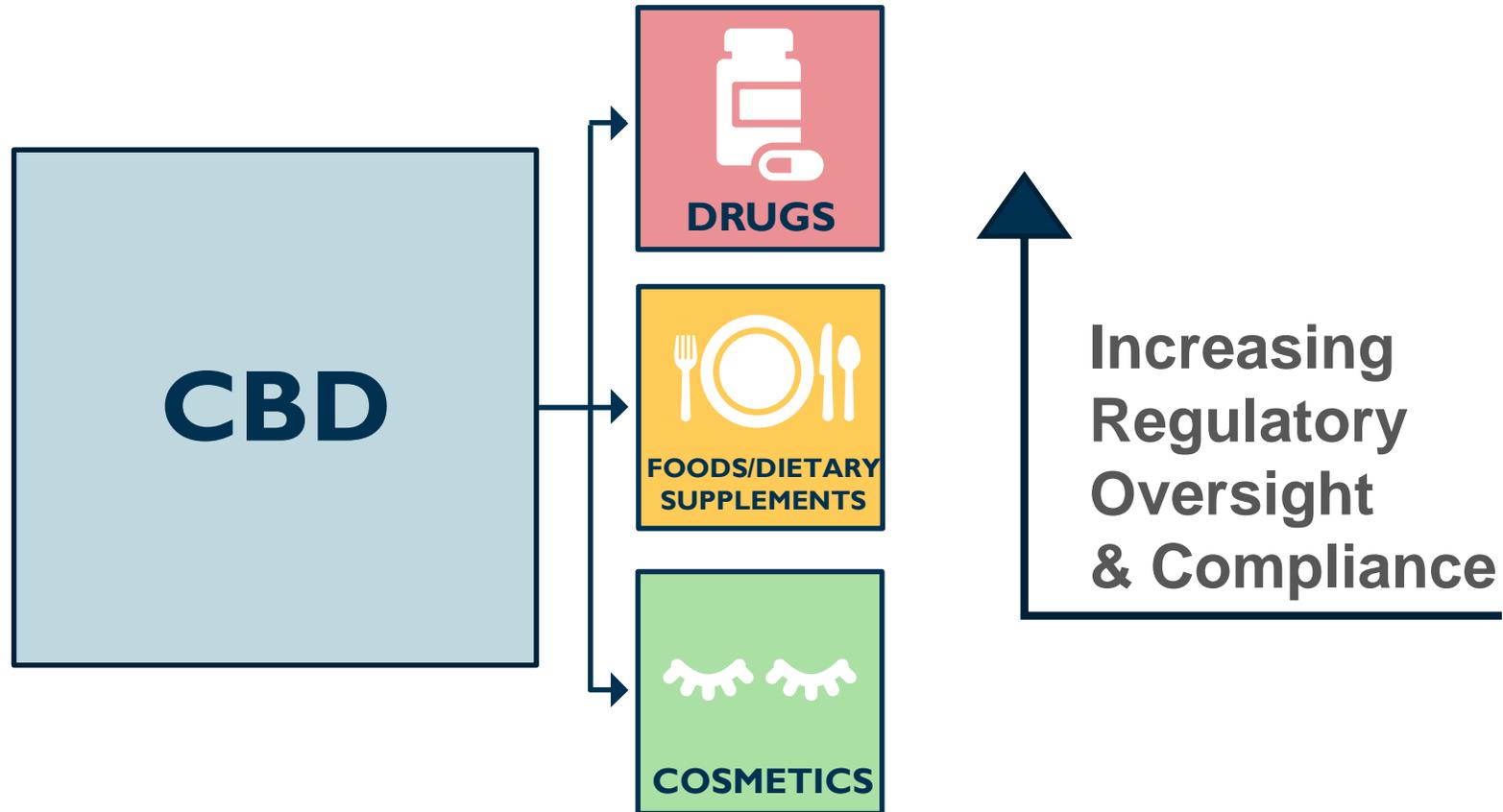
GET SMART

DIFFERENT PRODUCTS = DIFFERENT REGULATORY FRAMEWORK

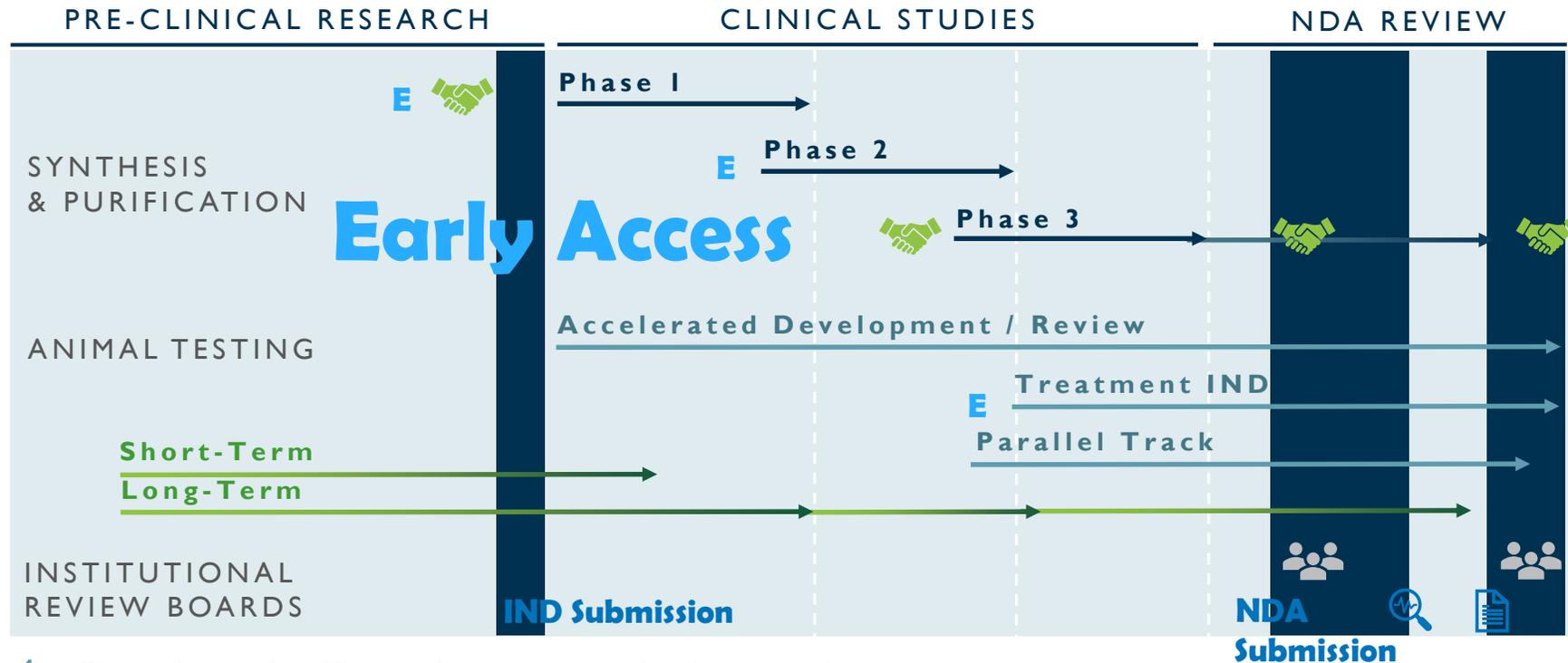
FAEGRE BAKER
DANIELS

FAEGREBD.COM →

DIFFERENT PRODUCTS = DIFFERENT REGULATIONS



DRUG APPROVAL PROCESS



1. Requires significant investment in time and resources
2. Agency review and sponsorship involvement is intensive
3. Strict compliance with manufacturing, labeling, marketing and post-market surveillance (pharmacovigilance)

FOOD INGREDIENT REVIEW & APPROVAL



Any substance that is intentionally added to food is a food additive, and subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excepted from the definition of a food additive. (§201(s) FFDCA)

NEW INGREDIENTS IN DIETARY SUPPLEMENTS

Grandfathered Ingredients

Pre-DSHEA (marketed prior to
October 15, 1994)

Removal of grandfather
ingredients requires FDA to
demonstrate that it holds an
unreasonable or significant risk
of injury or illness

Status determined by company

New Dietary Ingredient Notification

New Dietary Ingredient marketed
after October 15, 1994

Exception: in the food supply in
the world

Exception: cannot be a dietary
ingredient if first used in a drug
clinical trial

GRAS/ Self-Affirmed GRAS

“Generally recognized as safe”

Private Self-affirmation or public
notification process to FDA
demonstrating recognition by a
panel of experts

COSMETIC INGREDIENTS

- Neither the law nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients. The law also does not require cosmetic companies to share their safety information with FDA
- Certain prohibited ingredients
 - bithionol, vinyl chloride, halogenated salicylanilides, etc.
- Certain Warning Statements
 - “Warning—The safety of this product has not been determined.”
- Possible Federal Laws being considered to increase regulatory oversight



WARNING LETTER

**FDA and FTC jointly
sends warning letters
to companies selling
their products
containing CBD**

**VIA OVERNIGHT DELIVERY
RETURN RECEIPT REQUESTED**

March 8, 2019

PatNetwork Holdings, Inc.
7001 Mr. Cery Blvd, President
3531 Griffin Road
Fort Lauderdale, FL 33312

RE: 564030

Dear Mr. Blum:

This is to advise you that the U.S. Food and Drug Administration (FDA) reviewed your website at the internet address www.diamondcbd.com in September 2018 and has determined that you take orders there for various products you claim to contain cannabidiol (CBD), including "Liquid Gold Gummies (Sweet Mix)," "Liquid Gold Gummies (Sour Mix)" and "blue CBD Crystals Isolate 1500mg." The claims on your website establish that these products are drugs under section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(B)] because they are intended for use in the cure, mitigation, treatment, or prevention of disease. As explained further below, introducing or delivering these products for introduction into interstate commerce for such uses violates the Act. You can find the Act and FDA regulations through links on FDA's home page at www.fda.gov. In addition, the Federal Trade Commission has reviewed your website for potential violations of Sections 5(a) and 12 of the FTC Act, 15 U.S.C. §§ 45(a) and 52.

Examples of some of the claims observed on your website that provide evidence that your products are intended for use as drugs include the following:

On the webpage titled "WHAT IS CBD?":

- "A 2015 study found that CBD may be neuprotective [*sic*] in adult and neonatal ischemia, brain trauma, Alzheimer's disease, Parkinson's disease, Huntington's chorea, and amyotrophic lateral sclerosis (Lou Gehrig's disease)."
- "CBD was administered after onset of clinical symptoms, and in both models of arthritis the treatment effectively blocked progression of arthritis."

active ingredient in a drug product that has been approved under section 305 of the

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QUESTIONS?

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Morning Keynote

Remarks from the Congressional Perspective

The Honorable Andy Harris, MD

Reflections from Consumers, Patients and Healthcare Providers

10:00am – 10:45am

Moderator: Stacey Worthy, *Aimed Alliance*

Panelists: Dr. Edward Benarczyk, *American Pharmacists Association*
Chuck Ingoglia, *National Council for Behavioral Health*
Dr. Samer Narouze, *American Society of Anesthesiologists*
Sally Greenberg, *National Consumers League*

KEEPING THE MEDICAL IN MEDICAL ~~MARIJUANA~~-CBD

Edward M Bednarczyk, PharmD, FCCP,
FAPhA

Clinical Associate Professor, Pharmacy
Practice

Director cHOPE

University at Buffalo, SUNY, School of
Pharmacy and Pharmaceutical Sciences

January 15th, 2020



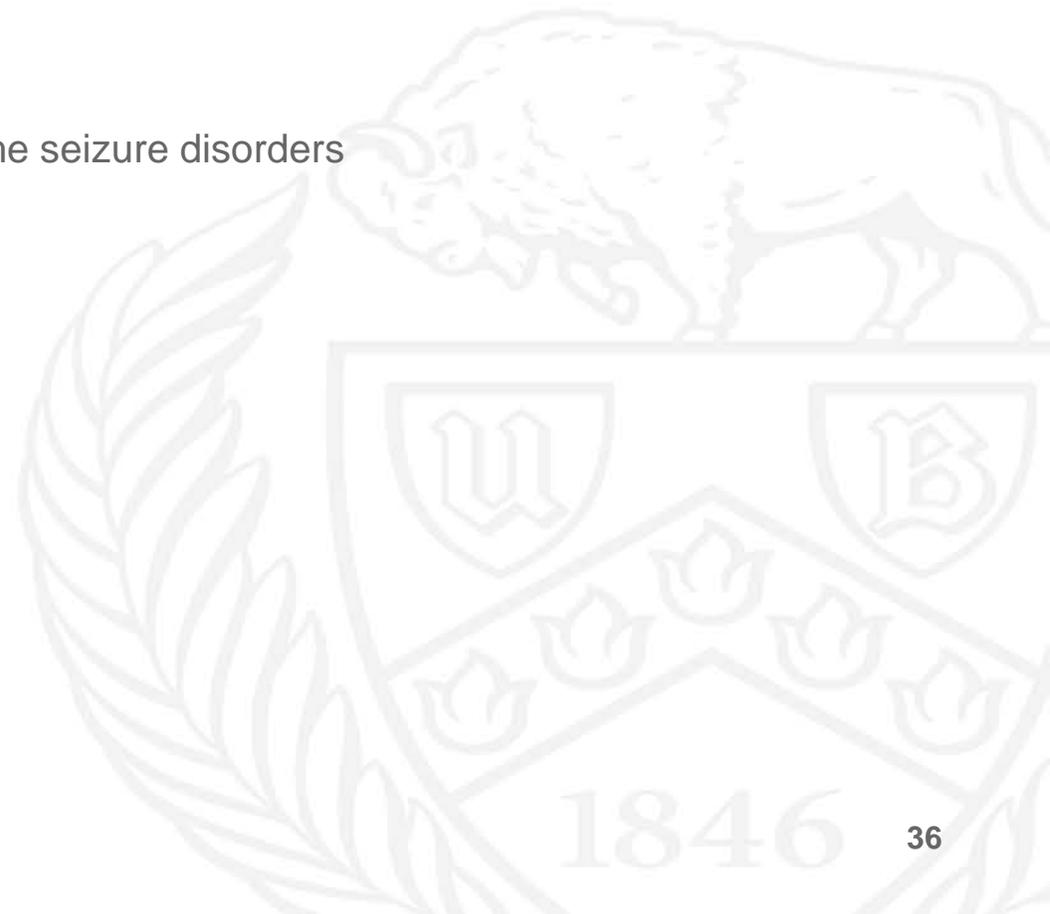
Conflict of Interest Statement

- No conflicts of interest to disclose



Objectives

- After this presentation, a participant will be expected to:
 - Describe the dosage forms of CBD permitted under the Farm Bill
 - List adverse effects reported with CBD in studies supporting use in some seizure disorders
 - List potential drug interactions with CBD
 - Describe a dosing strategy for CBD



Laws

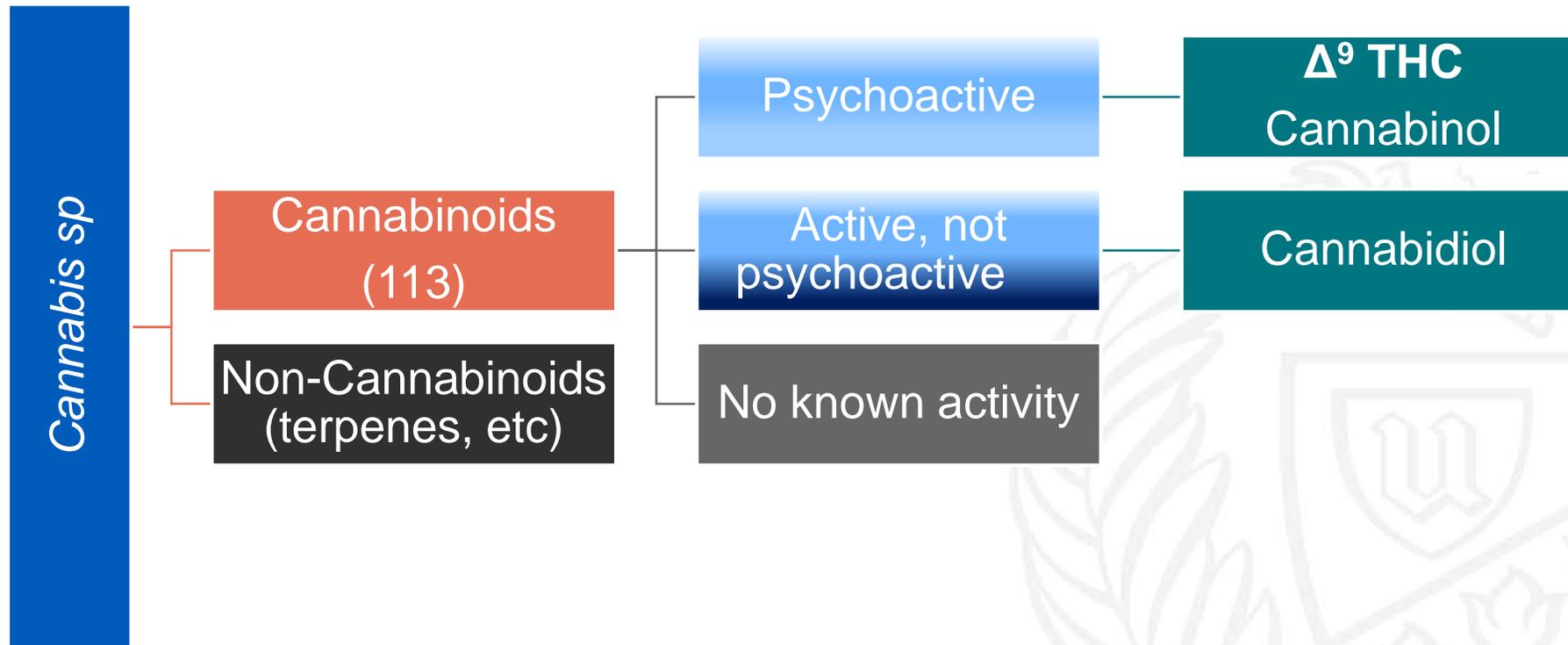
States that Permit Medical Marijuana		CBD States
<p>Alaska 1998 Arizona 2010 Arkansas 2016 California 1996 Colorado 2000 Connecticut 2012 Delaware 2011 Florida 2016 Hawaii 2000 Illinois 2013 Louisiana 2018 Maine 1999 Maryland 2014 Massachusetts 2012 Michigan 2008 Minnesota 2014 Montana 2004</p>	<p>Missouri 2014 Nevada 2000 New Hampshire 2013 New Jersey 2010 New Mexico 2007 <u>New York 1980, 2014</u> North Dakota 2016 Ohio 2016 Oregon 1998 Pennsylvania 2016 Rhode Island 2006 Utah 2018 Vermont 2004 Washington 1998 Washington DC 2010 West Virginia 2017</p>	<p>Alabama 2014 Georgia 2015 Indiana 2017 Iowa 2014 Kentucky 2014 Mississippi 2014 North Carolina 2014 Oklahoma 2015 South Carolina 2014 South Dakota 2017 Tennessee 2014 Texas 2015 <u>Virginia</u> 2015 Wisconsin 2014 Wyoming 2015</p>

What is Marij(h)uana?

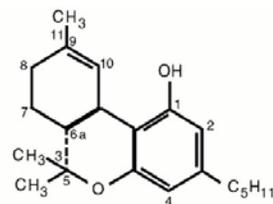
- *Cannabis sativa, indica, ruderalis*
- DEA Schedule I
 - High potential for abuse
 - No currently accepted medical use
 - Lack of accepted safety
- >500 phytochemicals, 113 classified as cannabinoids
 - **Δ^9 tetrahydrocannabinol (THC)**
 - **Cannabidiol**
 - Cannabinol
 - Δ^8 THC
 - Cannabigerol
 - Cannabichromene



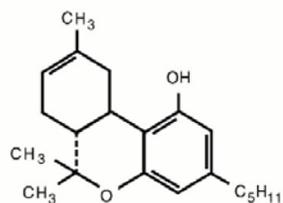
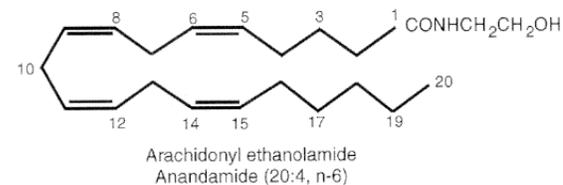
Isolated Compounds



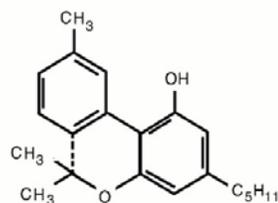
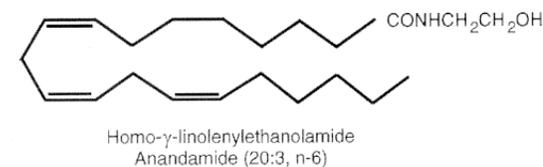
Phytocannabinoids/Endocannabinoids



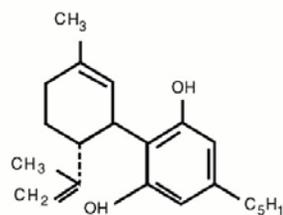
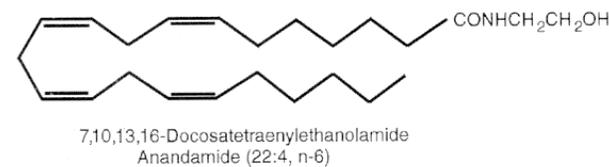
Δ^9 -Tetrahydrocannabinol (Δ^9 -THC)



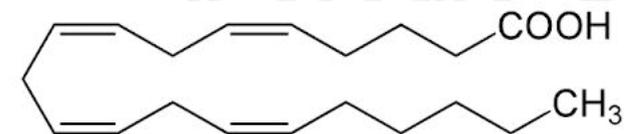
Δ^8 -Tetrahydrocannabinol (Δ^8 -THC)



Cannabinol (CBN)



Cannabidiol (CBD)



Receptors

- CB1 (neuronal)
 - Basal ganglia (motor activity)
 - Cerebellum
 - Hippocampus
 - Neocortex
 - Hypothalamus
- CB2 (peripheral)
 - B lymphocytes, natural killer cells
 - Brain, role unclear
- Endogenous cannabinoids
 - Anandamides
- “CB2-like” receptors
- “CB1-like receptors”



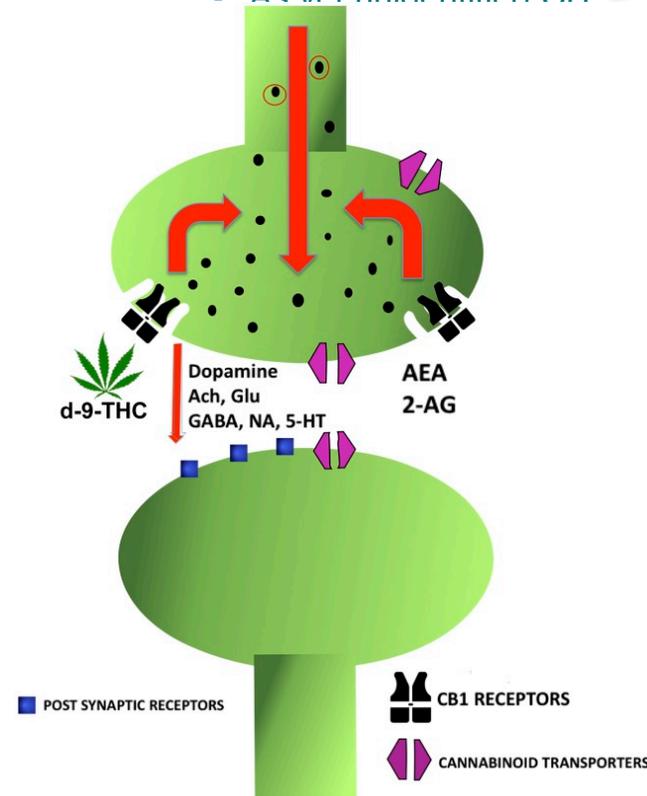
Pharmacology

Δ^9 THC

- Secondary inhibition of Ca, K, Na channels by non-competitive antagonism
- G-protein receptors, GPR55, GPR55940
- G-protein coupled receptors; non-competitive inhibitor at μ and δ -opioid receptors, NE, DA, 5HT
- Ligand gated ion channels; allosteric antagonism at 5-HT₃, nicotinic receptors, enhance activation of glycine receptors
- Activate transient receptor potential channels (TRPV's) – capsaicin?
- Activate Peroxisome proliferator activated receptors (PPAR) α, γ

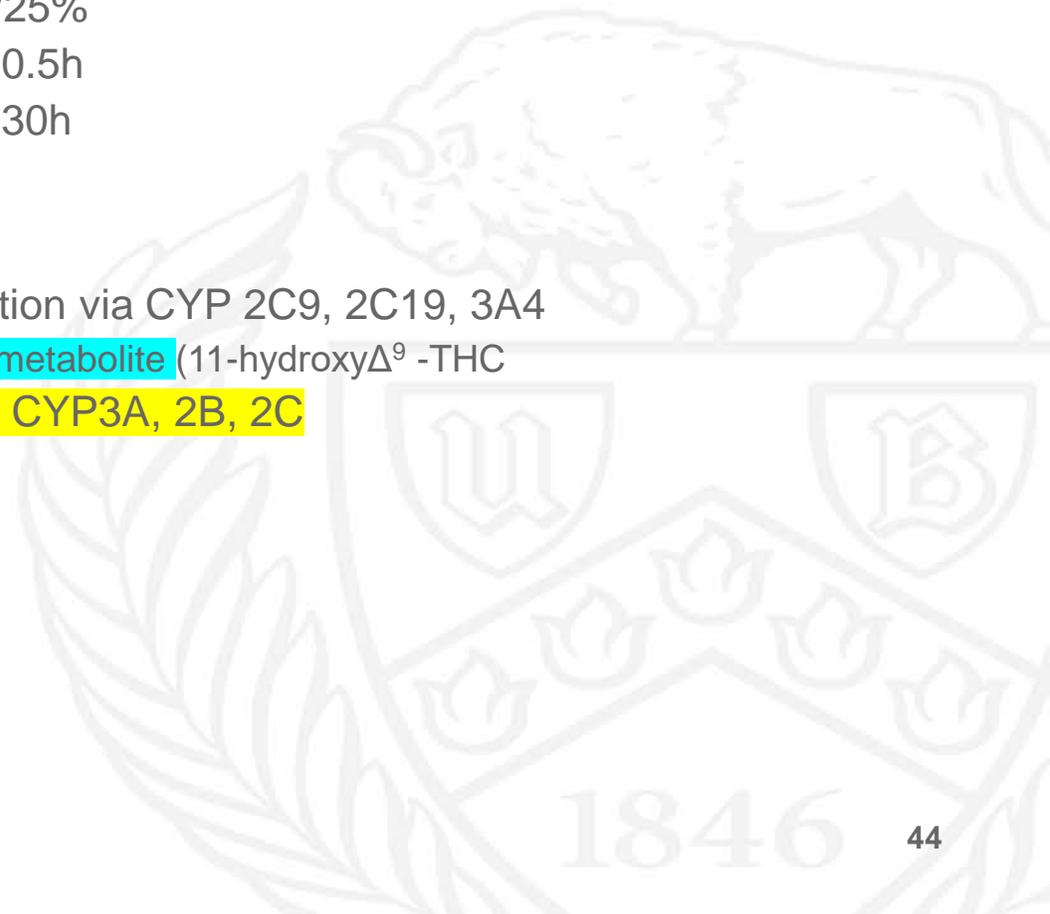
CBD

- Binds to CB1, 2
 - Low affinity
 - Secondary effects?
 - Other pathway?
 - “Inverse agonist”
 - As yet unidentified CR



Δ^9 Tetrahydrocannabinol (THC) PK

- IV
 - α T1/2 0.5h
 - β T1/2 30h
- PO
 - Bioavailability 5-20%
 - GI degradation
 - First pass metabolism
 - α T1/2 3.8h
 - β T1/2 25h
- Inhalation
 - 50%/50%/25%
 - α T1/2 0.5h
 - β T1/2 30h
- CYP450
 - Hydroxylation via CYP 2C9, 2C19, 3A4
 - Active metabolite (11-hydroxy Δ^9 -THC)
 - Inducer at CYP3A, 2B, 2C



Cannabidiol

- Aerosol
 - Peak 5-10 min
 - ~31% bioavailability
- Oral ingestion
 - 6% bioavailability
 - Vd ~32L/kg
 - T1/2 18-32h
 - Cl 57.6-93.6L/hr
- Inhibitor of CYP 2A6, 3A7, 1B1, 1A2, 3A4, 2C9, 2C19, 2B6, 3A5, 1A1
 - ?THC
 - Phenytoin
 - **Warfarin**
 - Diazepam
 - Amitriptyline, imipramine, clomipramine
 - **Clobazepam**
 - Clopidogrel

Evidence

- Institute of Medicine 1999
 - “The question is not whether ~~marijuana~~ CBD can be used as a herbal remedy, but rather how well this remedy meet’s today’s standards of efficacy and safety”
 - “Our society generally expects its licensed medications to be safe, reliable, and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not tolerated”

CBD Claims

CannabisRadar		
Chronic pain	Post-traumatic stress disorder (PTSD)	Fights Multi drug resistant bacteria
Inflammation	General anxiety disorder	Type 1 DM
Fibromyalgia	Panic disorder	Schizophrenia
Seizure (Epidiolex)	Social anxiety disorder	Exzema
Depression	Obsessive-compulsive disorder (OCD)	Acne
Reduces Oxidative Stress	Substance-abuse disorders	Alzheimer's Disease
Reducing artery blockage	Reducing blood pressure	Cancer
Reducing stress-induced cardiovascular response	Reducing cholesterol levels	

<https://thecannabisradar.com/cbd-oil/benefits/>

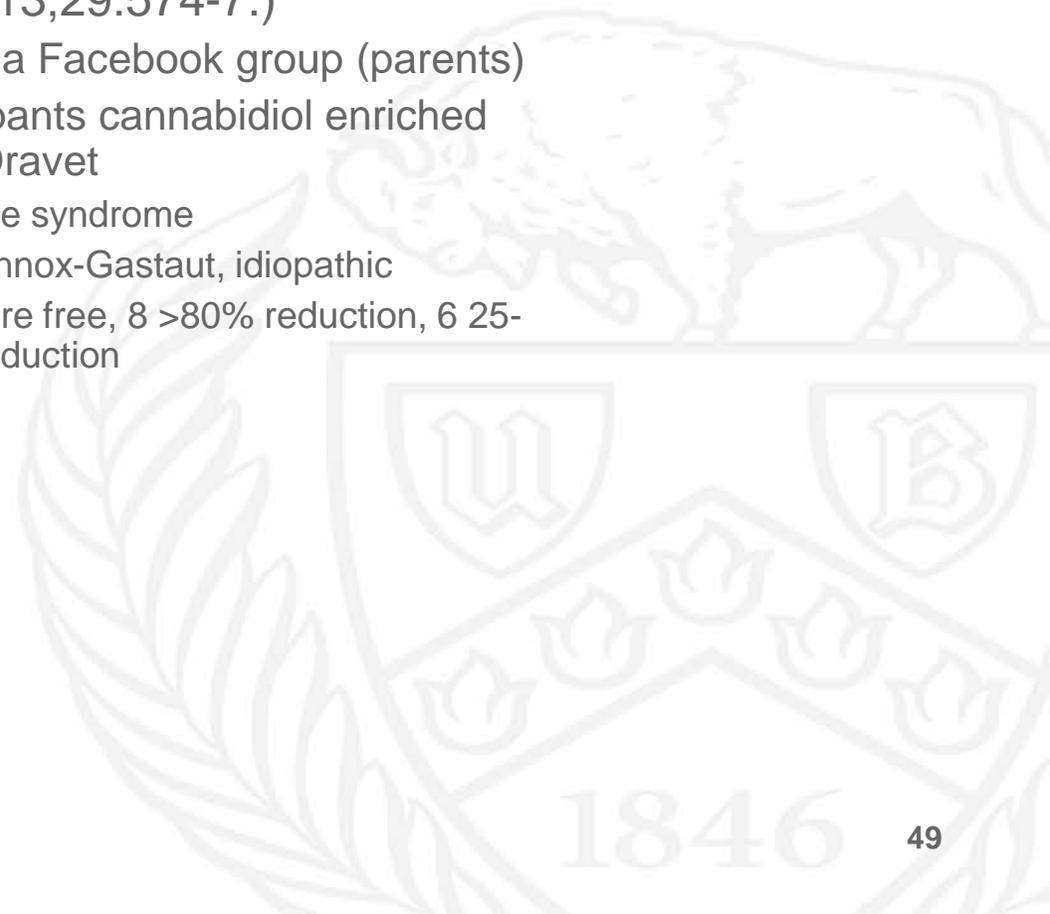


Seizure



MMJ in Seizure

- Hegde, et al (Epilepsy & Behavior 2012;25:563-66)
 - 2 pts used smoked MMJ
 - Improved seizure frequency
 - Exacerbation with d/c
- Multiple small papers showing no consistent effect of MMJ
- Porter & Jacobson (Epilepsy & Behavior 2013;29:574-7.)
 - Survey of a Facebook group (parents)
 - 19 participants cannabidiol enriched MMJ 13 Dravet
 - 4 Doose syndrome
 - 1 @ Lennox-Gastaut, idiopathic
 - 2 seizure free, 8 >80% reduction, 6 25-60% reduction



MMJ in Seizure

- Retrospective Study
 - 74 patients
 - CBD/THC 20:1
 - CBD dose 1-20mg/kg/day
 - Parents assessed seizure frequency
 - 89% of patients reported decrease in seizure frequency
 - 13, 75-100% reduction
 - 25, 50-75% reduction
 - 19, <25% reduction, 5 increased seizures

- AE's
 - Somnolence/Fatigue 16 (22%)
 - GI disturbances /Irritability 5 (7%)
 - Seizure aggravation 13 (18%)
 - No detail on concentrations of CBD, THC or other Anti-seizure medications

MMJ in Seizure

- Prospective study
 - Dravet Syndrome
 - N=120
 - Placebo:cannabidiol
 - 20mg/kg
 - Previous medications continued
 - Topiramate, levetiracetam, valproate, clobazam, stiripentol
 - GWPharma

	Placebo	Cannabidiol
Baseline	14.9(3.7-718)	12.4(3.9-1717)
End of Rx	14.1 (0.9-709)	5.9 (0-2159)
% change	13.3 (-91.5-230)	-38.9 (-100-337)
AE's		
Diarrhea	6 (10)	19 (31)
Fatigue	2 (3)	12 (20)
Decreased appetite	3 (5)	17 (28)
Somnolence	6 (10)	22 (36)
Convulsion	3 (5)	7 (11)

Devinsky, O NEnglJMed
 2017;376(21):2011-220

Available Products

- Cannabidiol (Epidiolex)
 - FDA Approved 6/25/18
 - DEA Schedule V
 - Dravet syndrome
 - Lennox Gastaut syndrome

- common side effects:
 - sleepiness, sedation and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise and weakness; insomnia, sleep disorder and poor quality sleep; and infections



Hemp and CBD

- December 20, 2018 President Donald Trump signed the [Agricultural Improvement Act of 2018](#) (AKA “the Farm Bill”) into law. The bill, (passed [389-to-47 vote in the House and by 87-to-13 in the Senate](#))
- It appears to permit the sale of CBD derived from hemp (low THC cannabis)
 - 0.3%
 - “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.”

Hemp and CBD

- Topical formulations are not being challenged by DEA or FDA, unless unsubstantiated health claims are made
- Oral formulations ARE being challenged...
- July 2019 FDA had a public comment forum focused on cannabidiol as a supplement
- No change in guidance has come from FDA since this meeting
- “cease and desist” letters have gone out to a few manufacturers and medical groups



“Gummy candies infused with organic broad-spectrum CBD can make a delicious snack that may help balance energy”
-Amount?

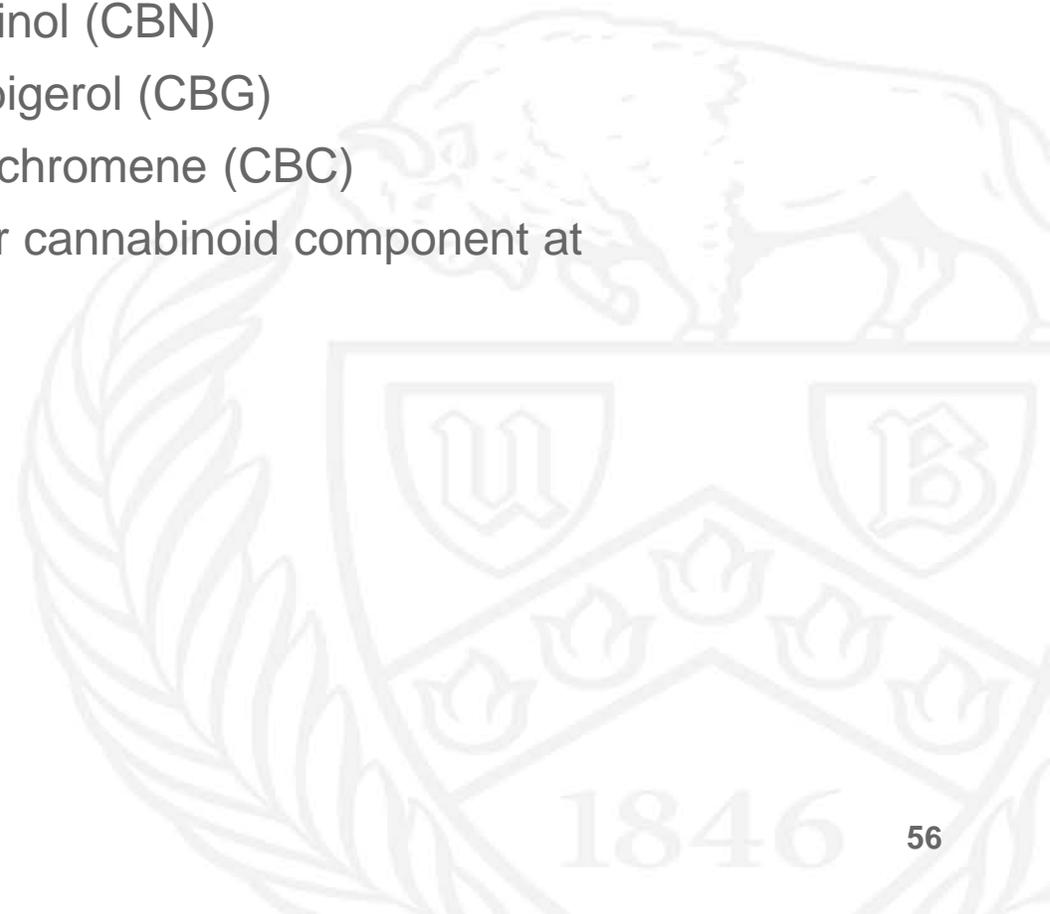
Pharmacist/Physician dilemma

- Shouldn't sell CBD outside of the DEA/FDA guidance
- Patients are purchasing products that don't comply with the DEA/FDA guidance
- Questions of purity are ongoing
 - Certificate of analysis?
- Doses are not established



Product

- (i) Tetrahydrocannabinol (THC)
- (ii) Tetrahydrocannabinol acid (THCA)
- (iii) Tetrahydrocannabivarin (THCV)
- (iv) Cannabidiol (CBD)
- (v) Cannabinadiolic acid (CBDA)
- (vi) Cannabidivarin (CBDV)
- (vii) Cannabinol (CBN)
- (viii) Cannabigerol (CBG)
- (ix) Cannabichromene (CBC)
- (x) Any other cannabinoid component at > 0.1%



Summary

- CBD use has exploded in a largely uncontrolled fashion
- CBD, at doses used in clinical trials, is associated with meaningful toxicity
- CBD interacts, or has the potential to interact with drugs metabolized by the liver
- Dosing and efficacy are not established for almost all indications





Chuck Ingoglia, MSW

*Executive Director
National Council for
Behavioral Health*

CBD

Physicians and Patients Perspectives



CBD Summit Washington, DC 2020

Samer Narouze, MD, PhD

**Professor Anesthesiology and Surgery, NEOME and OUCOM
Chairman, Center for Pain Medicine, Western Reserve Hospital
Cuyahoga Falls, OH**

DISCLOSURE

I have no financial relationships with commercial support to disclose.

 @NarouzeMD

Endocannabinoid System (ECS)

Plays an important role in

- Modulation of immune-neuro-psych activities.
- It's role is characterized as “eat, sleep, relax, forget, and protect”
- “mind-body” medicine.
- It has been suggested that migraine, fibromyalgia, depression, irritable bowel syndrome, anorexia, and multiple sclerosis could represent clinical eCB deficiency syndromes (CEDS).

Endocannabinoid System (ECS)



At 71, She's Never Felt Pain or Anxiety. Now Scientists Know Why.

At 71, She's Never Felt Pain or Anxiety. Now Scientists Know Why.



Jo Cameron, 71, has a rare genetic mutation that keeps her from feeling pain or anxiety, according to a



Jo Cameron, 71, has a rare genetic mutation that keeps her from feeling pain or anxiety, according to a new scientific report. Researchers hope the finding can help develop more effective treatments for pain.
Mary Turner for The New York Times

BJA⁵

British Journal of Anaesthesia, 123 (2): e249–e253 (2019)

doi: 10.1016/j.bja.2019.02.019

Advance Access Publication Date: 28 March 2019

Case Report

Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity

Abdella M. Habib^{1,2}, Andrei L. Okorokov¹, Matthew N. Hill³, Jose T. Bras^{4,5}, Man-Cheung Lee^{1,6,7}, Shengnan Li¹, Samuel J. Gossage¹, Marie van Drimmelen⁸, Maria Morena³, Henry Houlden⁵, Juan D. Ramirez⁹, David L. H. Bennett⁹, Devjit Srivastava^{10,*} and James J. Cox^{1,*}

 @NarouzeMD

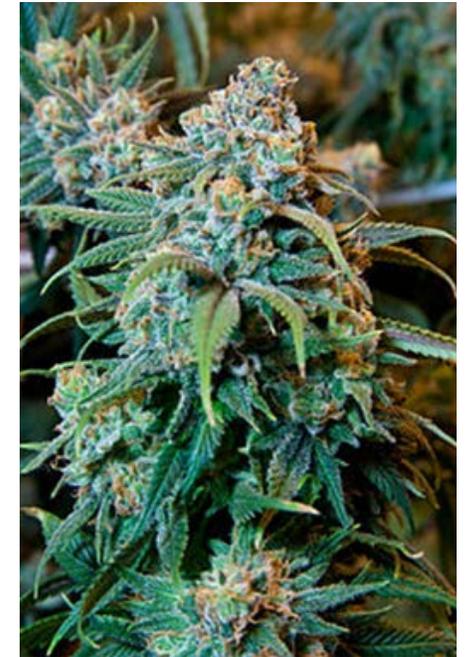
Phytocannabinoids

delta 9-THC and CBD are the two best known and characterized Phytocannabinoids

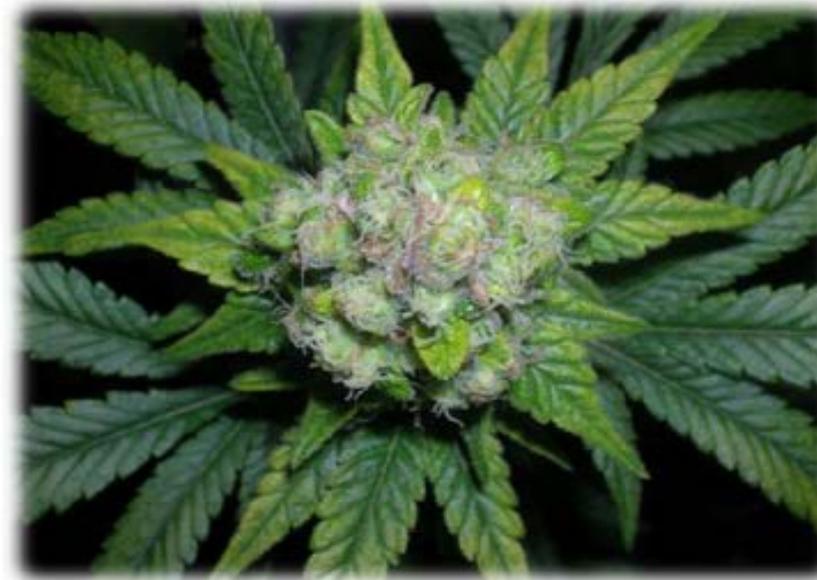
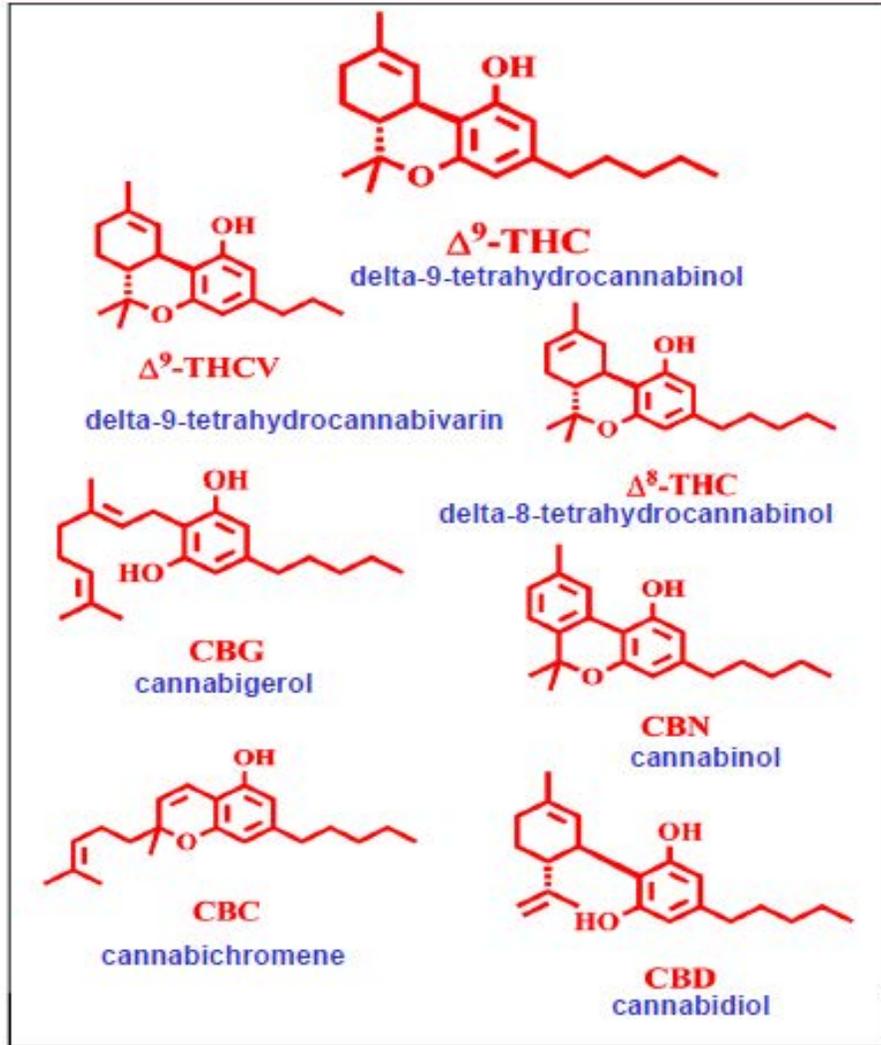
delta 9-THC is considered a “classic cannabinoid”

activation of CB1Rs, eliciting the cannabinoid-induced tetrad

(hypothermia, hypolocomotion, catalepsy and analgesia)



Marijuana contains ~120 cannabinoids plus other chemicals in varying concentrations



CBD

- CBD is a **non-psychoactive** cannabinoid
- Anti-inflammatory, antioxidant, anti-epileptic, antirheumatic, anxiolytic, analgesic, and neuroprotective
- CBD positively **modifies the negative effects of delta 9-THC** by:
reducing its psychoactive effects
increasing its clinical efficacy and the duration of its beneficial effects



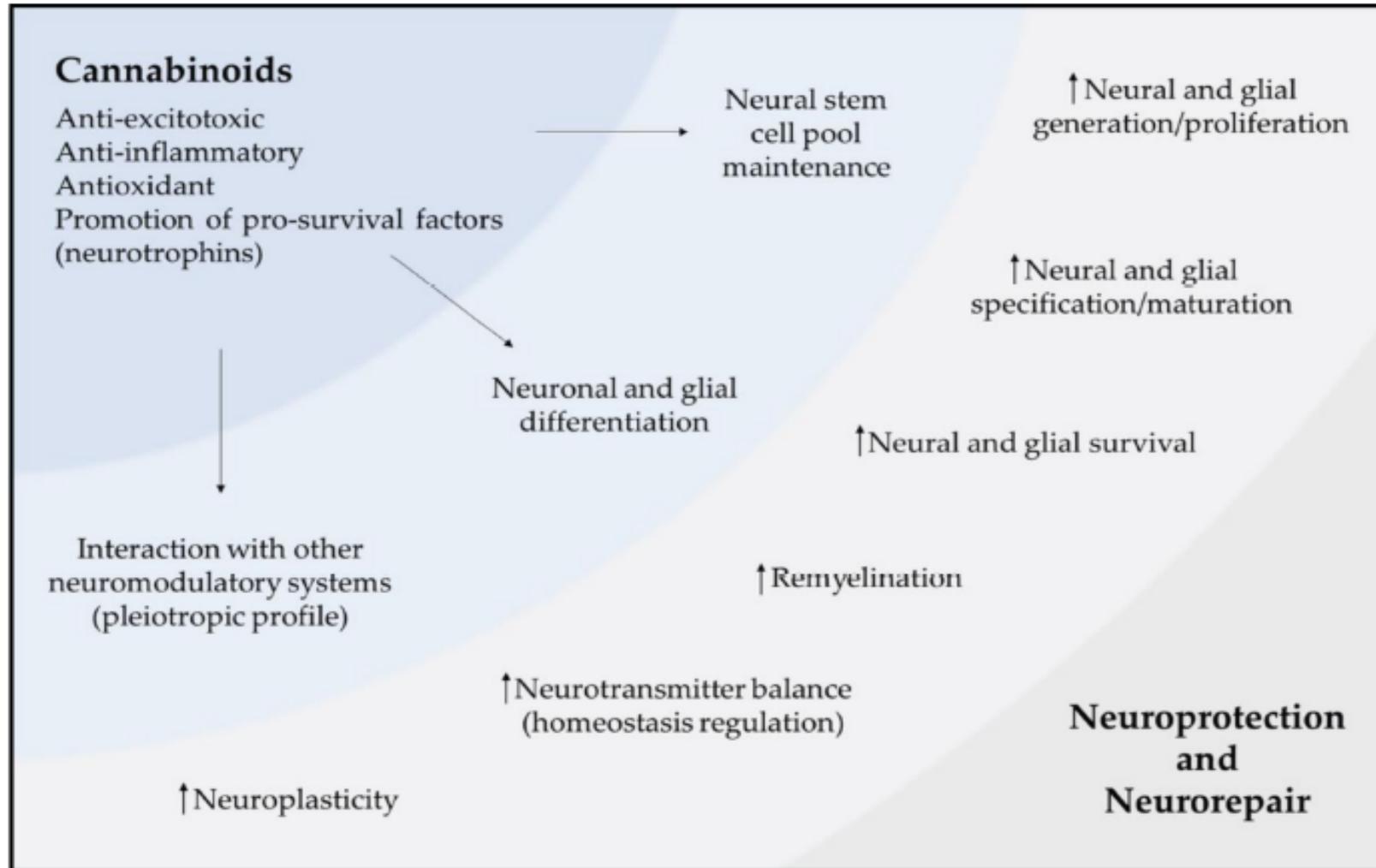
CBD

- CBD has low affinity to CB1Rs and CB2Rs.
- No agonist activity or **antagonist of both CB1Rs and CB2Rs**
- Negative allosteric modulator of CB1Rs
- Inhibits the cellular reuptake of AEA, **increasing the eCB tone**
- Modulates: TRPV, glycine, GABAA and PPAR receptors
- Agonist of GPR55 and antagonist of GPR18



The anti-inflammatory and immunosuppressive effects of CBD are mainly due to **activation of adenosine type 1 receptors**

Cannabinoids & Neuroprotection



Pharmaceutical Cannabinoids

- **Nabilone and dronabinol** are synthetic versions of the chemical THC.
- They are FDA approved for chemotherapy induced nausea and vomiting in patients who have failed to respond to conventional antiemetic treatments.
- Dronabinol is additionally approved for anorexia associated with weight loss in patients with AIDs.
- **Epidiolex (cannabidiol)**, is a purified derivative version of CBD and is FDA-approved in 2018 for the treatment of two rare types of epilepsy, Lennox-Gastaut Syndrome and Dravet Syndrome.
- **Sativex (nabiximols in USA)** is a synthetic, oromucosal spray that contains THC and CBD extracts from the plant Cannabis sativa at a 1:1 ratio. It is currently **investigational in USA** and seeking FDA approval. It is approved in about 30 countries for the treatment of MS muscle spasms.

ASA Patient/Consumer Cannabinoid Survey 2019

N= 943

57% believe more research is needed

34% don't feel the need to discuss using these products with their doctor

58% think they have fewer side effects than other medications

40% believe CBD sold at grocery stores, truck stops, health food stores or medical marijuana dispensaries is approved by the FDA.

The younger the generation, the more likely they were to believe that is the case.



People

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PARENTS

Kim Kardashian Celebrates 'CBD & Meditation'-Themed Baby Shower Ahead of Welcoming Her Fourth Child



CBD KITCHEN

OVER 50 PLANT-BASED RECIPES
FOR TONICS, EASY MEALS, TREATS
& SKINCARE MADE WITH THE
GOODNESS EXTRACTED FROM HEMP



Photography by Clare Winfield



Photo via @CNN

Business

Carl's Jr. is testing out a CBD-infused burger for 4/20

The fast-food restaurant will test selling cannabidiol-infused burgers at one of its Denver locations on April 20 for a price of \$4.20 each.



CISION
PR Newswire



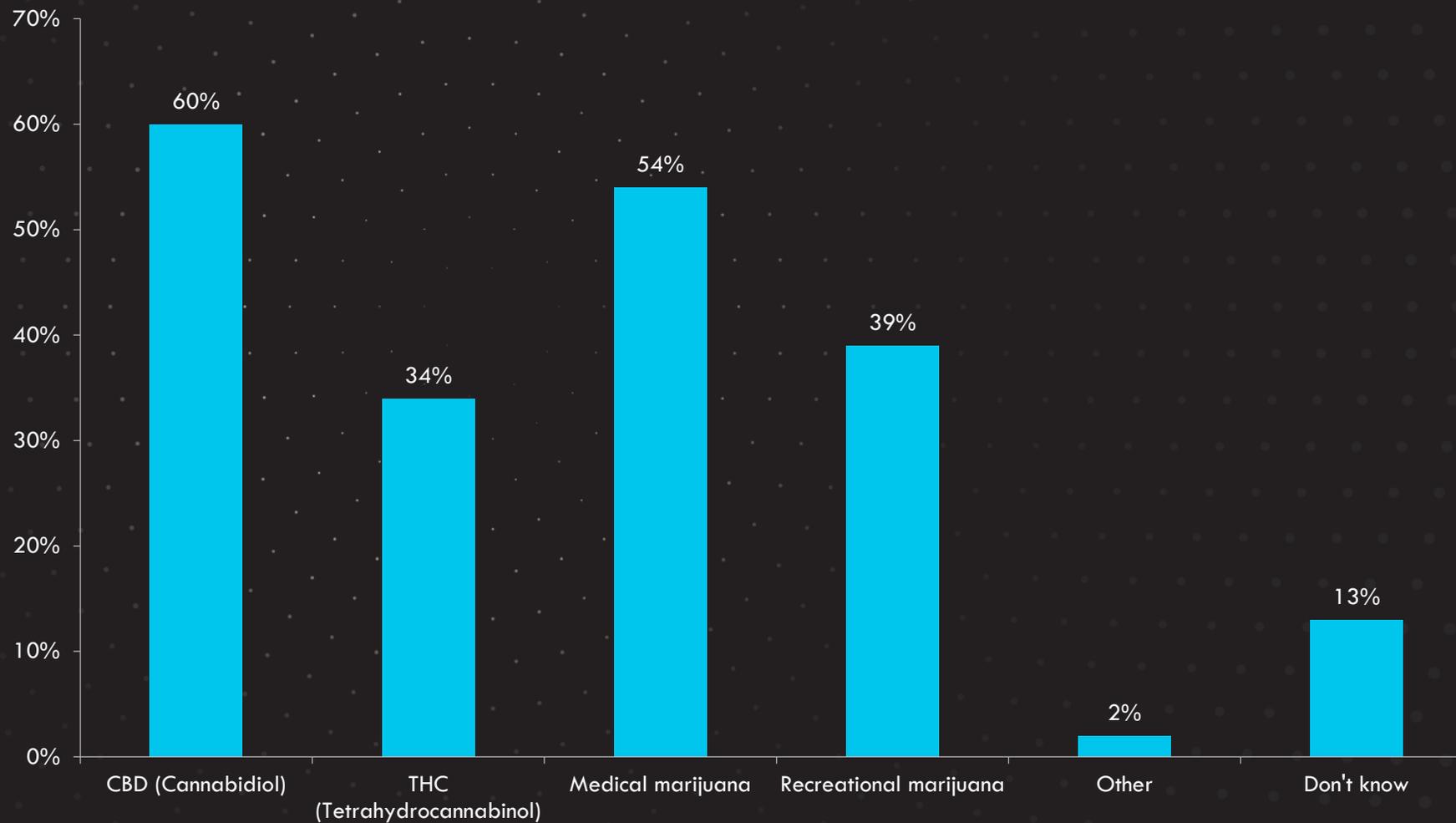
Acabada Launches As The World's First & Only CBD-Infused Activewear Brand

An innovative, luxury pro-activewear line infused with CBD announces its inaugural collection available online this week



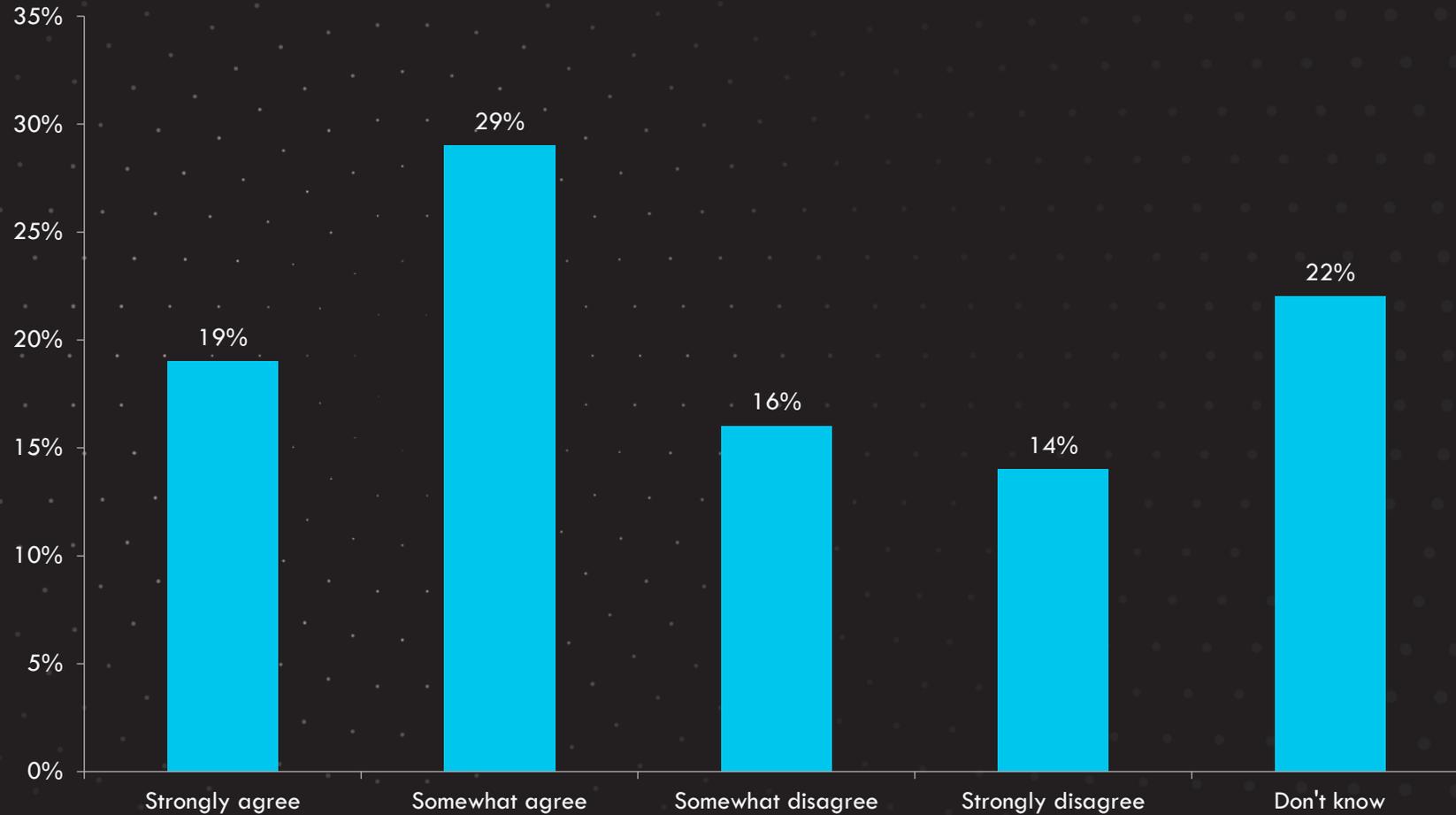
@NarouzeMD

Which of the following have you used, or would you consider using, to manage pain?

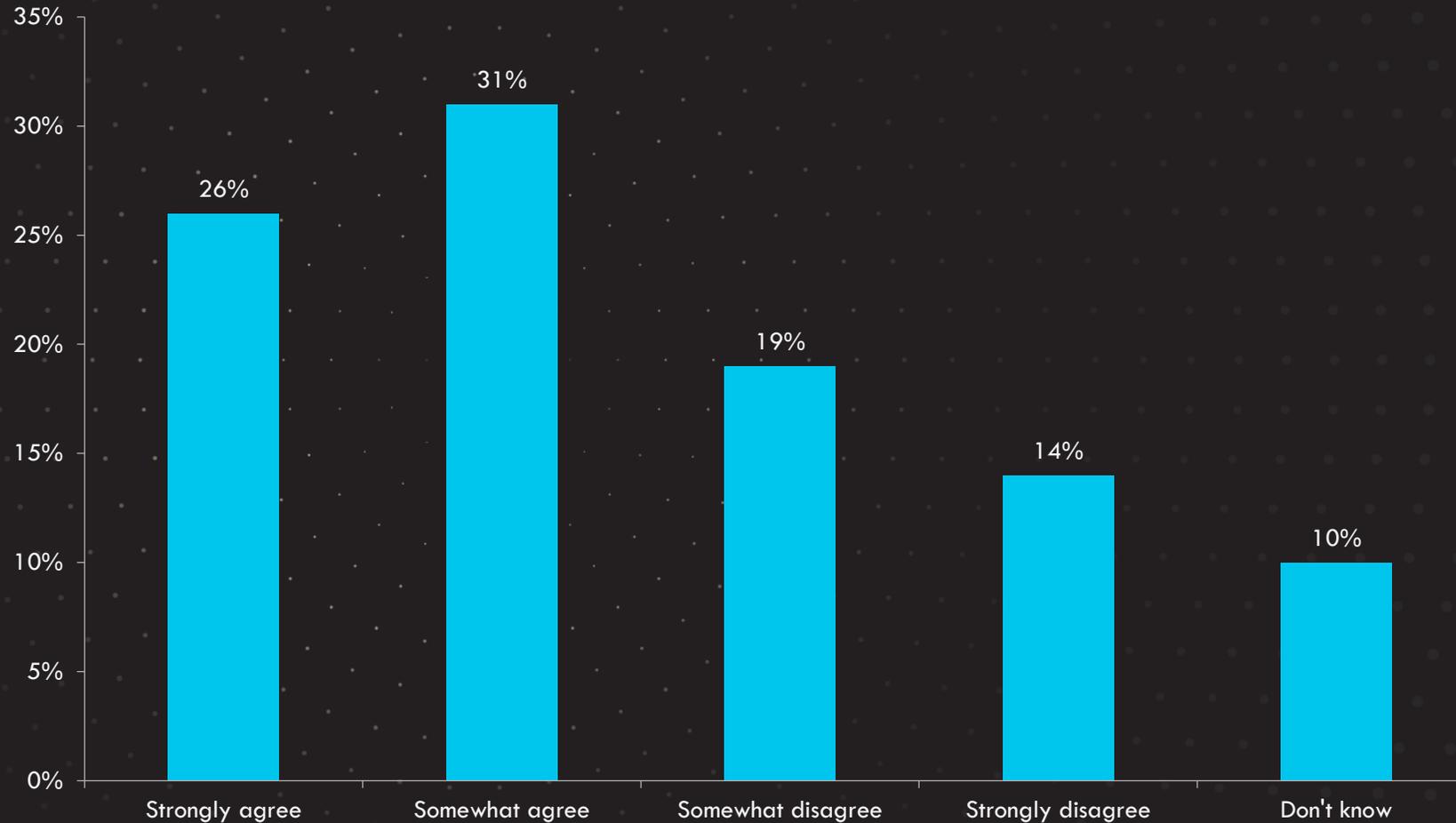


[Base = (Used or would use marijuana and/or cannabinoids to manage pain) Total: N = 637]

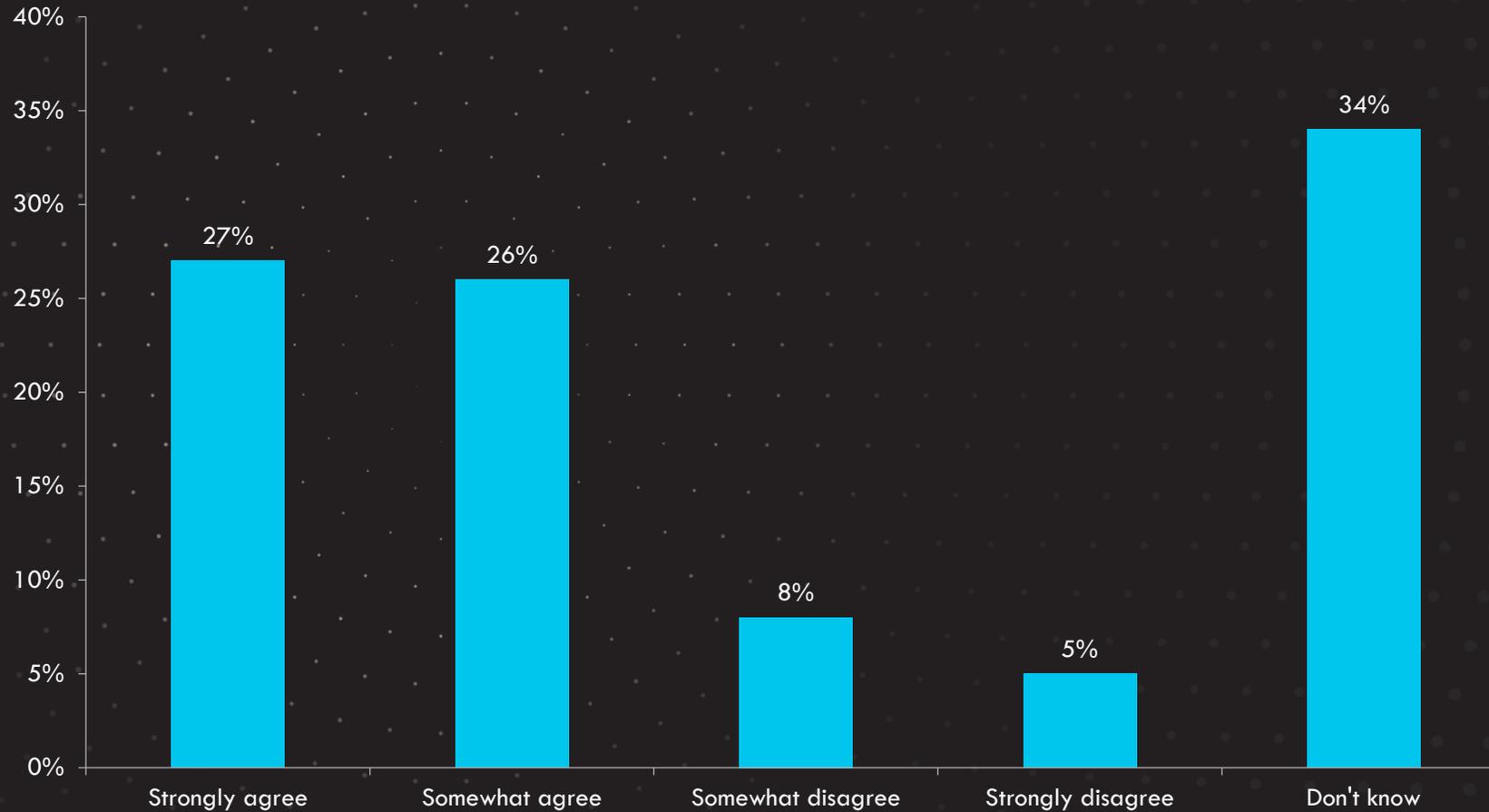
You know what you're getting with marijuana and/or cannabinoids



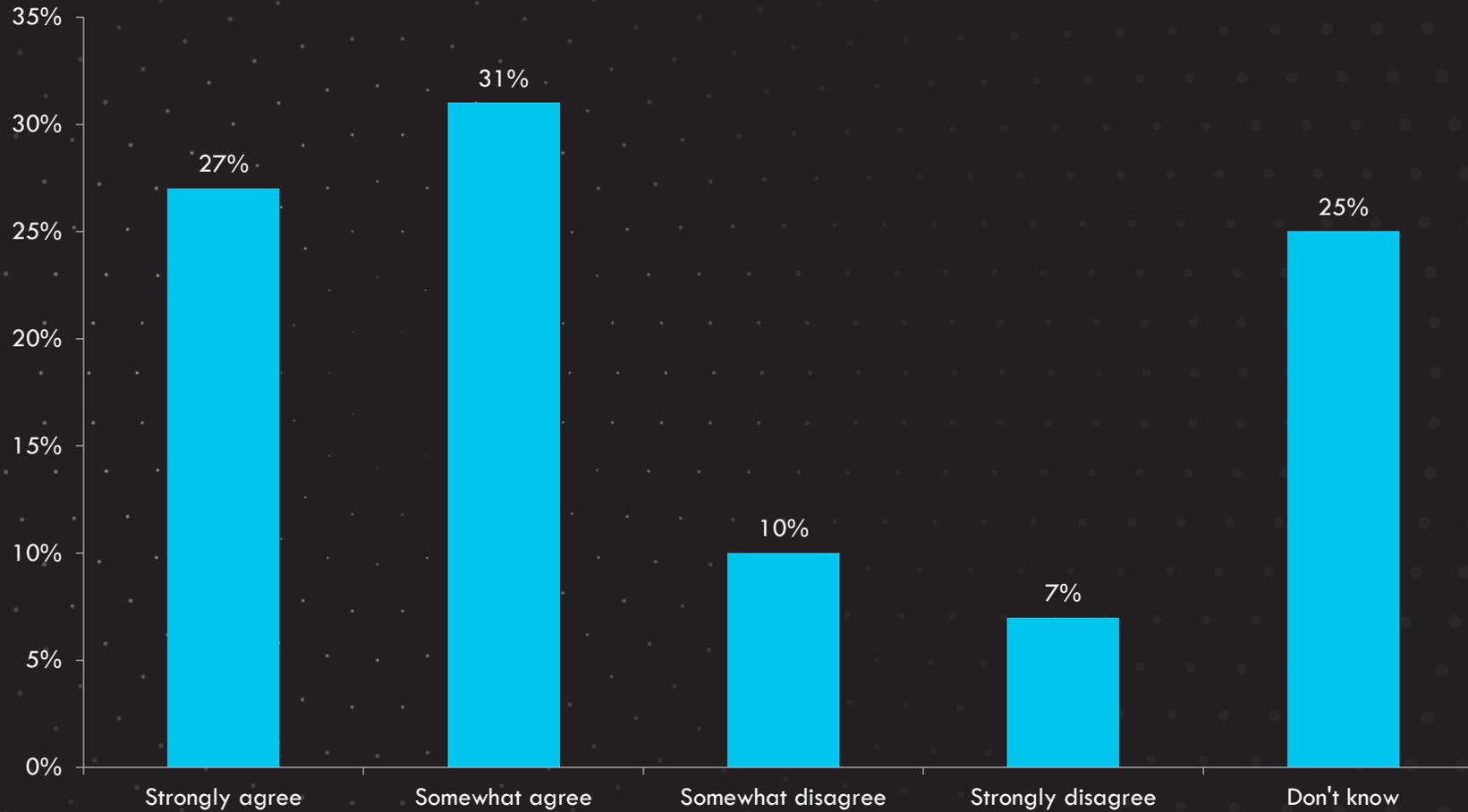
More research is needed to determine if marijuana and/or cannabinoids are safe and effective for pain



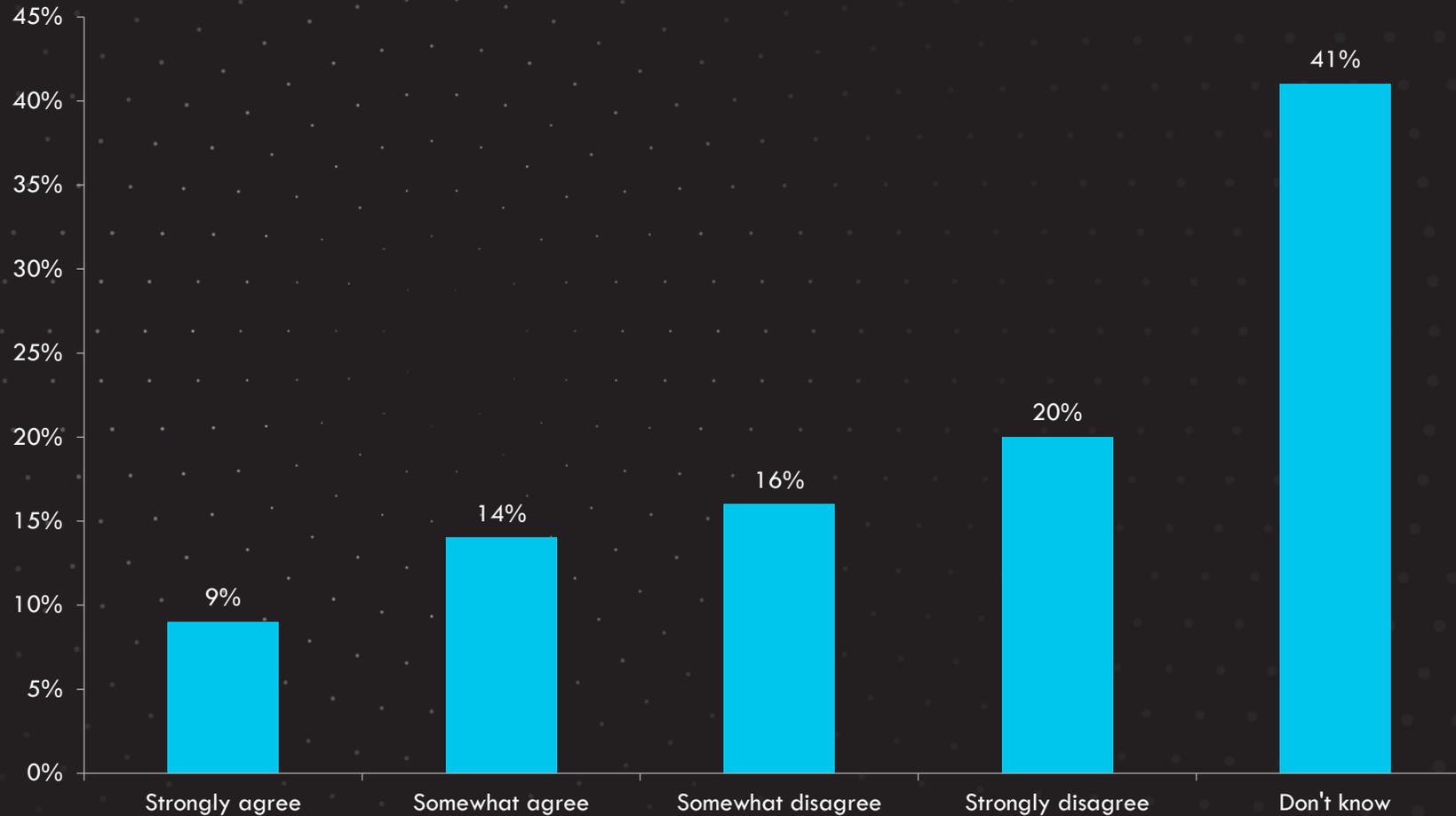
THC causes a mind altering 'high' and CBD does not



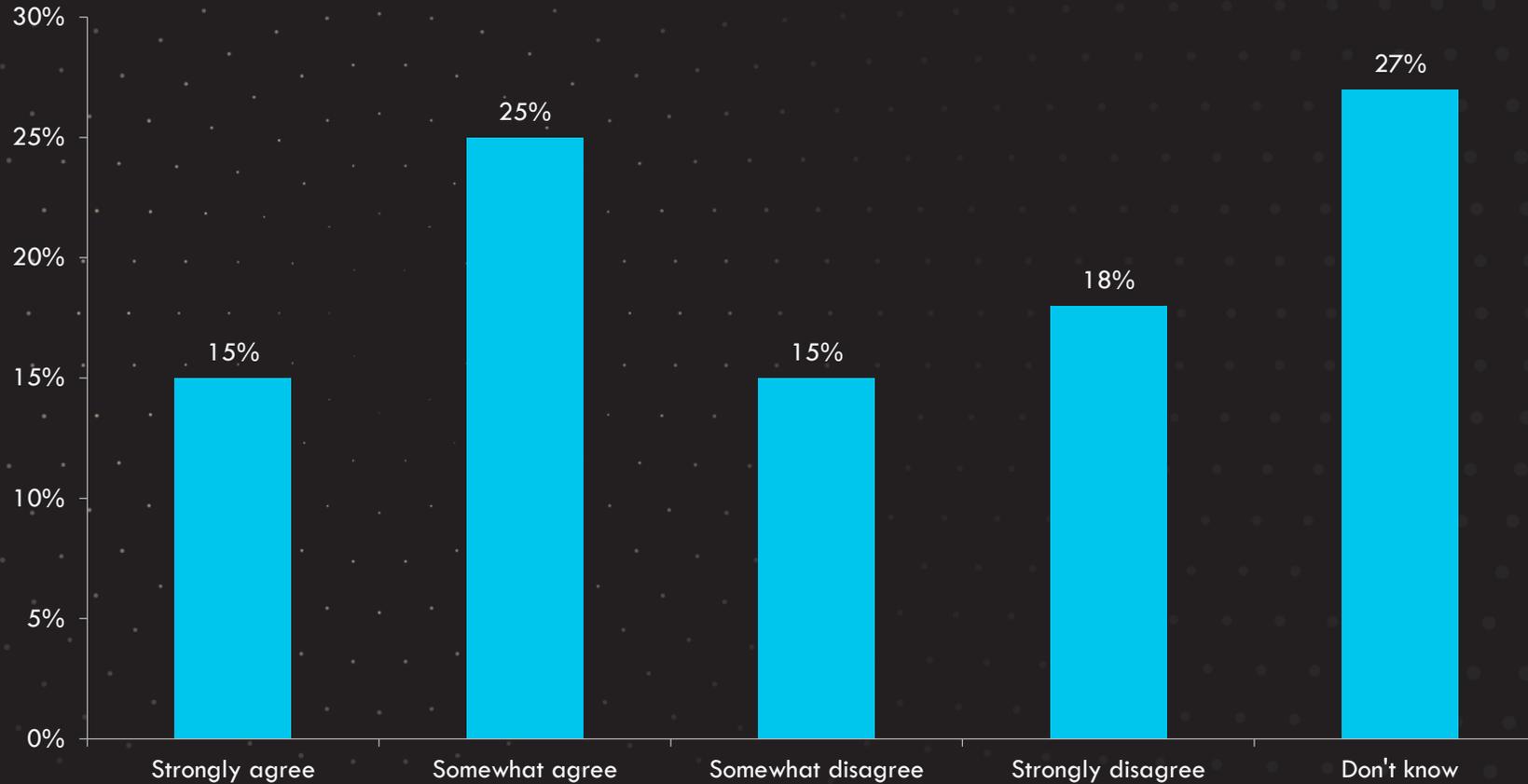
Marijuana and/or cannabinoids have fewer side effects than other medications



Marijuana and/or cannabinoids can cause health problems such as liver damage



CBD sold at grocery stores, truck stops, health food stores/medical marijuana dispensaries is FDA approved, which ensures safety & effectiveness



VA Clinician Survey 2020

N=269

Pain Medicine, 0(0), 2020, 1–7
doi: 10.1093/pm/pnz322
Preliminary Research Article



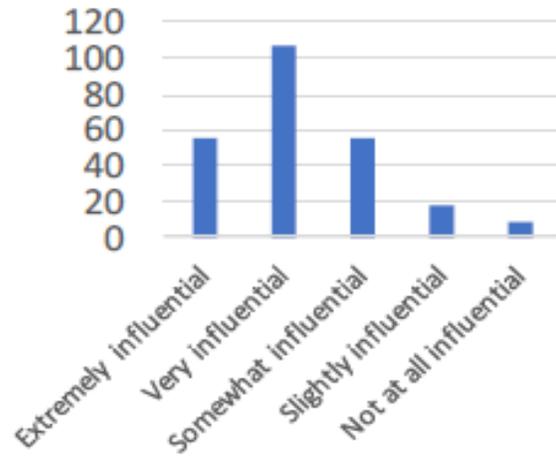
Clinician Knowledge, Attitudes, and Practice Regarding Cannabis: Results from a National Veterans Health Administration Survey

**Devan Kansagara, MD, MCR,^{*,†} Benjamin J. Morasco, PhD,^{*,‡} Megan O. Iacocca, MS,^{*}
Matthew J. Bair, MD, MS,[§] Elizabeth R. Hooker, MS, MPH,^{*} and William C. Becker, MD^{¶,||}**

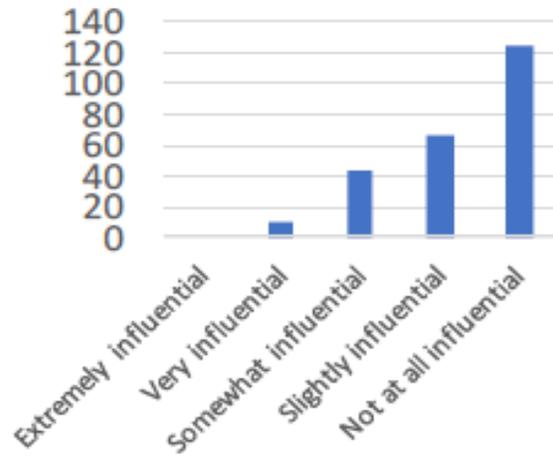
^{*}Center to Improve Veteran Involvement in their Care (CIVIC), VA Portland Health Care System, Portland, Oregon; Departments of [†]Medicine and ;
[‡]Psychiatry, Oregon Health and Science University, Portland, Oregon; [§]VA Center for Health Information and Communication, Indiana University School
of Medicine and Regenstrief Institute, Indianapolis, Indiana; [¶]Pain Research, Informatics, Multimorbidities, & Education (PRIME) Center of Innovation,
VA Connecticut Healthcare System, West Haven, Virginia; ^{||}Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Sources of influence

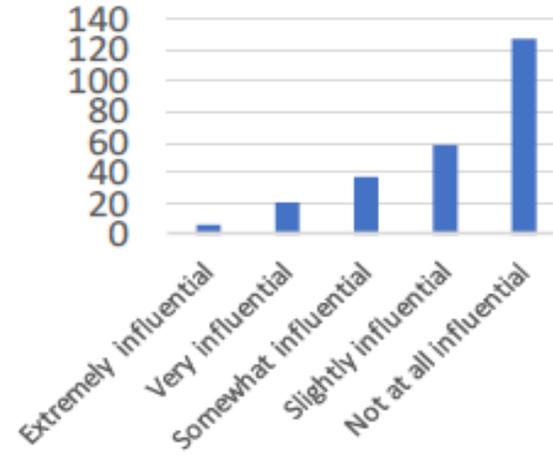
To what degree does peer-reviewed literature influence your thinking about medical cannabis?



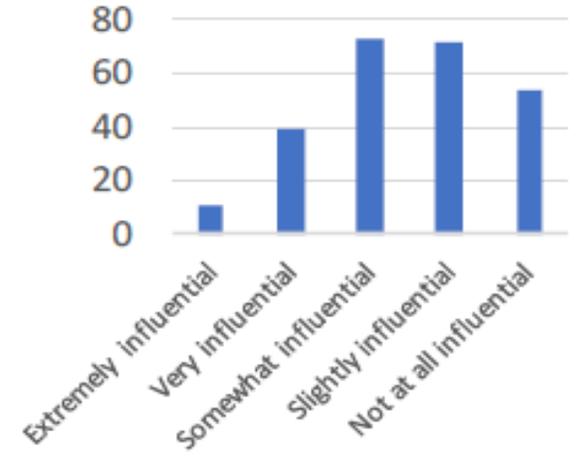
To what degree does the media influence your thinking about medical cannabis?



To what degree do experiences of friends and family influence your thinking about medical cannabis?



To what degree do patients' experiences influence your thinking about medical cannabis?



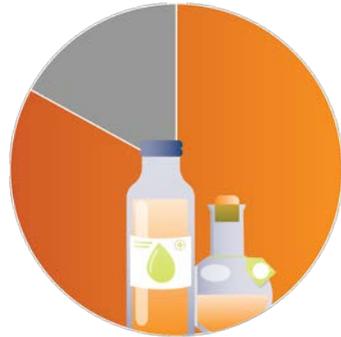
Conclusion

- There is a plethora of recent reports indicating the fast growing interest among the public and healthcare professionals in using cannabinoids in treating chronic pain and anxiety to help curbing the opioid/benzo epidemic.
- While I believe there are potential therapeutic applications for cannabinoids, public interest and commercialization outpaced clinical research.
- There is a good basic science literature about the therapeutic effects of cannabinoids, but there is a paucity of translational research.
- I trust the FDA regulatory process and we need high quality rigorous trials following FDA-standards for safety and efficacy. It is crucial that, cannabinoids meet the rigor of FDA-quality studies like any other medications.
- One should know exactly the dose, the frequency of use and like any other pharmacy-grade products, cannabis preparations should follow the same regulations and quality assurance and be free of any contaminants.

National Poll Results

Individuals across the entire country regionally, demographically and in partisan terms support CBD regulation:

83% of voters support allowing the FDA to test and regulate CBD.



87% of CBD users are supportive of regulation.

87% Democrats

80% Republicans

85% Young voters

85% Seniors

84% College voters

82% Non-college voters

Myths v. Facts



✗ MYTH:

CBD products relieve stress, decrease anxiety, and improve health.



CBD products are all natural and therefore safe and healthy.



No one has ever been harmed by using CBD products.



CBD product labeling can be trusted as accurate.

✓ FACT:

While CBD products are commonly promoted as an effective treatment for a broad variety of medical conditions, there is not enough scientific evidence and data to prove these health benefits. These unproven claims put patients at risk as these products have not been demonstrated to be safe or effective.

The U.S. Surgeon General warned that the long-term effects of CBD consumption are largely unknown. Clinical trials show CBD is associated with significant and potentially dangerous drug interactions, **liver damage**, or other adverse health effects. A recent independent **testing of the 240 top-selling CBD products found that 70 percent were highly contaminated** with substances including lead, arsenic, herbicides, pesticides, and toxic mold. The FDA has warned women who are pregnant or breastfeeding to stay away from these products.

Dozens of CBD-related incidents across the country have been reported in the U.S. **More than 50 people in Utah were made sick** by consuming synthetic substances that were marketed as CBD oil. Others have reportedly lost their jobs after failing drug tests revealing THC from CBD products. **The American Association of Poison Control Centers has reported over 1,200 cases related to CBD in 2019.**

Numerous reports demonstrate that CBD products are frequently mislabeled. A study published in the Journal of the American Medical Association found that **seven of 10 CBD products are mislabeled**. Consumers using unapproved CBD products run the risk of ingesting harmful contaminants.

Tell Me Something I Don't Know: Science, Marketing, and Testing Today

10:55am – 11:35am

Moderator: Janey Terry, *National Safety Council*

Panelists: Dr. Betsy Booren, *Consumer Brands Association*
Dr. Elizabeth Miller, *USP*
Dr. Jesse Miller, *NSF International*

CBD POLICY SUMMIT

DR. BETSY BOOREN
CONSUMER BRANDS
ASSOCIATION

JANUARY 15, 2020



Iconic Brands



The American CBD Consumer:

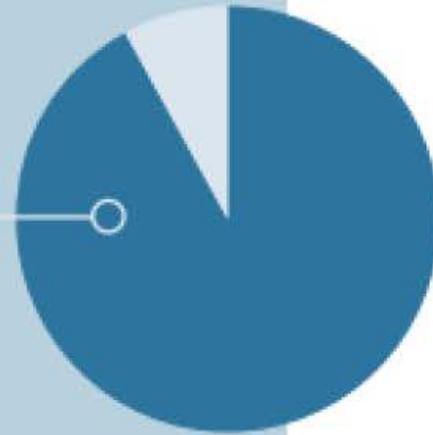
Growing market, growing misunderstanding.

Nearly four-in-ten Americans incorrectly assume CBD is just another name for marijuana.



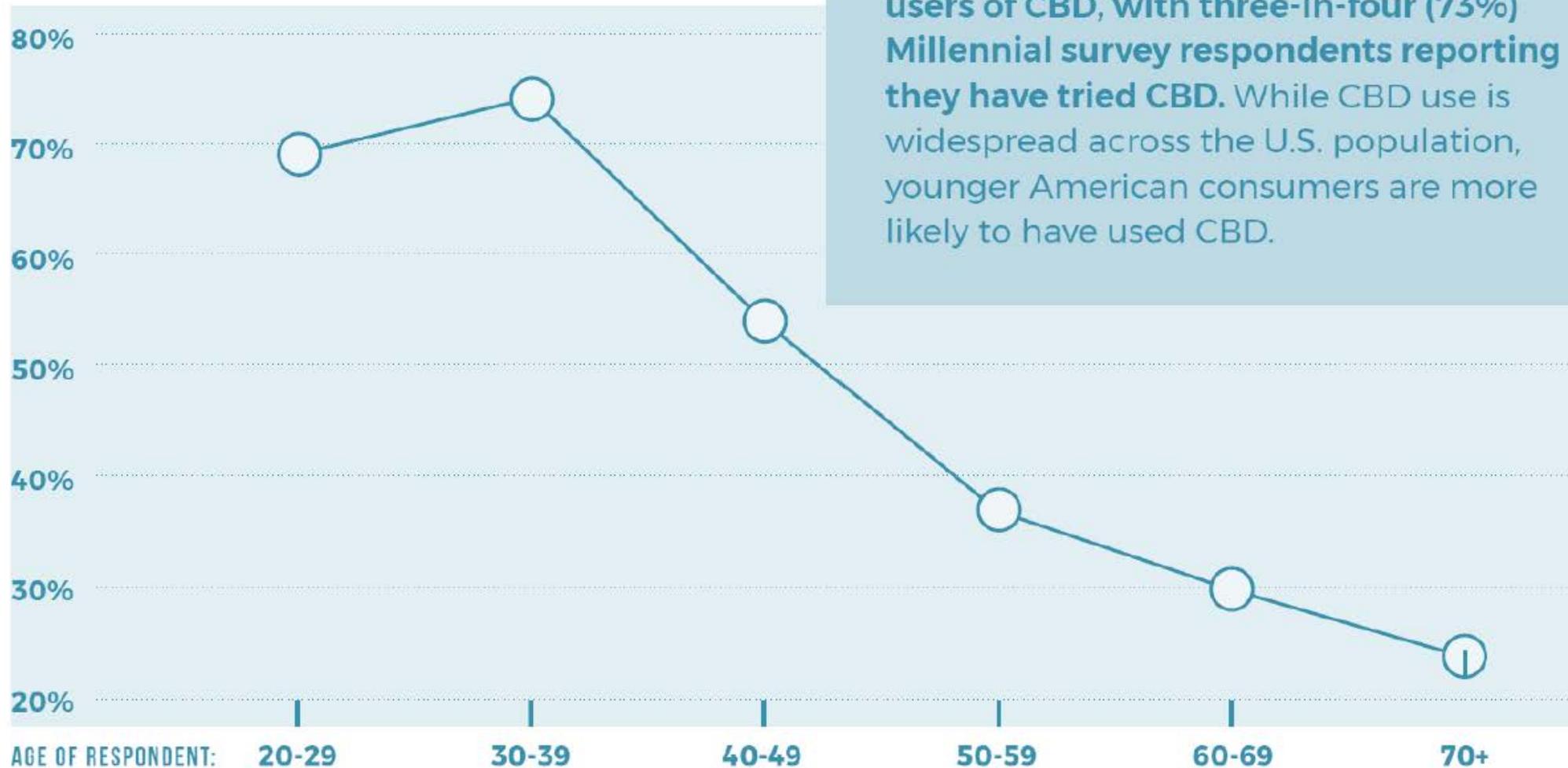
92%

of American consumers incorrectly assume or have no idea if CBD is federally regulated.



WHO IS USING CBD?

Percentage of CBD Usage by Age



Younger Americans



Millennials are the most common users of CBD, with three-in-four (73%) Millennial survey respondents reporting they have tried CBD. While CBD use is widespread across the U.S. population, younger American consumers are more likely to have used CBD.

THE CBD WILD WEST

Consumer demand outpacing regulation

Unknown supply chain

Exponential market growth

Uncertain
safety

Questionable
health benefits

Lacks federal
oversight

We need

Clear, science-based national regulatory framework that promotes safety, ingredient purity and transparency for consumers.

Consumers agree

8 in 10 Americans believe CBD products should be regulated at the federal level, or federally in concert with the states.

WHAT'S NEXT



THE URGENT NEED FOR CBD CLARITY

How confusion and Lack of Regulation
Threaten Consumer Safety and Trust

Grocery Manufacturers Association



Elizabeth Miller, PharmD

*Vice President,
U.S. Public Policy and
Regulatory Affairs
USP*



NSF AND THE ROLE WE PLAY IN *CANNABIS*

NSF INTERNATIONAL

789 N. Dixboro Road, Ann Arbor, Michigan 48105 USA

Jesse D. Miller, Ph.D.

Director of R+D, Hemp Services

WHAT IS NSF INTERNATIONAL?

NSF International is an independent, not-for-profit, non-governmental public health and safety organization.

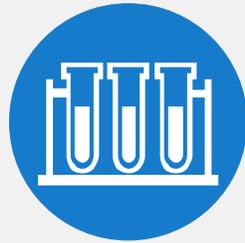
Our mission and focus is **protecting and improving human health.**

NSF HELPS PEOPLE LIVE SAFER.



STANDARDS

Facilitating the development of standards to protect food, drinking water, indoor air, dietary supplements, consumer products and environmental safety



TESTING

Testing products to these and other standards



CERTIFICATION

Certifying products to these standards



AUDITING

Conducting safety and quality audits for a wide range of industries



ADVISORY

Providing strategic and technical consulting for the dietary supplement, pharmaceutical, medical device, food and beverage industries



TRAINING

Developing training and education programs

◀ *Separate from certification* ▶

TODAY, NSF IS A GLOBAL LEADER IN PUBLIC HEALTH AND SAFETY.



Developer of **80+** currently active national consensus standards and **85** published protocols



Steadfast ties with key associations and government agencies



Pan American Health Organization/World Health Organization Collaborating Center on Food Safety, Water Quality and Indoor Environment



Service provider to thousands of organizations in **175+ countries**





THE PROBLEM

TEST RESULTS YOU CAN'T TRUST

NSF INTERNATIONAL

789 N. Dixboro Road, Ann Arbor, Michigan 48105 USA

INDUSTRY TESTING EXAMPLE

LABORATORY SERVICES PRICE LIST

CANNABINOID POTENCY

\$45

- THC, THCa, CBD, CBDa, CBN, CBG.
- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 2 business days (10:30am delivery).
Next day and same day service available.

HOMOGENEITY (w/ POTENCY)

\$130

- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 2 business days (10:30am delivery).
Next day and same day service available.

TERPENE PROFILE

\$65

- 23 terpenes analyzed with GC/MS.
- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 2 business days (10:30am delivery).
Next day and same day service available.

RESIDUAL SOLVENTS

\$45

- 11 solvents analyzed with GC/MS.
- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 2 business days (10:30am delivery).
Next day and same day service available.

MICROBIAL CONTAMINANTS

\$105

- STEC E.Coli, Salmonella, and Total Yeast & Molds.
- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 3 days (10:30am delivery).

PESTICIDE SCREENING

\$125

- 13 pesticides analyzed with LC/MS/MS.
- Sample size requirements per M 1504 and R 1504.
- Turnaround time: 2 business days (10:30am delivery).
Next day and same day service available.





METHOD VALIDATION AND QA/QC

HERE IS WHY

METHOD VALIDATION COSTS MONEY

- > Reference standards
- > Personnel
- > Equipment and Service Contracts
- > Consumables
- > Positive/Negative Controls
- > DOE Across Multiple Operators
 - Replicates
 - Operators
 - Spiking and recovery levels

FOR EACH MATRIX





QUALITY SYSTEMS COST MONEY

- > Reference standards
- > Personnel
- > Equipment and Service Contracts
- > Consumables
- > Positive/Negative Controls
- > QA review of Data
- > LIMS System
- > QA Department
- > Accreditations



CONTACT US

- Technical Questions:
- Jesse D. Miller, Ph.D.
- jdmiller@nsf.org
- 734.707.5413

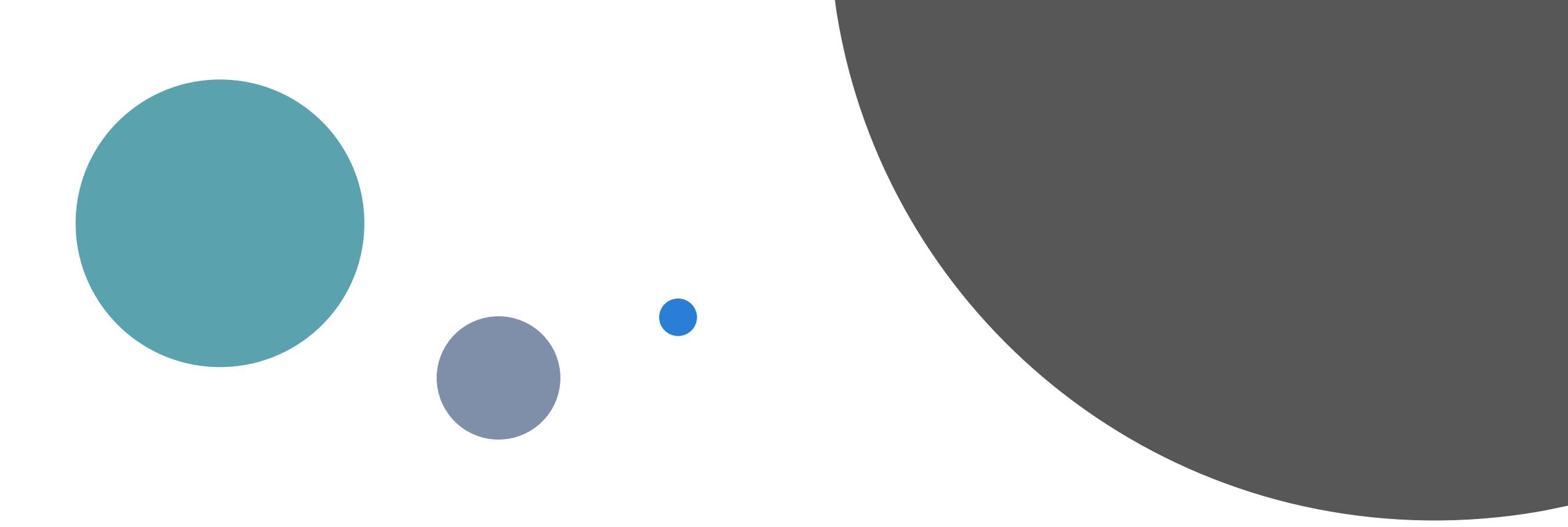
- General Inquiry:
- hemp@nsf.org

What Research Is Needed? How Do We Get There?

11:35am – 12:05pm

Moderator: Libby Baney, *Faegre Baker Daniels LLP*

Panelists: Dr. Duffy MacKay, *CV Sciences*
Dr. Susan Weiss, *National Institute on Drug Abuse*



What Research is Needed? How Do We Get There?

The CBD Summit
A National Dialogue on Public
Safety, Research, and Policy
Duffy MacKay, ND
CV Sciences, Scientific and Regulatory
Affairs



Different Products - Different Regulatory Frameworks
 Different intended Use

Different Scientific Questions and Different Evidentiary Burden

✓ Intended use dictates scientific standards for safety, manufacturing, and scientific evidence

Question #1 -
What research
is needed?



What is the article?



What is the intended use?



What is the article?

What is the article?

- CBD = CBD
- Hemp extract = CBD + minor cannabinoids, terpenes, fatty acids, and 100's of other compounds
- Different ingredients require different scientific and safety considerations

Hypothetical

- The [.....] Summit, a National Dialogue on Public Safety, Research, and Policy

The [.....] Summit, a National Dialogue on Public Safety, Research, and Policy

Alcohol

- Kombucha and fermented beverages
- Wine and Beer
- Liquor
- Prohibited - Alcohol + caffeine products

Caffeine

- Foods – coffee, tea, chocolate,
- Supplements – guarana, yerba mate, cola nut, GT-extract, caffeine (under certain conditions)
- Drugs – Caffeine - monographed and approved for specific indications
- Prohibited – pure powdered caffeine

***Comprehensive, flexible, and fit-for-purpose hemp derived ingredient policies are needed – not CBD policy!*

What is intended use?

	Intended use	Science (safety)	Science (benefit)	article
Food	Taste, aroma, nutritive value	<p>Composition of ingredient</p> <p>Entire population</p> <p>Multiple servings/sources</p> <p>Minimal control of consumer intake</p>	<p>Demonstrate contribution to nutrition</p> <p><i>*FDA standards exist for required level of scientific evidence for food, supplements, and cosmetics</i></p>	<p>Hemp seed derived</p> <p>Fatty acids, protein, etc.</p>
Dietary Supplement	Support structure and function	<p>Composition of ingredient</p> <p>Establish safety per conditions of use in labeling</p> <p>Can use label to exclude sub-populations like pregnancy and children</p>	<p>Demonstrate effect on ECS, occasional stress, occasional sleep problems ,well-being, normal aches and pains due to over-exertion, quality of life, etc. (SSA standard)</p>	<p>Hemp derived (nutrients + cannabinoids)</p>
Cosmetic	Cleansing and beautifying	<p>Establish safety for topical application – contact allergies, etc.</p>	<p>Establish effect on skin moisture and appearance</p>	<p>Hemp derived</p>
Drug	Treat disease	<p>FDA approval (benefit vs. risk)</p>	<p>FDA approval (cause and effect)</p>	<p>Cannabis derived</p>



Question #2) How do we get there?

1) Regulatory Clarity – FDA guidance on the type and scope of hemp ingredients that do not trigger IND exclusion (or issue regulations that allows ingredients that contain CBD)

- Creates market predictability for food, supplement, and cosmetic companies
- Responsible industry will invest to fill scientific gaps to align with regulations

2) Remove the significant federal obstacles to hemp and cannabis scientific research (e.g., stigma and red tape, single cannabis source, DEA licensing, etc.)

Breaking the gridlock: Regulation of dietary supplements in the United States

Akshay Kapoor and Joshua M. Sharfstein*

“A major reason for this policy gridlock is the inability of different parties to come to an agreement on a path forward.”

ment against rogue products, a stronger disclaimer explaining the limited role of FDA in evaluating structure/function product claims, the establishment of standard laboratory techniques for characterization of products, and more clear authority for the agency when safety concerns arise. Copyright © 2015 John Wiley & Sons, Ltd.

“The purpose of this paper is to set out a new framework for regulation in which consumers, industry, and regulators can all find common ground.”

Introduction

An estimated one hundred million Americans purchase dietary supplements each year.^[1] These include such therapies as iron for iron-deficiency anemia, Vitamin D for rickets, and calcium supple-

ments. Beyond the types of claims for dietary supplements permitted under law, manufacturers and sellers of dietary supplements frequently make unproven and unauthorized claims that their products prevent, treat, or cure disease. In recent years, the FDA has cited manufacturers of hundreds of products for promising relief

conceptual shift from ‘benefit versus risk’, the model for prescription drugs, to ‘access with safety’.

after the passage of major legislation on dietary supplements, substantial sections of the market for these products remain disorganized, deceptive, and dangerous.

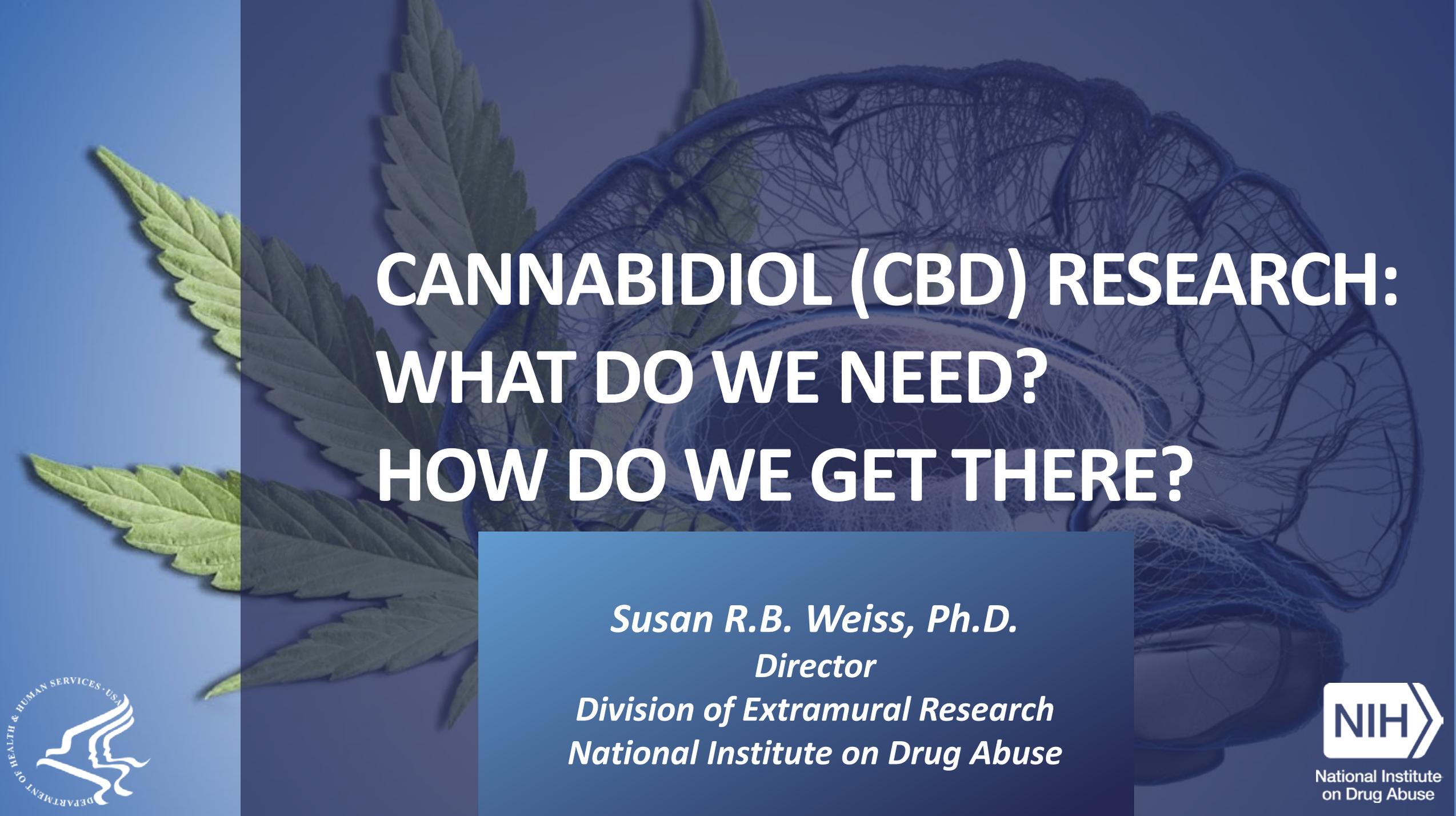
Hundreds of products marketed as supplements have been spiked with illicit pharmaceuticals, risking serious injury and death.^[2] In the first three months of 2015 alone, the US Food and Drug Administration (FDA) warned about or recalled over 30 tainted sexual enhancement products including *Libigrow*,^[3] *Rhino*

and illegal claims to treat, prevent, diagnose, or cure specific disease.^[23] The Government Accountability Office found that one in five dietary supplements sold for weight loss or immune system support included prohibited disease-related claims on their labels.^[20] Such claims not only mislead consumers into buying the advertised products, subjecting them to unknown risk with no clear evidence of efficacy, but can also lead consumers not to seek treatment proven to be safe and effective.



Summary

- Hemp can be legally used to derive a range of ingredients with significantly different composition that can be marketed for a range of intended uses.
- Different ingredients, different products, different regulatory frameworks – requires different scientific questions that require different levels of evidence.
- Scientific evidence that supports product safety for intended use is the minimum requirement for all hemp derived consumer products.
- To account for the complex and evolving nature of cannabis science, policy, and regulation – policy changes may be needed (*Breaking the Gridlock – Josh Sharfstein*).
 - Product registration to permit easier enforcement against rogue products
 - Stronger FDA disclaimer explaining the limited role of FDA in evaluating supplement and cosmetic claims
 - Establish standard laboratory techniques and specifications for characterization of products
 - Stronger authority for the agency when safety concerns arise
- Removing FDA prohibitions to allow full-FDA regulation of hemp derived CBD will foster academic and industry research on safety and benefits for non-drug products.



CANNABIDIOL (CBD) RESEARCH: WHAT DO WE NEED? HOW DO WE GET THERE?

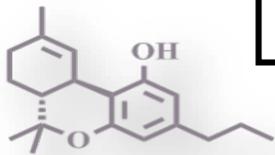
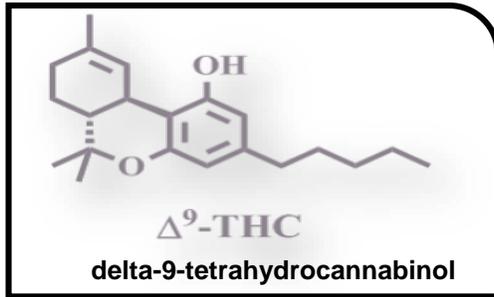
Susan R.B. Weiss, Ph.D.
Director

Division of Extramural Research
National Institute on Drug Abuse

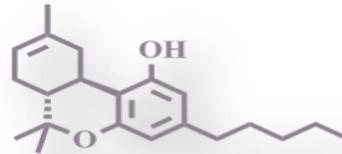


National Institute
on Drug Abuse

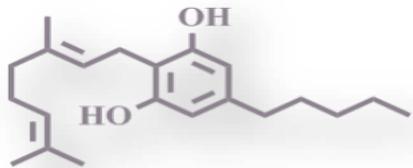
CANNABIS/MARIJUANA CONTAINS >100 CANNABINOIDS PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS



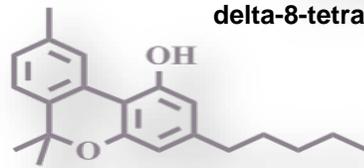
Δ^9 -THCV
delta-9-tetrahydrocannabivarin



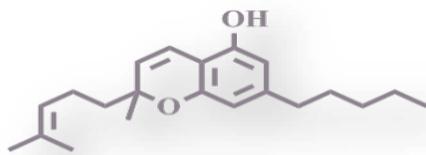
Δ^8 -THC
delta-8-tetrahydrocannabinol



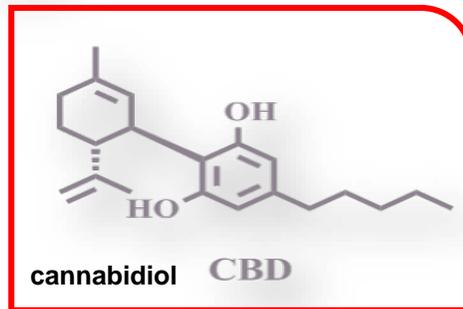
CBG
cannabigerol



CBN
cannabinol



CBC
cannabichromene



- Plant with long history of use worldwide
- Illegal under US Federal law (Schedule I substance)
- Legal for broad medical use in 33 States + D.C.
- Legal for adult use in 13 States + D.C.
- High CBD variety (or extracts) legal in 13 states with narrow medical marijuana laws only
- CBD from Hemp (defined as cannabis sativa <0.3% THC) no longer in the CSA
- Versions of active ingredients approved for medical indications in U.S. and other countries
 - Synthetic - Marinol, Syndros, Cesamet
 - Plant Derived- Sativex (THC/CBD)
 - Plant Derived-Epidiolex (CBD: FDA approved: Schedule V)



What is Cannabidiol (CBD)?

- Constituent of the Cannabis plant (hemp or marijuana)
- Multiple mechanisms of action: 5HT1a receptors; glycine receptors; orphan G-protein coupled receptors; FAAH inhibition; more...
- Weak or no direct activity on CB1 or CB2 receptors (where THC acts)
- Does not have rewarding effects
- May counteract some effects of THC
 - Bred out of “high potency” cannabis
- May have a wide range of medical and other health uses
- FDA approved medication (Epidiolex) for severe childhood epilepsy
- Widely available in dietary supplement, foods, cosmetics, pet products—*not FDA regulated*





NEW TERRITORY: AGRICULTURE IMPROVEMENT ACT 2018 (FARM BILL)

- Removed Industrial Hemp (defined as cannabis sativa plant containing less than 0.3% THC) from Controlled Substances Act
- Re-affirms the regulatory role of the FDA for hemp – derived products
 - Medications (to treat illnesses or symptoms)
 - Dietary Supplements (wellness)
 - Food Additives
- Public Hearing: May 31; >120 speakers provided input as FDA considers how to go about regulating CBD
- *Expected to be a \$2B industry by 2020 and growing*
- Concerns re: current market: Unregulated Products; Unverified Claims; Uninformed Users (e.g., side effects, drug interactions).

The implications for research with CBD are not yet clear.



STRESS OR ANXIETY

Studies have shown that CBD oil use can help reduce anxiety and/or stress for people who may suffer from conditions like PTSD, social anxiety, and many others.

RELIEVING PAIN

People suffering with chronic pain issues like Fibromyalgia and others, are finding relief when using CBD oil on a regular basis.



SEIZURES & EPILEPSY

CBD has shown to be very promising in helping control and reduce seizures in children and some adults.

SLEEP

Studies have shown that with certain doses of CBD Oil, people had reported that their sleep improved greatly.



CANCER

Numerous studies have been done and are continuing to be done showing that CBD oil may be helping with the adverse effects of some certain types of cancer and may hinder the migration of cancer cells.

For more detailed information and links to the studies and information included here, please visit www.FindingHappyinHealthy.com



NIH/NIDA **CANNABIS** RESEARCH FUNDING

RCDC Categories	NIH FY 16 (in Millions)	NIH FY17 (in Millions)	NIH FY18 (in Millions)	NIDA FY17 (in Millions)	NIDA FY18 (in Millions)
Cannabinoid Research	\$115	\$140	\$147	\$88	\$90
Therapeutic Cannabinoid	\$28	\$36	\$37	\$16	\$20
Cannabidiol	\$12	\$15	\$19	\$11	\$14
Endocannabinoid System Research	\$51	\$63	\$63	\$30	\$28

CANNABIDIOL RESEARCH: CURRENT INVESTMENTS AND FUTURE NEEDS



NIH: 59 ACTIVE STUDIES

- **BASIC SCIENCE:** Mechanisms of action; pharmacokinetics; pharmacodynamics
- **THERAPEUTIC POTENTIAL:** Addiction: OUD, Alcohol, Nicotine; Social Anxiety, PTSD, Digestive Disorders, Cancer, Pain, Epilepsy
- **SAFETY CONCERNS/RISKS:** Neurodevelopment, drug/drug interactions, long-term and cumulative exposure to multiple products, liver toxicity, vulnerable populations (e.g., pregnant women)

CANNABIDIOL RESEARCH:



CLINICAL TRIALS.GOV:

1/9/2020: 188 STUDIES: 10 ARE FEDERALLY FUNDED, 80 INDUSTRY FUNDED

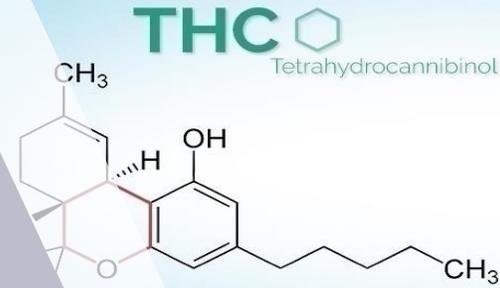
- **THERAPEUTIC POTENTIAL:** Irritable Bowel Syndrome, Hepatitis, Epilepsy (other forms), Prader-Willi Syndrome, Rett Syndrome, Infantile Spasms, Graft vs. Host Disease, Pain, Cancer (multiple myeloma, glioblastoma), Schizophrenia, Acne, Dysmenorrhea
- **SAFETY:** Drug/drug interactions, pharmacokinetics, tolerability, absorption of topical products

Note that some studies use Sativex: 50% THC/50% CBD

CANNABIS RESEARCH BARRIERS

SCIENTIFIC

- Complexity of plant (100 cannabinoids + other components), entourage effect?
- Route of administration
- Need proper controls, sufficient study duration
- Should be learning from what is already happening in the states and in other countries (e.g., patient registries; adverse outcomes).
- Should be studying products that people are using to understand full range of health consequences.



5,000 Comments in 5 Minutes
(actually 4,494 comments in 10 minutes)

Tish Pahl, Esq.

Principal, Olsson Frank Weeda Terman Matz PC

#CBDPolicySummit

**5,000 comments in 5 minutes
(actually, 4,494 comments in 10 minutes)**

Tish Pahl, Esq.

Principal, Olsson Frank Weeda Terman Matz PC

“Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds”

- Federal Register notice, 84 Fed. Reg. 12969 (April 3, 2019), Dkt. FDA-2019-N-1482
- FDA asked for “scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds”
- Received 10 hours of oral testimony; 4,494 comments

What's in the docket?

- Hundreds of comments from stakeholders in the dietary supplement and drug industries, law firms, trade associations, researchers, cannabis advocacy groups, consumer groups, regulators, and healthcare advocacy coalitions
- Thousands of comments from individuals
- Though intended to broadly cover cannabis and cannabis-compounds, became a referendum on CBD

The consumer voice

- Thousands of comments from individuals
- First and last comments in the docket were from individuals using CBD products for sleep, anxiety, and pain
- CBD is everywhere, in everything
- CBD is being taken for everything, including pain, anxiety, depression, sleep, seizures, arthritis, cancer, fibromyalgia, Alzheimer's, autism, Parkinson's and symptoms associated with those and other conditions

Among
stakeholders,
recognizing
CBD is
everywhere,
there was
some
consensus!

- Need for regulatory framework, clarity and vigorous enforcement of wrongdoing
- Need for more research, ease barriers and/or incentivize cannabis research
- Lack of clarity and lax enforcement has led to proliferation of bad actors
- Consumers are confused
- Need to clearly distinguish CBD supplements from CBD drugs based on strength, concentration and claims

Among
stakeholders,
recognizing
CBD is
everywhere,
there was
some
consensus!

- Standards for
 - Manufacturing
 - Labeling
 - Testing
- Adverse event/MedWatch reporting
- No drug/therapeutic claims except in FDA-approved drugs and biologics
- Use of NDI process for CBD-containing supplements

Where there
isn't
consensus

CBD SAFETY

- CBD is safe and is providing relief to consumers
 - June 2018 WHO Report on CBD
 - FDA's Scheduling Memo
 - Scores of clinical studies in thousands of patients over decades
 - Lots of common foods and supplements have drug/drug interactions
 - Studies on liver toxicity are flawed
- We don't know if CBD is safe in foods and dietary supplements for consumer use
 - Just because it's not intoxicating doesn't mean it's safe
 - Data are limited (not randomized clinical trials, small populations, short duration, open label, reviews and case studies aren't clinical data, etc.)
 - Liver toxicities, adverse effects, drug/drug interactions

Where there isn't consensus

- Up to 1500 mg per serving is safe and well-tolerated
- Simultaneous marketing of cannabis compounds in dietary supplements won't discourage research and development of FDA-approved products
- Safety signals observed at 5 mg/kg/day
 - Substantial safety factors need to be established
- No one would bother developing clinical data and going through FDA drug approval process if you can just market a consumer product

What wasn't in the docket

- Human consumption data to support CBD in conventional foods
- Data on safe and efficacious use in animals
- Food industry interests

Questions?

Tish Pahl, Esq.
tpahl@ofwlaw.com



#CBDPolicySummit

Fireside Chat with FDA Principal Deputy Commissioner Amy Abernethy, MD, PhD

Moderated by:

Liz Richardson

Project Director, Healthcare Products

The Pew Charitable Trusts

Impact of FDA Actions on the Future of Research

1:15pm – 2:15pm

Moderator: Dr. Ron Manderscheid, *NACBHDD*

Panelists: Alice Mead, *Greenwich Biosciences*

Dr. Phil Nadeau, *COWEN*

Dr. Mallory Loflin, *VA San Diego Healthcare System & UCSD School of Medicine*

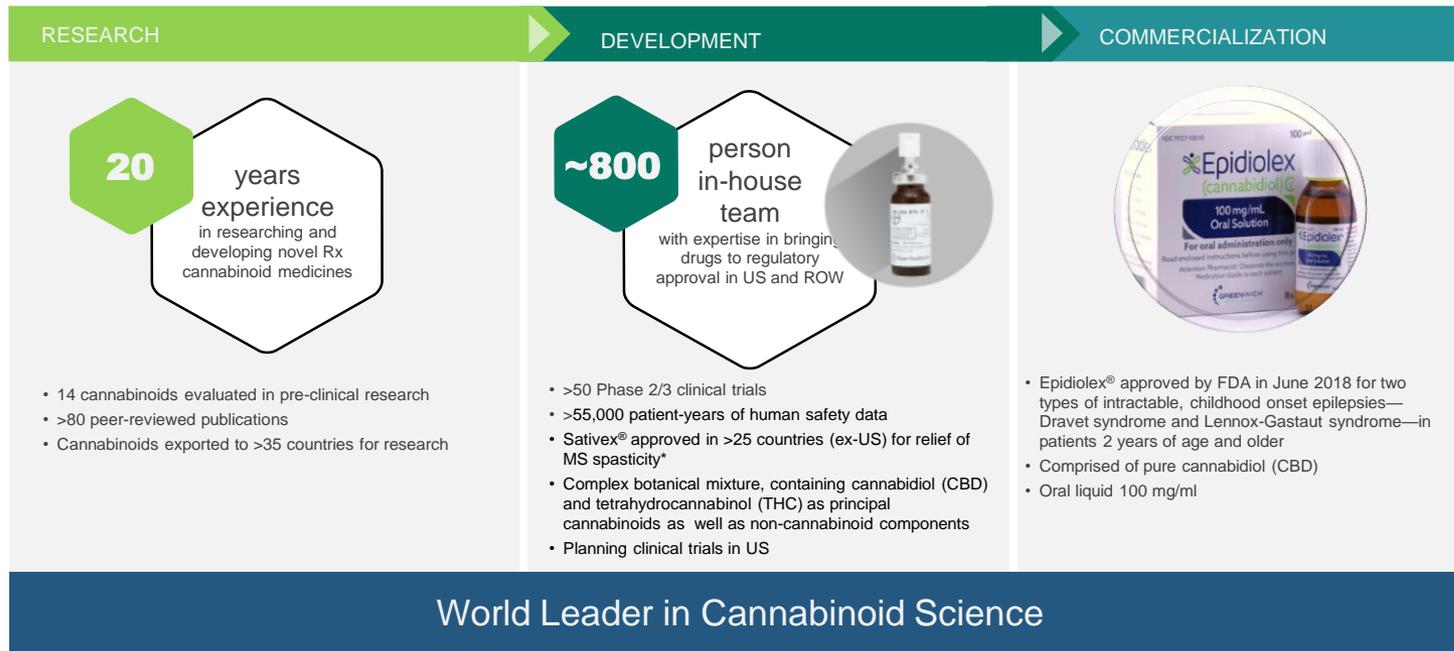
Andrew Sperling, *National Alliance on Mental Illness*



Considerations for Regulating CBD Products as Treatments for Medical Conditions

Alice P. Mead
Greenwich Biosciences

Greenwich Biosciences



*Sativex is not approved in the US for any indication

Why Go Down the FDA Pathway?

**Vulnerable
populations
and patients with
serious illnesses**



Does the drug work?

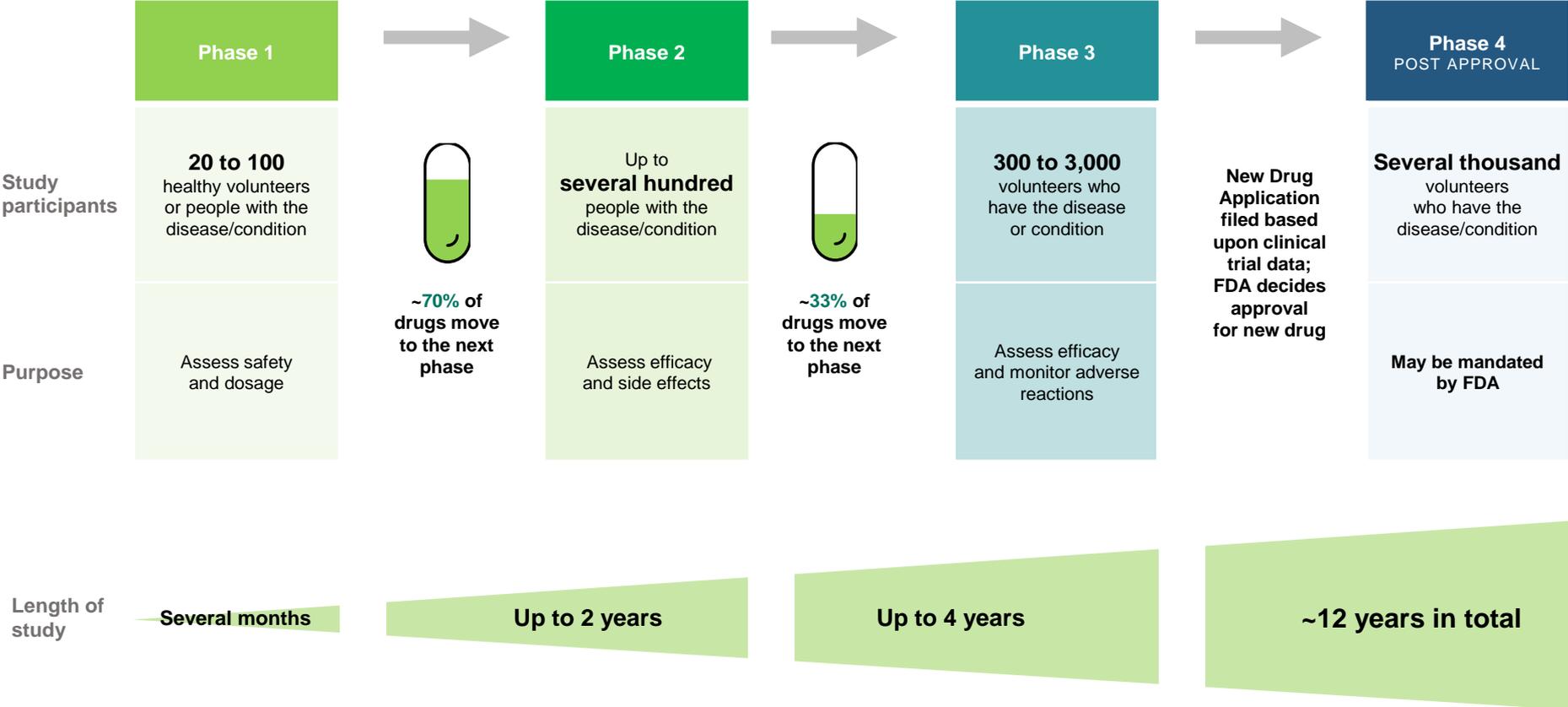
- What does it work for?
- What doesn't it work for?
- How well does it work?
- Does something else work better?
- How long does it take to work?
- Will it stop working?
- How much should I take?
- How long should I take it for?
- Should I take it with or without food?



Is the drug safe?

- What are the side effects?
- How closely should I be monitored?
- Can I take it if I'm pregnant or trying?
- Can my child take it?
- Can the elderly take it?
- Is it free of contaminants?
- Will it conflict with my other drugs?
- How is it manufactured?
- Is it consistently manufactured?

What Differentiates an FDA Approved Medicine from other Products?



The drug development process: <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm>. Accessed August 30, 2017.

What Additional Studies must be done to show that Medicines are Safe?



- ✓ Multiple animal toxicology studies



- ✓ At least one hundred patient-years of data required



- ✓ Collection of all adverse events (side effects)
 - Mild/moderate/severe
 - Related and unrelated



- ✓ Studies... studies... and more studies
 - Drug/drug interaction
 - Food/drug interaction
 - Abuse potential
 - Renal or hepatic impairment
 - QT (cardiac)



- ✓ Monitoring of all adverse events indicative of abuse or dependence

CBD not free of side effects

Self-reported side effects of CBD products and oral cannabis extracts* (>10% of patents)¹⁻³

Weight Gain Vomiting
Seizures Somnolence
Fatigue Obsessive Behavior Insomnia
Increased Appetite Irritability GI Disturbances
Anxiety Nausea
Increased Seizures

Controlled studies with regular monitoring

Liver toxicity

was found in 10% of participating patients in Epidiolex trials

*Liver transaminases were not monitored

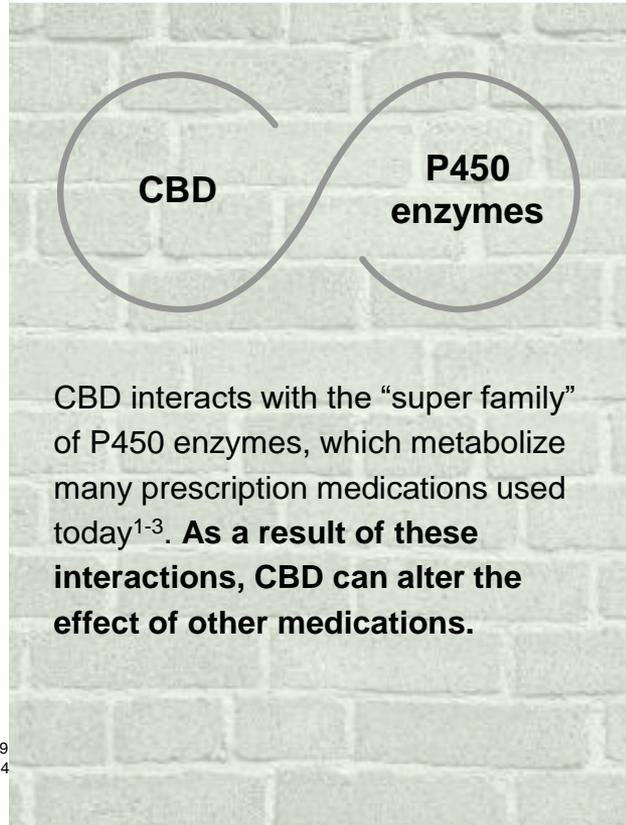
1. Hussain et al. (2015) Ep & Beh. 47: 138-141; 2. Press & Knupp. (2015) Epi & Beh. 45:49-52; 3. Treat et al. (2017) Epilepsia; 58(1): 123-127.

Side Effects cont.



Lack of healthcare professional oversight poses a serious concern in patients who take multiple drugs because—

- CBD can alter the effect of other medications
- CBD could decrease or increase the potency of the other drugs the patient is taking

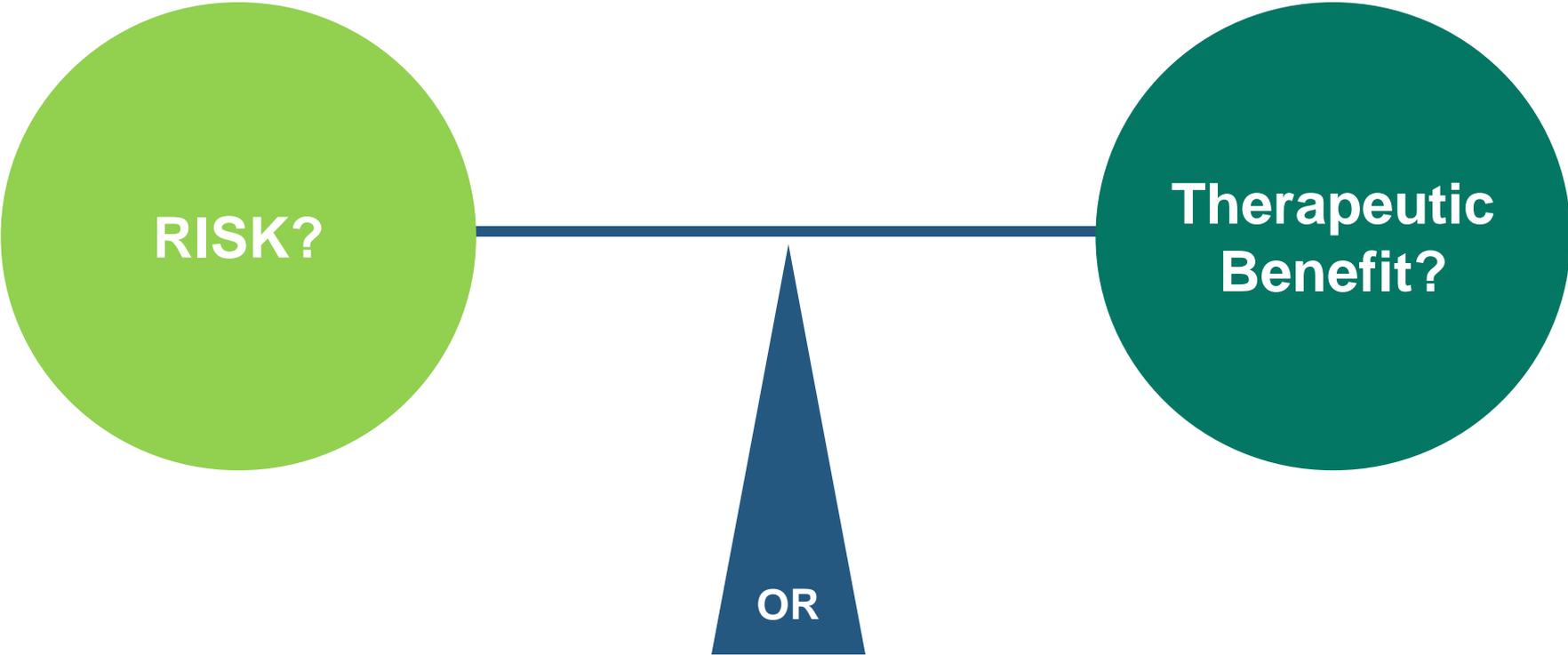


Some commonly prescribed drug classes, supplements, or drinks⁴:

- Antiseizure drug
- Proton pump inhibitors
- Antidepressants/Prozac
- Anti-virals
- Anti-bacterials
- Oral contraceptives
- Multiple anti-fungals
- St. John’s Wort
- Grapefruit juice

1. Bergamaschi MM, Queiroz RH, Zuardi AW, et al. *Curr Drug Saf.* 2011;6:237–249
2. Iffland, K and Grotenhermen F. *Cannabis Cannabinoid Res.* 2017; 2(1): 139–154
3. Grayson et al. *Epilepsy & Behavior Case Reports.* 2018; 9: 10-11
4. <https://reference.medscape.com/drug/epidiolex-cannabidiol-1000225#3>

Balance of Benefit and Risk



45 acre / 18 hectare glasshouse

Material to supply 36,000 children for one year



- Grown in computer controlled greenhouses
- Temperature, humidity, and lighting controlled
- Natural, proprietary growth medium devoid of heavy metals
- No pesticides used; biocontrols
- Propagation by clones; no genetically modified plants

Epidiolex Process—Drug Substance

DRUG SUBSTANCE

CBD Botanical Raw Material

Milling

Decarboxylation

CO₂ Extraction

CBD Botanical Drug Extract (Crude Form)

Multi-step Crystallisation

Pure CBD



CO₂
Extraction



Filtration &
Drying

MEDICINES for PATIENTS

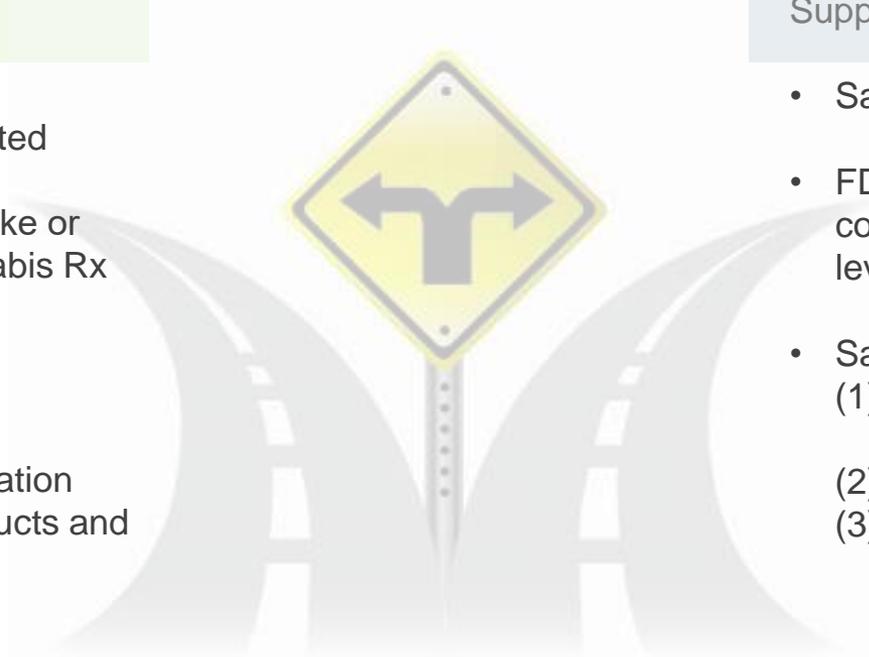
FDA-approved | Rx drugs

- Research into medicinal potential just getting started
- FDA's decision could make or break the future of cannabis Rx medicine
- Strengthen incentives
- Clear and wide differentiation between consumer products and medicines

CONSUMER PRODUCTS

Supplements | Conventional foods

- Safety concerns with CBD
- FDA should identify safe concentration and daily intake levels
- Safety margin to account for:
 - (1) Known and unknown safety issues
 - (2) Vulnerable populations
 - (3) High consumer demand and the likelihood of cumulative exposure

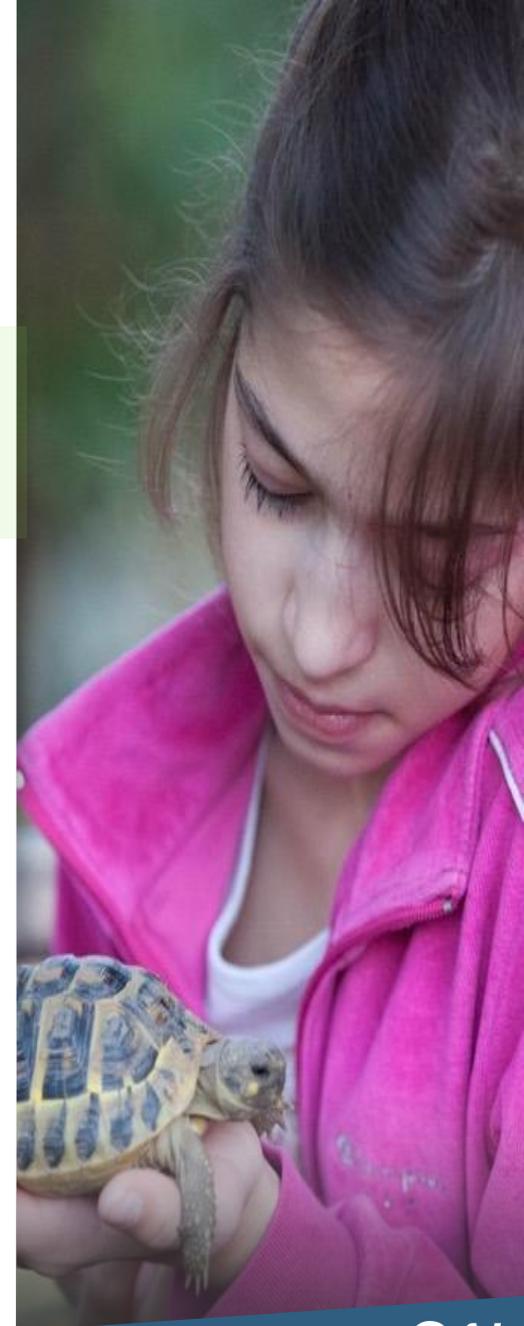


Work toward innovative cannabis medicines has just begun

CANNABINOID POTENTIAL

GW studying
cannabinoids for 8
serious illnesses
with unmet need

Research needed
in many other
indications with
significant unmet
need





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Thank You

apm@greenwichbiosciences.com

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IMPACT OF FDA ACTIONS ON THE FUTURE OF CBD RESEARCH: A BIOTECH ANALYST'S PERSPECTIVE

JANUARY 2020

Phil Nadeau, Ph.D.

646 562 1336

phil.nadeau@cowen.com

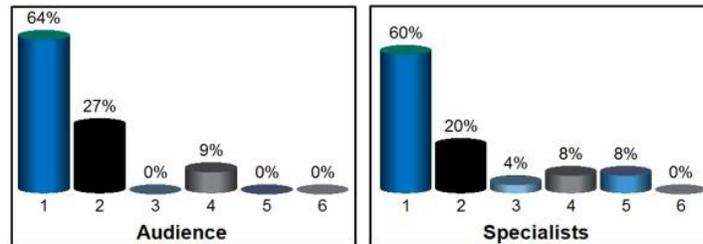
Investors And Physicians Expect Increasing Use Of CBD In Medicine

Results From A Survey Of Investors (“Audience”) And Physician Experts (“Specialists”) Conducted In Conjunction With Cowen’s March 2019 Health Care Conference

COWEN

26) To how many patients did you recommend CBD (not FDA approved) in 2018?

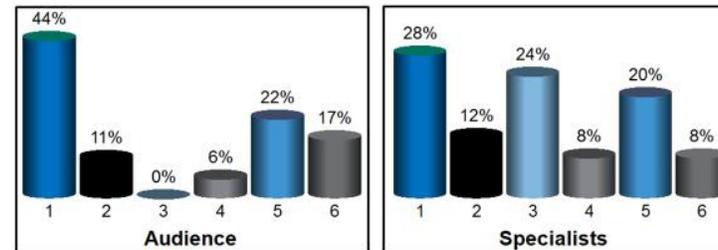
1. 50 or less
2. 51-100
3. 101-150
4. 151-200
5. 201-250
6. 251+



COWEN

28) To how many patients do you expect to recommend CBD (not FDA approved) in five years?

1. 50 or less
2. 51-100
3. 101-150
4. 151-200
5. 201-250
6. 251+

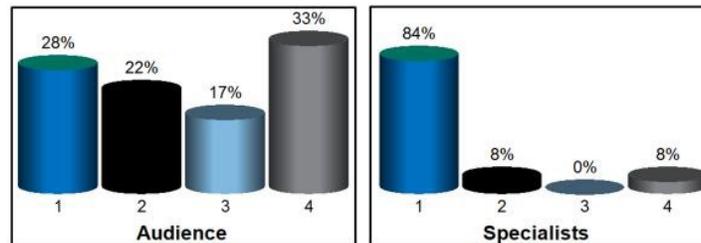


However, Survey Suggests Physicians Are Hesitant To Be Very Involved In Use Of Non-FDA Approved Cannabinoids

COWEN

11) How often do you recommend a particular supplier?

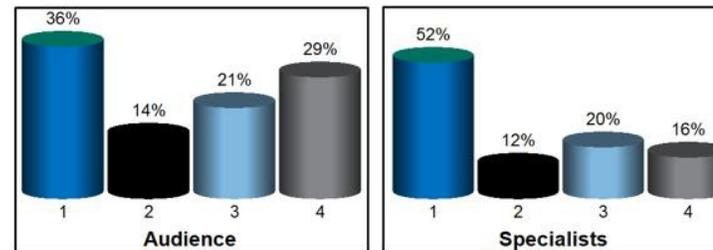
1. Less than 25% of the time
2. 25-50% of the time
3. 51-75% of the time
4. Over 75% of the time



COWEN

14) How often do you assist patients in titrating and determining their personal, optimal dosing regimen?

1. Less than 25% of the time
2. 25-50% of the time
3. 51-75% of the time
4. Over 75% of the time



“Audience” = Investors, “Specialists” = Physician Experts

Source: Cowen and Company 2019 Health Care Conference

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FDA Licensure Confers Benefits

Indication

FDA Approval Includes Assessment Of Benefit-Risk, And Clear Instructions On Indication And Dosing

- The FDA-approved product insert provides physicians with information that helps drive adoption, such as a concise indication statement, as well as dosing information
- To become approved by FDA a product must be rigorously tested in clinical trials
- Our survey suggests physicians are more comfortable using FDA-approved products

Payor Coverage

FDA-Approved Products Are Covered By Insurance

- Managed care generally does not cover OTC products
- However, it will reimburse for use of FDA-approved pharmaceuticals that contain CBD (e.g. Epidiolex)

Barrier To Entry

FDA-Granted Exclusivities Can Prevent Competition For A Period, Allowing Investors To Realize A Return On Their R&D Investment

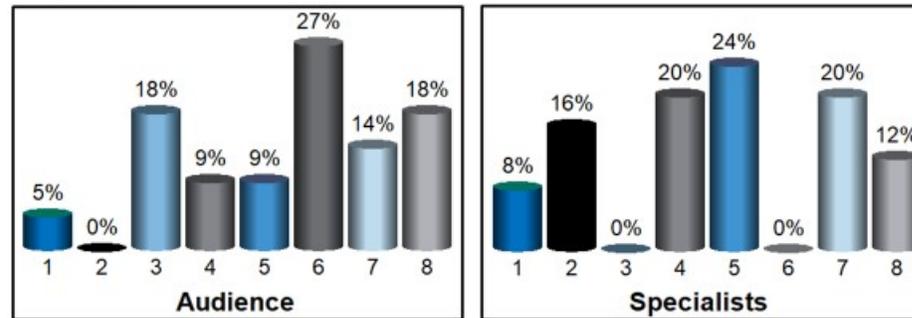
- The structure of CBD is in the public domain, so companies can not get composition of matter patents...
- ...But, a period of exclusivity without competition is necessary for investors to realize a return on their investment
- FDA-granted exclusivities such as Orphan Drug Exclusivity (ODE) are one way to prevent competition in a specific indication for a period of time (ODE lasts 7 years from FDA approval).

Case Study: We Expect GW's Epidiolex To Be Widely Adopted In The Treatment Of Refractory Epilepsies Following FDA Approval

COWEN

8) The percentage of patients with Dravet and Lennox-Gastaut expected to be treated with GW's Epidiolex in three years is closest to:

1. 0-10%
2. 11-20%
3. 21-30%
4. 31-40%
5. 41-50%
6. 51-60%
7. 61-70%
8. 71%+



“Audience” = Investors, “Specialists” = Physician Experts

Source: Cowen and Company 2019 Health Care Conference

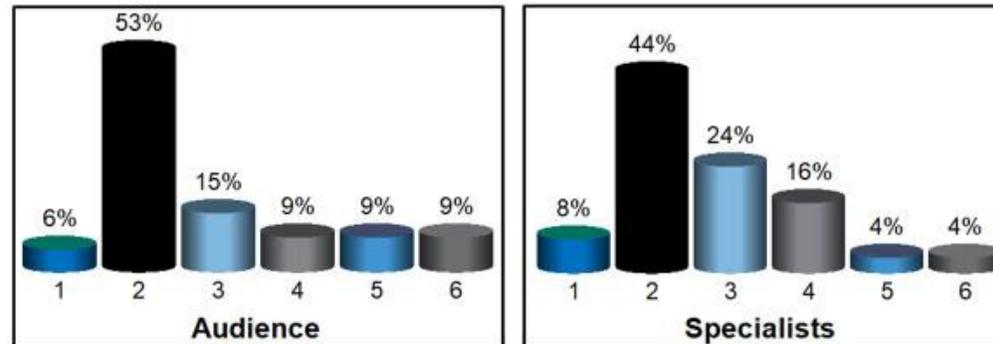
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Physicians Anticipate Rarely Substituting An Non-FDA Approved Version Of CBD In Place Of Epidiolex

COWEN

7) How often will a patient with a refractory seizure disorder obtain CBD-enriched medical marijuana rather than fill a prescription for Epidiolex?

1. Never
2. Less than 25% of the time
3. 25-50% of the time
4. 51-75% of the time
5. 75% or more
6. Always



Source: Cowen and Company, 2019 Health Care Conference

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“Audience” = Investors, “Specialists” = Physician Experts

Epidiolex Will Hopefully Produce An Attractive Return On GW's Investment To Develop It

Invest

Drug Development Is Expensive...

- GW Pharma spent approx. \$552MM on Research And Development From 2014 when company sponsored studies of Epidiolex began through 2018 when Epidiolex was FDA approved.

Return

...But Successful Products Can Generate Attractive Returns For Investors Nonetheless

- We project that Epidiolex will achieve >\$1B in revenue at peak
- We project cumulative net profits to GW since the launch of Epidiolex eclipsing \$552MM in 2022
- Therefore, GW should recoup its investment with an attractive return before FDA-granted Orphan Drug Exclusivity expires in 2025

Rate

Investors Require The Expected Return On Invested Capital To Be In Excess Of The Weighted Cost Of Capital In Order To Fund A Project

- Because of the risk associated with drug development, biotechs have high WACCs
- According to Bloomberg, GW's WACC is 12.2%.

ADDENDUM

Stocks Mentioned In Important Disclosures

Ticker	CompanyName
GWPH	GW PharmaceuticalsPlc

Analyst Certification

Each author of this research report hereby certifies that (i) the views expressed in the research report accurately reflect his or her personal views about any and all of the subject securities or issuers, and (ii) no part of his or her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed in this report.

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The recommendation contained in this report was produced at January 13, 2020, 19:46 ET. and disseminated at January 13, 2020, 19:46 ET.

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

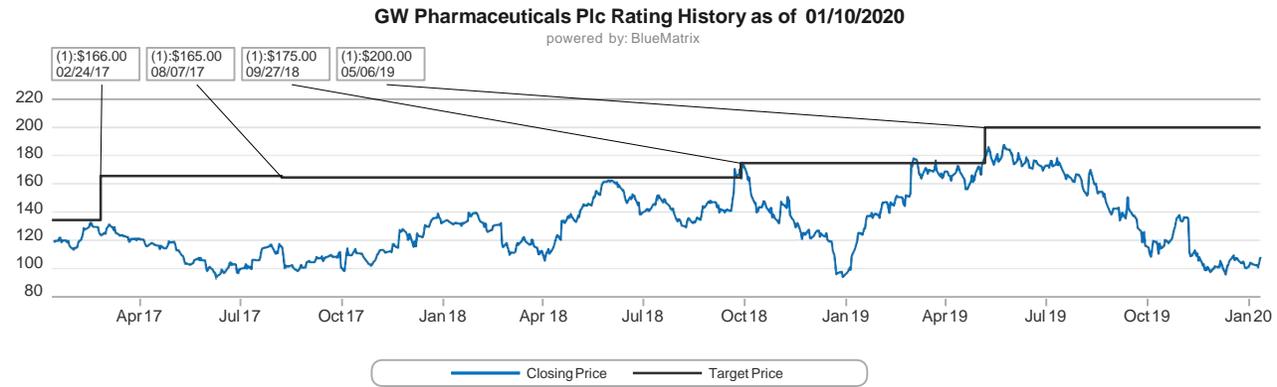
Cowen and Company Equity Research Rating Distribution

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy(a)	505	63.05%	130	25.74%
Hold(b)	291	36.33%	12	4.12%
Sell(c)	5	0.62%	0	0.00%

(a) Corresponds to "Outperform" rated stocks as defined in Cowen and Company, LLC's equity research rating definitions. (b) Corresponds to "Market Perform" as defined in Cowen and Company, LLC's equity research ratings definitions. (c) Corresponds to "Underperform" as defined in Cowen and Company, LLC's equity research ratings definitions. Cowen and Company Equity Research Rating Distribution Table does not include any company for which the equity research rating is currently suspended or any debt security followed by Cowen Credit Research and Trading.

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Legend for Price Chart:

I = Initiation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | \$xx = Price Target | NA = Not Available | S = Suspended

Source: Cowen and Company 2019 Health Care Conference

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Source: Cowen and Company 2019 Health Care Conference

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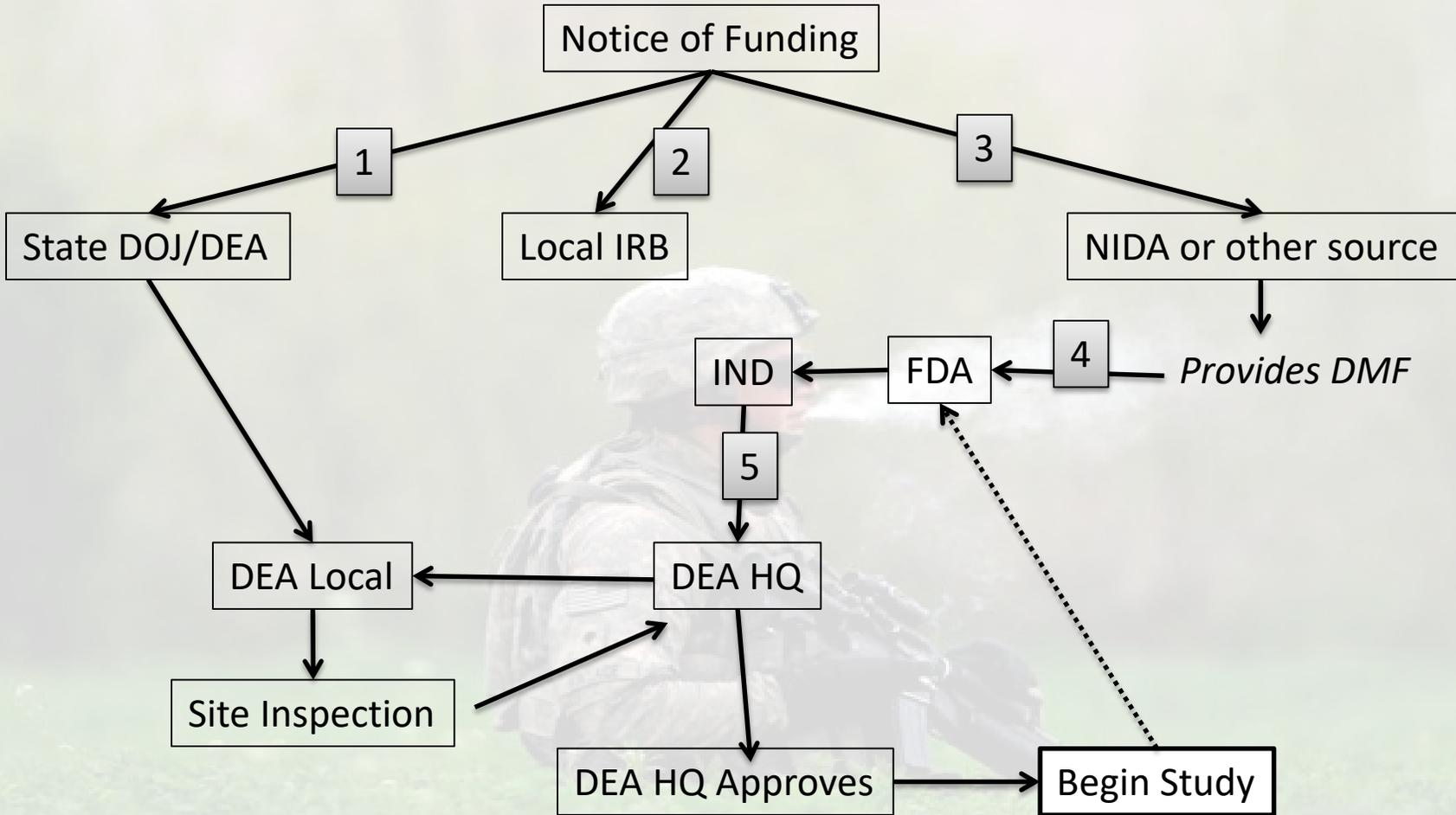
Impact of FDA Action on Research

Mallory Loflin, PhD

Assistant Professor of Psychiatry
University of California San Diego

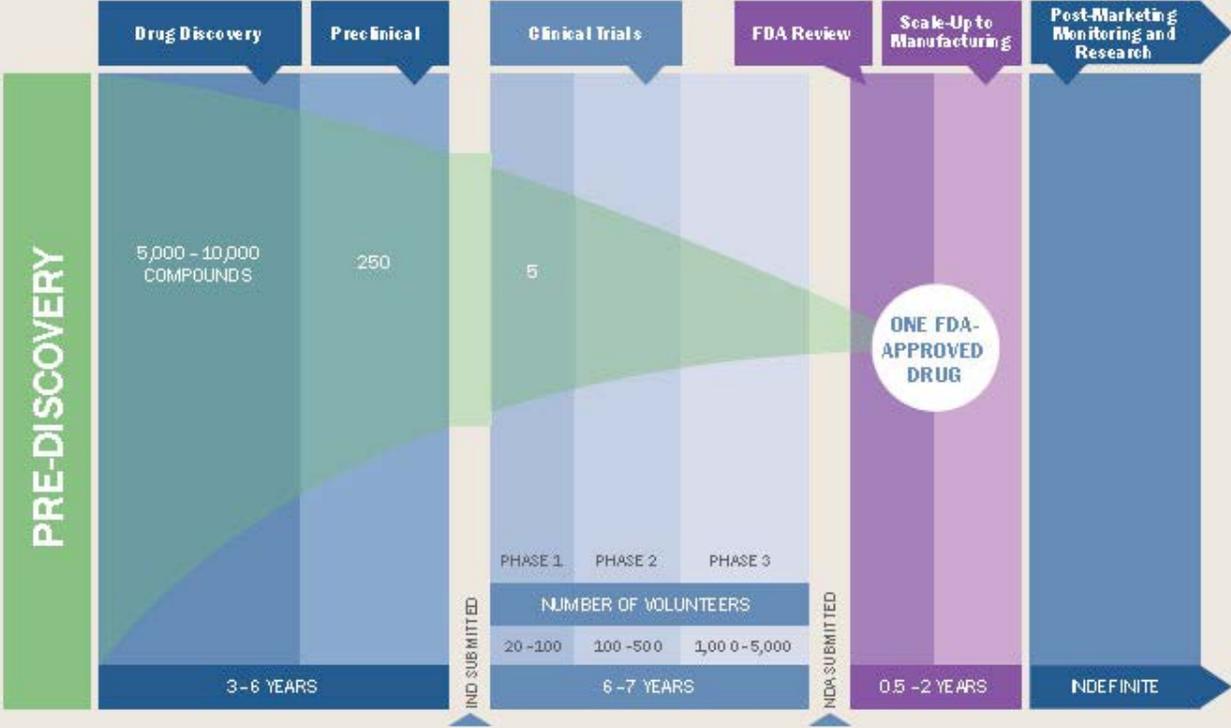
Principal Investigator/Clinical Scientist
Veterans Affairs San Diego Healthcare System

Process of Approval ~ 6-12 mo.



Traditional Drug Development Process

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



Cannabis and Cannabinoid Research
Volume X, Number X, 2019
© Mary Ann Liebert, Inc.
DOI: 10.1089/can.2018.0008

Prescribing Health Care Providers' Attitudes, Experiences, and Practices Surrounding Cannabis Use in Patients with Anxiety Disorders and Post-Traumatic Stress Disorder

Jake Rosenberg,¹ Mallory J.E. Loflin,^{2,3} Yasmin L. Hurd,⁴ and Marcel O. Bonn-Miller^{5,*}

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			Total (N = 84)
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	
Label accuracy, No. of products (%) [95% CI]				
Accurate ^a	18 (45.00) [30]	5 (25.00)	3 (12.50)	26 (30.95)
Under ^b	10 [14]			
Over ^c	12 [18]			
Labeled concentration, mg/mL				
Mean (95% CI)	56. [51]			
Median (range)	22. [0.00]			
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10. [29]			
Median (range) [% of deviation]	2.7 [12]			

^a Cannabidiol content tested within 10% of label

^b Cannabidiol content exceeded labeled value by

^c Cannabidiol content tested more than 10% below

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

Cannabinoid	Average Observed Concentration Across Tests, mg/mL	
	Mean (SD)	Median (Range)
Cannabidiol ^a	30.96 (80.86)	9.45 (0.10-633.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.06 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ -9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ -9-Tetrahydrocannabinolic acid	0	0

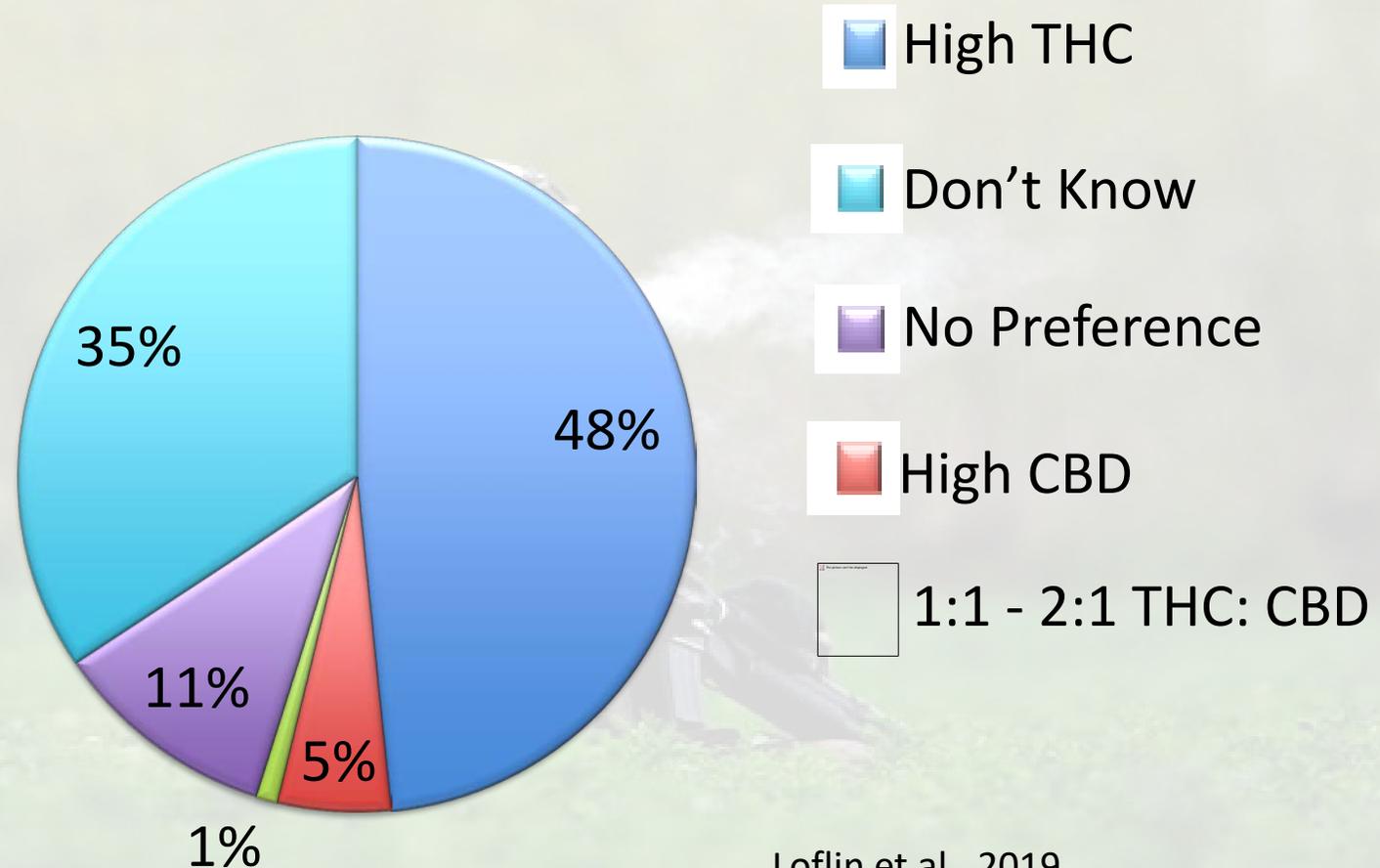
^a The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

14.01%-31.35%], cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

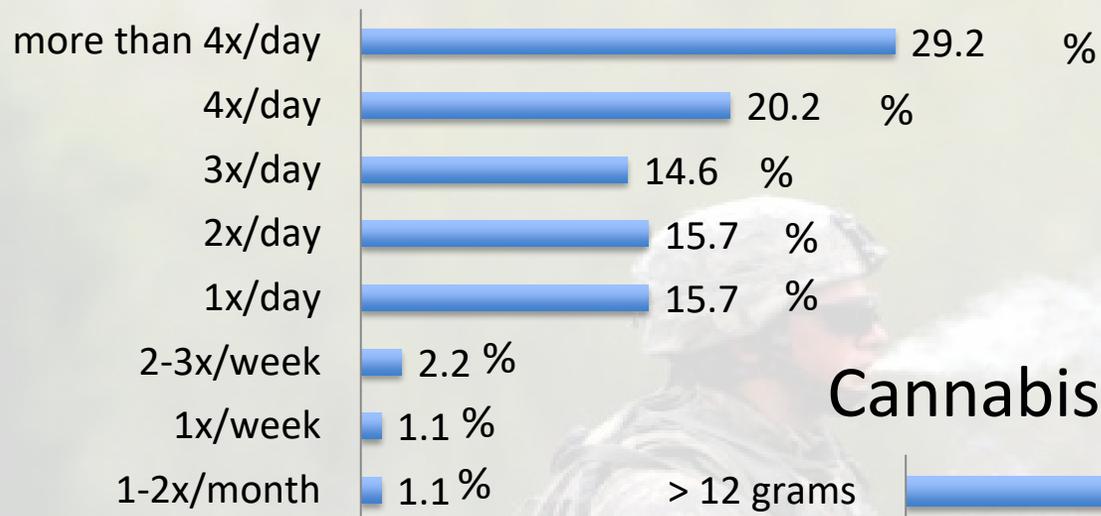
Preclinical and in-vivo use don't match

Preferred Cannabis "Type"

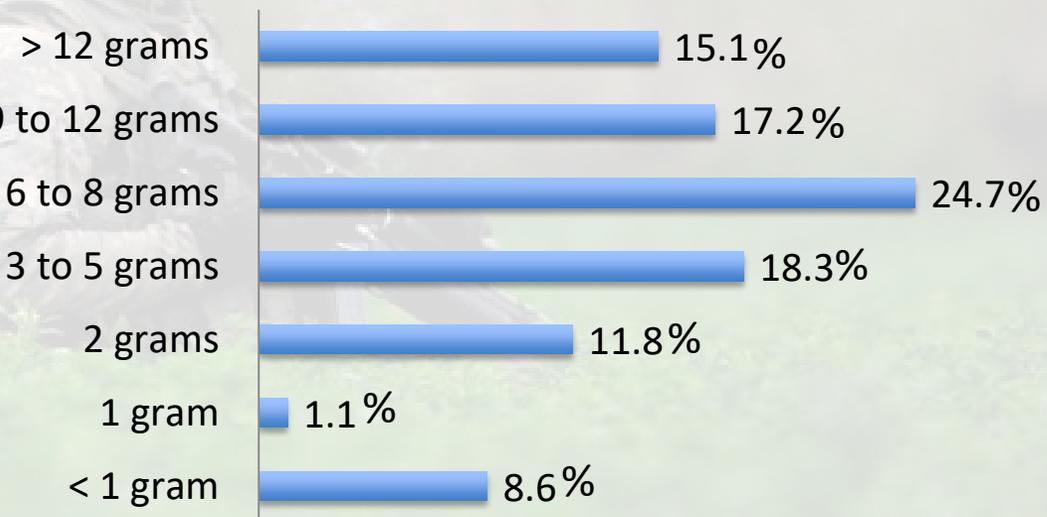
(N = 93)



Cannabis Use Frequency:



Cannabis Use Quantity:





Andrew Sperling, JD
*Director, Legislative Affairs
National Alliance on Mental
Illness (NAMI)*

The Politics of the CBD Craze: Charting Forward a Legislative Path

2:15pm – 3:15pm

#CBDPolicySummit

Katlin McKelvie Backfield, JD

Senior FDA Counsel

Senate Committee on Health, Education, Labor and Pensions

Kristin Seum, JD

FDA Counsel

House Committee on Energy & Commerce

Subcommittee on Health

Aliza Silver, JD, MPH

Health & Oversight Counsel

Senate Committee on Health, Education, Labor and Pensions

Kimberlee Trzeciak

Chief Health Policy Advisor

House Committee on Energy and Commerce

Moderated by:

Wade Ackerman, *JD Partner, Covington & Burling LLP*

Real World Implications of FDA (In)Action

3:30pm – 4:15pm

Moderator: Dr. Ilisa Bernstein, *American Pharmacists Association*

Panelists: John Horton, JD, *LegitScript*
Steve Mister, JD, *Council for Responsible Nutrition*
Rich Cleland, JD, *Federal Trade Commission*

Developments in Enforcement of CBD and Cannabis Products

Richard Cleland

Assistant Director, Division of Advertising
Practices

Federal Trade Commission

January 15, 2017

My comments reflect my own views and not necessarily those of the Commission or any individual Commissioner.

FDA/FTC Jurisdiction

- FDA and FTC have concurrent jurisdiction but different focuses when it comes to CBD.
- FDA has primary jurisdiction over the labeling of OTC drugs, food, dietary supplements, and cosmetics. Based on FDA warning letters, FDA's focus is on whether marketers are making unapproved drug claims and whether the product can be lawfully sold as a dietary supplement or an ingredient in food.
- FTC has primary jurisdiction over the advertising of OTC drugs, food, dietary supplements, and cosmetics. The FTC's primary focus is on false and unsubstantiated advertising claims.

See Memorandum of Understanding Between Federal Trade Commission and the Food and Drug Administration, 36 Fed. Reg. 18, 539 (Sept. 16, 1971).

False and Deceptive Advertising

- Section 5 of the FTC Act prohibits unfair or deceptive acts or practices in commerce.
- Section 12 of the FTC Act prohibits the false advertisement of food, drugs, cosmetics, devices, and services.

False and Deceptive Advertising

- False statements
 - CBD is clinically proven to cure Alzheimer's
- Unsubstantiated statements
 - CBD eliminates pain associated with arthritis
- Failure to disclose material facts
 - Safety claims

Substantiation

- Advertisers must have a reasonable basis to support objective performance claims before those claims are disseminated.
- Claims that CBD provides a health benefit must be supported by competent and reliable scientific evidence.

Disease Claims

Disease treatment claims will normally require one or more human clinical trials. See, e.g., *Thompson Med. Co.*, 104 F.T.C. 648, 821 (1984); *FTC v. Nat'l Urological Grp.*, 2017 WL 6759868, at *29 (N.D. Ga. 2017), *aff'd*, 2019 WL 4463503 (11th Cir. 2019); *POM Wonderful, LLC*, 2013 FTC LEXIS 6, at *67-68, 109 (Jan. 10, 2013), *aff'd*, 777 F.3d 478 (D.C. Cir. 2015); *FTC v. Wellness Support Network, Inc.*, 2014 U.S. Dist. LEXIS 21449, *52-53 (N.D. Cal. 2014); *FTC v. Health Research Labs., LLC*, No. 2:17-cv-00467 (D. Me. Jan. 16, 2018) (stipulated judgment); *FTC v. Nobetes Corp.*, No. 2:18-cv-10068 (C.D. Cal. Dec. 13, 2018) (stipulated judgment).

Joint FTC/FDA Warning Letters

- Advanced Spine and Pain, LLC (03/28/2019)
 - Cancer, Alzheimer’s, schizophrenia, substance abuse, Parkinson’s, rheumatoid arthritis, & more
- Nutra Pure LLC (03/28/2019)
 - Alzheimer’s, neuropsychiatric disorders, PTSD, OCD, & more
- PotNetwork Holdings, Inc. (03/28/2019)
 - Liquid Gold Gummies & “blue CBD Crystals Isolate”
 - Alzheimer’s, Lou Gehrig’s disease, arthritis, diabetes, & more
- Rooted Apothecary, LLC (10/10/2019)
 - Teeth/TMJ – Essential Oil + CBD Infusion
 - Ears – Essential Oil + CBD Infusion

FTC CBD Warning Letters 09/09/2019

- 4Bush Holdings, LLC
- NuLife LLC
- Ocanna Co.

FTC CBD Warning Letters 09/09

- One company's website claimed CBD "works like magic" to relieve "even the most agonizing pain" better than prescription opioid painkillers. To bolster its claims that CBD has been "clinically proven" to treat cancer, Alzheimer's disease, multiple sclerosis (MS), fibromyalgia, cigarette addiction, and colitis, the company stated it has participated in "thousands of hours of research" with Harvard researchers.
- Another company's website claimed that CBD products are proven to treat autism, anorexia, bipolar disorder, post-traumatic stress disorder, schizophrenia, anxiety, depression, Alzheimer's disease, Lou Gehrig's Disease (ALS), stroke, Parkinson's disease, epilepsy, traumatic brain injuries, diabetes, Crohn's disease, psoriasis, MS, fibromyalgia, cancer, and AIDS. The company also advertised CBD as a "miracle pain remedy" for both acute and chronic pain, including pain from cancer treatment and arthritis.
- The third company's website promoted CBD gummies as highly effective at treating "the root cause of most major degenerative diseases, including arthritis, heart disease, fibromyalgia, cancer, asthma, and a wide spectrum of autoimmune disorders." The company also claimed its CBD cream relieves arthritis pain and that its CBD oil may effectively treat depression, PTSD, epilepsy, heart disease, arthritis, fibromyalgia, and asthma.

Looking Forward

- Increased private class actions.
- Increased enforcement on the federal and state levels.
- Stepped up FTC enforcement focusing on unsubstantiated disease claims.

Contact Information

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Federal Trade Commission

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(202) 326-3088



LegitScript



CBD Marketing and Problematic Claims

John Horton, President and CEO, LegitScript

GOVERNMENT & PRIVATE ACTION

FDA

- ✓ **22 warning letters** related to CBD issued in 2019
- ✓ ~**65** CBD-related warning letters issued in total
- ✓ FDA official: “[W]e’ll continue to **monitor the marketplace** and **take action** as needed against companies that violate the law ...”

FTC

- ✓ Regularly issues joint warning letters with FDA
- ✓ Issued **three warning letters** independently in September 2019
- ✓ Has publicly signaled it will be moving past the warning letter phase into the **enforcement phase**

States

- ✓ Small-scale enforcement actions against CBD products that are **illegal at the state or local level**
- ✓ Some states continue to issue guidance and statements clarifying that some **CBD is not legal** at the state level

Private Suits

- ✓ Private **class action suits** filed against CBD companies. One suit claims that **marketing CBD products as dietary supplements**, which FDA explicitly disallows, misleads consumers. The other targets **disease claims**.

US REGULATORY LANDSCAPE

FDA & FTC FOCUS ON CLAIMS



NOV 2019

FDA NEWS RELEASE

FDA warns 15 companies for illegally selling various products containing cannabidiol as agency details safety concerns

Violations include marketing unapproved new human and animal drugs, selling CBD products as dietary supplements, and adding CBD to human, animal foods



OCT 2019

FDA, FTC warn company marketing unapproved cannabidiol products with unsubstantiated claims to treat teething and ear pain in infants, autism, ADHD, Parkinson's and Alzheimer's disease



JULY 2019

FDA NEWS RELEASE

FDA warns company marketing unapproved cannabidiol products with unsubstantiated claims to treat cancer, Alzheimer's disease, opioid withdrawal, pain and pet anxiety

CBD PROBLEMATIC CLAIMS

PRODUCT DESCRIPTIONS

AUTISM
The Journal of Autism and Developmental Disorders have found that the (CB2) was significant immune response cannabinoid receptors increased in the that " data indicating therapeutic tar

BIPOLAR DISORDER
According to the Life Sciences journal, studies show a connection between cannabidiol and its potential to offer an antipsychotic effect in bipolar patients. "Preclinical and clinical studies suggest that cannabidiol (CBD), a major component of Cannabis sativa, could produce antipsychotic effects without causing extra-pyramidal side-effects"

[View Source](#)

Autism and bipolar disorder

Combine the healing power of Crystals with the medicinal power of CBD



The image shows a black jar with a gold lid and a glass jar containing a yellow salve. The lid is labeled "Crystal Infused Salve", "Pain/Inflammation CRYSTAL GOLD", and "250mg CBD Oil".

Pain, inflammation, healing

What People Use CBD For



The image contains three separate panels. The first panel shows hands being massaged and is labeled "Arthritis & Inflammation". The second panel shows a person sitting on the floor in a slumped position and is labeled "Depression". The third panel shows hands massaging a person's lower abdomen and is labeled "Endometriosis".

Arthritis, depression, endometriosis

CBD PROBLEMATIC CLAIMS

PRODUCT DESCRIPTIONS

HOW DOES CBD WORK?

The Endocannabinoid System (or ECS) in the human body reacts to the compounds found in Cannabis. CBD is known for its ability to aid those suffering from a number of medical conditions such as:

- ✓ Everyday Aches & Pains
- ✓ Inflammation
- ✓ Obesity & Weight Control
- ✓ Anxiety & Stress
- ✓ Asthma
- ✓ Arthritis
- ✓ Epileptic Seizures
- ✓ Crohn's Disease & IBS
- ✓ Parkinson's Tremors

Obesity, cancer, Parkinson's, MS ...
everything but the kitchen sink



Our Full spectrum CBD Hemp oil

- Anxiety
- Depression
- Headache
- Chronic pain
- Insomnia
- Arthritis pain
- Obesity
- Stomach indigestion

CBDreamers

- ✚ Reducing inflammation
- ✚ Fighting against cancer
- ✚ Protection from neurodegenerative diseases
- ✚ Relieving multiple sclerosis
- ✚ Assisting with epilepsy patients
- ✚ It has potential in treating schizophrenia
- ✚ Relieving nausea, enhancing appetite
- ✚ Managing skin conditions
- ✚ Promoting the health of your heart

CBD PROBLEMATIC CLAIMS

TESTIMONIALS

<https://www.leeforganics.com/collections/cbd-wellness/products/recover>

Heidi Verified Buyer
★★★★★

BEST TOPICAL EVER USED!

I have increasing painful arthritis in my hands. This roll on is not only easy to use, I found that actually takes the pain away in my most painful and largest finger. I highly recommend you try this if you have any type of joint pain.

Arthritis

★★★★★ 07/23/19

Amazing!!!



Where do I begin , I've received 3 injections in my spine for pain , did not help . I've been desperate to relieve pain in my neck...

Chronic pain



Brian ★★★★★
March 4, 2019

Love this stuff! I use it when I wake up and before bed everyday. Helps me with my anxiety, sleeplessness and inflammation. I have tried a lot of brands out there and this one is by far the best!

Anxiety, insomnia, inflammation

CBD PROBLEMATIC CLAIMS

TESTIMONIALS



I was really happy about this. It took the edge off my anxiety and helped with my arthritis. I may need to double the dosage, because it didn't totally take away the pain, but I could notice a difference when I wasn't taking the product. Be careful that you don't take this while driving or doing something where you have to be alert, because his product makes me sleepy haha.

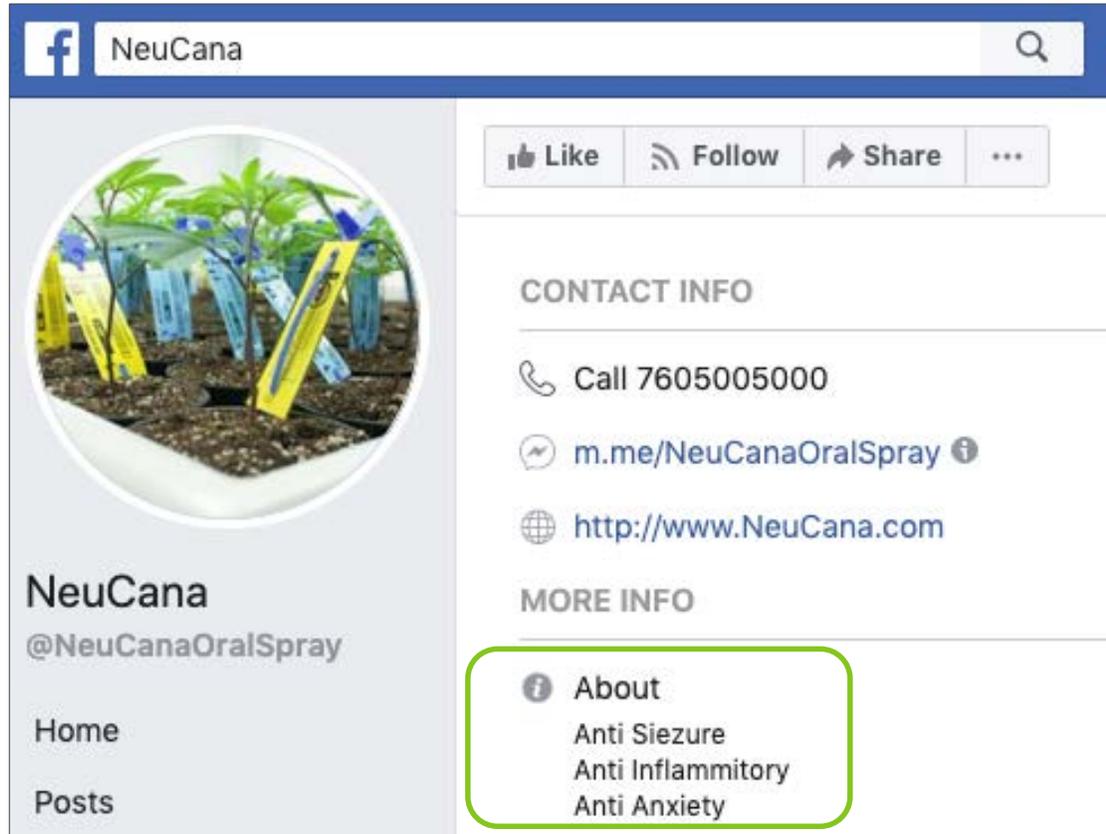
Anxiety, arthritis

<p>"CBD OIL has helped me quit taking Xanax 3 times a day after 7 years of being dependant. Thanks for the superior quality and natural products!"</p> <p>Mike K., Los Angeles</p>	<p>"This CBD oil is out of this world. The selection of Active's CBD is fantastic. You will get your money's worth and more shopping here."</p> <p>Jessica, Pacific Palisades, CA</p>	<p>"My new go to for anxiety relief! Thanks Active, and your team for providing top notch CBD! Definitely looking forward to the other products!"</p> <p>Will - Yorba Linda, CA</p>	<p>"Does The Trick! The 1000MG CBD oil helps with my arthritis and inflammation from pinched nerves allowing me to reduce my pain meds."</p> <p>Theodore K - Marina del Rey, CA</p>
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Anxiety, arthritis, inflammation

CBD PROBLEMATIC CLAIMS

SOCIAL MEDIA



Facebook profile page for NeuCana. The profile picture shows several small green plants in a white tray. The page includes a search bar, navigation buttons (Like, Follow, Share), and contact information: Call 7605005000, m.me/NeuCanaOralSpray, and http://www.NeuCana.com. The 'About' section is highlighted with a green box and lists: Anti Seizure, Anti Inflammatory, and Anti Anxiety.

Seizures, inflammation, anxiety

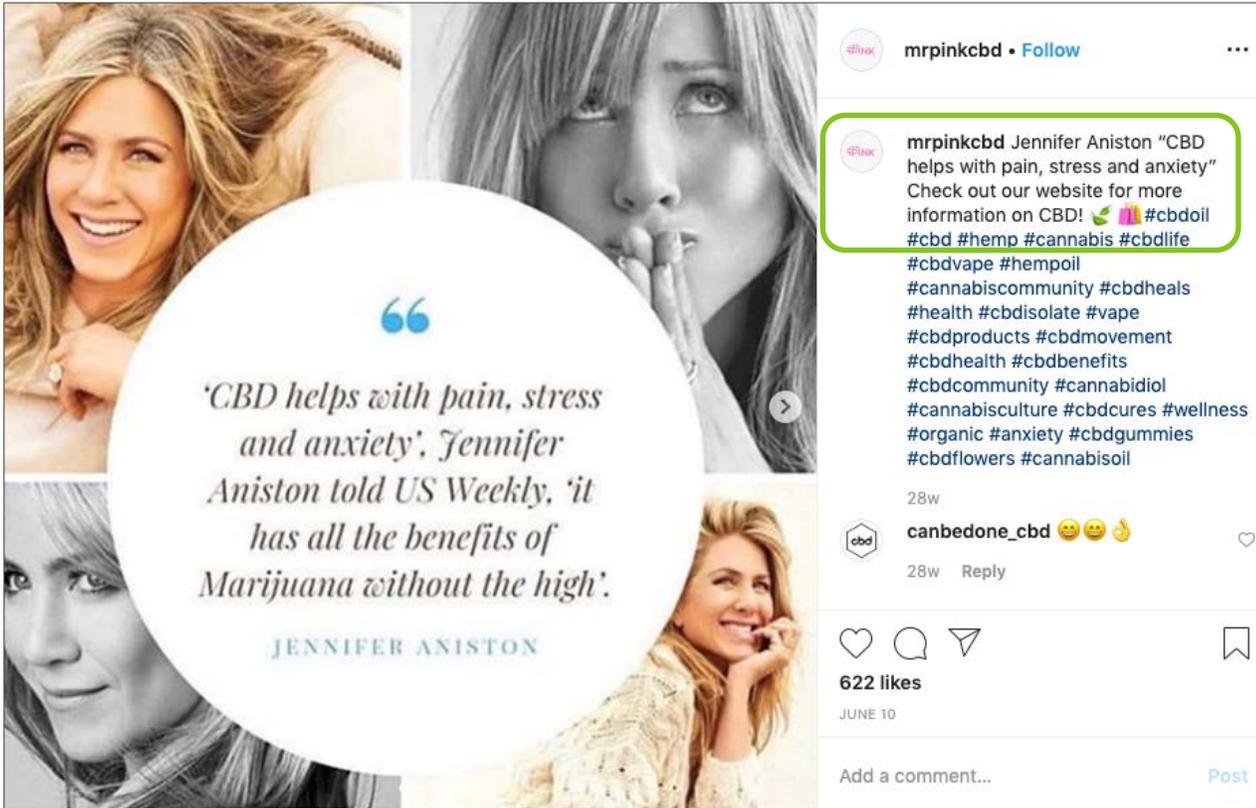


Facebook post from Cannabidiol Life. The post features a circular profile picture of a hand holding a green bottle of Cannabidiol Life with a coupon code. The main text reads: 'POSSIBLE EFFECTS OF USING CANNABIDIOL FOR CANCER SYMPTOM RELIEF'. The post lists three claims: '* Trigger the death of cancer cells', '* REDUCE THE SPREAD OF CANCER CELLS THROUGHOUT THE BODY', and '* Prevent unhealthy cell division'. A fourth claim is partially visible: '* Prevent the growth of tumors in the new blood vessels'. The post also includes a navigation menu on the left with options: Home, Stay Connected, Reviews, Trustpilot Reviews, Videos, Photos, Posts, About, and Community.

Cancer, tumors

CBD PROBLEMATIC CLAIMS

SOCIAL MEDIA



The image shows an Instagram post from the account 'mrpinkcbd'. The post features a quote from Jennifer Aniston: "‘CBD helps with pain, stress and anxiety’, Jennifer Aniston told US Weekly, ‘it has all the benefits of Marijuana without the high’." The quote is presented in a white circular graphic with a blue double-quote icon. The background of the post is a collage of photos of Jennifer Aniston. The post text includes the following hashtags: #cbd, #hemp, #cannabis, #cbdlife, #cbd vape, #hempoil, #cannabiscommunity, #cbdheals, #health, #cbd isolate, #vape, #cbd products, #cbd movement, #cbd health, #cbd benefits, #cbd community, #cannabidiol, #cannabis culture, #cbd cures, #wellness, #organic, #anxiety, #cbd gummies, #cbd flowers, and #cannabis oil. The post has 622 likes and was posted on June 10.

“
‘CBD helps with pain, stress and anxiety’, Jennifer Aniston told US Weekly, ‘it has all the benefits of Marijuana without the high’.
JENNIFER ANISTON

mrpinkcbd • Follow
Jennifer Aniston “CBD helps with pain, stress and anxiety” Check out our website for more information on CBD! 🌿📄 #cbd oil #cbd #hemp #cannabis #cbd life #cbd vape #hemp oil #cannabis community #cbd heals #health #cbd isolate #vape #cbd products #cbd movement #cbd health #cbd benefits #cbd community #cannabidiol #cannabis culture #cbd cures #wellness #organic #anxiety #cbd gummies #cbd flowers #cannabis oil

28w
canbedone_cbd 🤔👍👍
28w Reply

622 likes
JUNE 10
Add a comment... Post

Anxiety, pain



The image shows an Instagram post from the account 'mrpinkcbd'. The post features a text-based advertisement for CBD oil. The text describes the benefits of CBD oil, including relief from anxiety, depression, seizures, and muscle recovery. It also mentions that CBD oil is a natural, non-toxic supplement. The post includes the following hashtags: #nontoxic, #allnatural, #musclerecovery, and #supplements that work. The background of the post is a photo of a bottle of 'mrpinkcbd CBD OIL DROPS' next to a red jump rope.

mrpinkcbd • Follow
Rodeo Drive

mrpinkcbd Not only CBD oil can help to relieve health problems such as anxiety, depression, reduce seizures and also combat insomnia but it can also help for muscle recovery. Athletes who are looking to combat fatigue after vigorous exercise uses CBD oil as a muscle recovery supplement. Why? because it is a natural supplement and non-toxic to our body. Try our @mrpinkcbd it is the highest form of CBD formulated to support your body’s daily processes. Click the link on our bio. #nontoxic #allnatural #musclerecovery #supplements that work

Anxiety, depression, insomnia



LegitScript



CBD: The Price of FDA Inaction

Steve Mister

President & CEO

Council for Responsible Nutrition



21 USC 321(ff) – Definition of a Dietary Supplement

(ff) The term “dietary supplement” — (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

21 USC 321(ff) [continued]

(3) does—

(B) not include— (i) an article that is approved as a new drug under section 355 of this title, . . . or

(ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food **unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.**

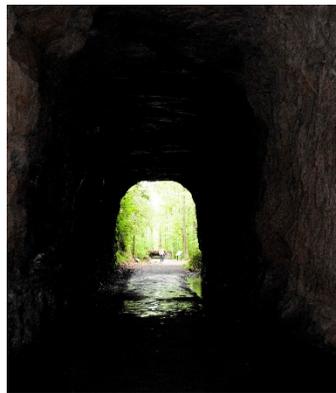
One year after the 2018 Farm Bill... FDA is disincentivizing CBD research.

- FDA actually disincentivizing the very research into the safety and health benefits of CBD that it wants.



No financial incentive to research CBD

- Without a clear signal from FDA that this definitional hurdle can be removed, many companies are unwilling to invest in research on CBD.
- Industry needs to know that if it presents the requisite safety data for a CBD product, that the product can be considered a dietary supplement.



FDA has discouraged use of the NDI process

- FDA is summarily discouraging firms from submitting an NDI notification for a CBD dietary supplement by its public statements and failure to distinguish between high dosage isolate CBD medications and other CBD-containing ingredients (e.g., “full spectrum hemp extract containing CBD”).
- Industry needs to know properly documented NDI notifications are welcome at the agency. If full spectrum hemp extract is not “the article” in the drug, FDA should say so.

No protection for proprietary data

- FDA's failure to provide protection for confidential and proprietary information related to CBD safety and health benefits discourages firms from sharing their CBD research with the agency.
- Firms need assurance that confidential and proprietary information will not be placed on the public docket and will have protection under the confidentiality provisions for NDIs, similar to the agency's protection of research related to NDAs.



One year after the 2018 Farm Bill...FDA is contributing to the unregulated marketplace.

- FDA's inaction has led to an essentially unregulated CBD marketplace that poses more risk to consumers than if FDA would recognize a legal pathway for CBD as a dietary supplement.



Consumer Interest in CBD Explodes

- Over 1,500 products in the market
- Estimated sales of CBD supplements in 2018 = \$238 million (*Nutrition Business Journal*)
- 20 million Americans say they have used CBD supplements (*CRN Consumer Survey*)
- Predicted sales of ingestibles by 2022 =
 - \$520 million (*Nutrition Business Journal*)
 - \$646 million (*Hemp Business Journal*)



Potential product quality issues identified



Amazon Prohibits CBD Sales, but it's still easy to buy on the site

Dangerous Street drugs found in some CBD products

Concerns over CBD products spark call for federal regulations

Investigation finds illegal synthetic marijuana in vape and edible products sold as CBD

Report: Majority Of Commercially Available CBD Products "Contaminated" With Heavy Metals

LegitScript CBD Study: Gaps in Potency, Carcinogens, High Heavy Metal Levels

Researchers: Some pet products touted as CBD don't contain any

Potential safety concerns:

- CBD levels don't match the dosage on the label
- Products contains THC in excess of 0.3%
- Product contain synthetic CBD, or something that is not CBD at all
- Product contains impurities or contaminants (pesticides, heavy metals, residual solvents, mold, aflatoxins)
- Product makes illegal drug claims that would discourage patients from seeking proven drug therapies
- Product is not made to GMPs (Part 111)



Products Labeled as Supplements Should Behave like Supplements

- Facility registered with FDA
- Subject to GMPs (Part 111)
- Ingredient supply chain is compliant with FSMA
- *Supplement Facts* compliant
- No disease claims
- Label contains AER contact information
- Company has AER system in place

BUT FDA is not enforcing these requirements!



One year after the 2018 Farm Bill...FDA is spurring industry confusion and needless litigation.

- FDA's failure to utilize its discretion under §321(ff) is creating unnecessary confusion in the market, litigation and regulatory issues that could be avoided.



FDA is injecting “safety” into §321(ff)—

- Safety should not be a factor in a §321(ff) determination
- It’s a race to market; an evaluation of the economics and the ability to preserve adequate incentives for future research of potential therapeutic uses—safety is not mentioned
- The provision was added by DSHEA to balance between supplement
- If safety was the central factor, it would not be a race to market; it would be a prohibition
- What exactly is “the article”?



Discretion under §321(ff) could be limited.

- Discretion for CBD does not open the floodgates for other ingredients—CBD is unique because its history as a controlled substance prevented marketing before the Rx drug was approved.
- The discretion under §321(ff) could come with conditions to provide some assurance of safety.



Litigation Floodgates have Opened

- At least six class actions filed in 2019 against CBD products.
- Current litigation is premised on assumption (based on FDA's broad and vague announcements) that all CBD—in any mixture, dosage or concentration—is precluded by §321(ff), and therefore, illegal.
- Lack of FDA regulation means no standards or guideline for proper manufacturing, dosage or claims.



One year after the 2018 Farm Bill... states are filling the vacuum.

- FDA is causing a complicated patchwork of burdensome and inconsistent state regulation of CBD.



State laws and legislation pending



- 27 states are already attempting to regulate CBD.
 - 17 states are attempting to outlaw CBD
 - 15 states are establishing their own requirements for CBD sales
 - Some are just waiting for FDA
- 130 state bills related to CBD were filed 2019, and many more are being introduced in 2020.
- When FDA does act, how do we undo the patchwork already created?
 - Is preemption even an option?

Conclusion

**The time for action was a year ago,
but we'll settle for NOW.**





Thanks for listening.

Steve Mister

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Concluding Remarks: So Where Do We Go From Here?

Amy Comstock Rick, JD

President and CEO, Food and Drug Law Institute

Ron Manderscheid, PhD

Executive Director, NACBHDD

#CBDPolicySummit



**Please join us for an
attendee reception!**

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