


Slide 2

Disclosures

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APRIL 2018 GREENWICH Biosciences Corporate Model Deck 2

Slide 3

Agenda

- Historical perspective on the use of cannabis in medicine
- Legal and regulatory status of various cannabinoids
- Differences between FDA-approved plant-derived cannabidiol, FDA- approved synthetic cannabinoids and other cannabis-derived products
- Randomized controlled data on the use of a cannabinoid in two epilepsy syndromes

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**Historical Perspective &
Regulatory Status of Cannabis**
Mark Bolton, JD

5/9/2019 4

20th Century History & Regulations

Cannabis removed from pharmacopeias in 1932 (UK) and 1941 (USA)

- Marijuana Tax Act effectively prohibited use in 1937 by imposing onerous administrative duties
- Controlled Substance Act (CSA) 1970
 - Prevention of drug abuse and drug dependence: Designated as Schedule I
 - High potential for abuse
 - No accepted medical use
 - Lack of accepted safety
- FDA Approved Products: Marinol, Syndros, Cesamet, Epidiolex
- 2018 Farm Bill - - Hemp derived CBD



What does the 2018 Farm Bill do?

Defines Industrial Hemp

Defines industrial hemp as the plant *cannabis sativa* L, and any part of that plant, including seeds, derivatives, and extracts, with a delta-9 tetrahydrocannabinol (THC) concentration of not more than 0.3% on a dry weight basis

Excludes Hemp from CSA

The law excludes hemp from the Controlled Substances Act (CSA) definition of "marihuana"; THC from hemp is also excluded from the CSA definition of THC, thereby making production of hemp legal

USDA Authority

Gives U.S. Department of Agriculture (USDA), State Departments of Agriculture and Tribes authority over hemp production; "production" is not defined

FDA Authority

The law expressly curtails USDA's authority by preserving the FDA's authority under the Federal Food, Drug & Cosmetic Act and the Public Health Service Act.

FDA-Approved vs. Non-FDA Approved Cannabinoid Products

	FDA-Approved Products: Plant-Based and Synthetic Medicines	Non-FDA Approved Products: Hemp-Derived Dispensary Products and Medical Marijuana
Clinical Testing Requirements	Randomized, placebo-controlled trials with results publicly disclosed; safety, efficacy and recommended dosing known	No randomized clinical trials. Public disclosure of smaller, informal studies not required.
Manufacturing	Produced according to regulated current good manufacturing practices (cGMP) for pharmaceutical products. Strict specifications to ensure batch consistency and stable shelf life.	Testing standards vary from state to state; some states no testing required. No federal standards. FDA does not inspect manufacturing sites for adherence to cGMP.
Quality Standards	Meet FDA standards for quality, stability, consistency. Tested to ensure they contain consistent concentrations of cannabinoids and other ingredients listed on the label.	Inconsistent regulation at the state level. No federal standards for testing to ensure accuracy and consistency.
Coverage	Eligible for insurance coverage	Insurance coverage is rare

Types of Optional Cannabis Testing^{1,2}

Potency Testing

Microbial Testing

Heavy Metal Testing

Pesticide Testing

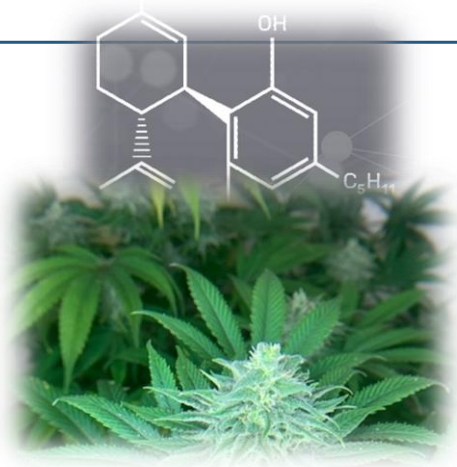
Residual Solvent Testing

Aflatoxin Testing

1. Testing. CannLabs website. <http://cannlabs.com/testing/>. Accessed January 4, 2016.
2. <https://cb.wa.gov/publications/Marijuana/BOTEC%20reports/1a-Testing-for-Contaminants-Final-Revised.pdf> (1/27/2019)

Is Cannabis a Medicine?

The cannabis plant contains molecules that can potentially improve the symptoms of disease.



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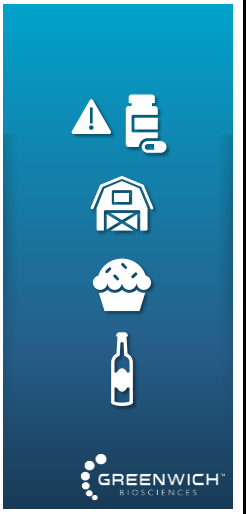
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What Is Cannabis Now?

- Lack of federal involvement in legalization has meant that marijuana products are not:
 - subjected to safety standards like pharmaceuticals;
 - subjected to agricultural safety and pesticide standards like crops,
 - measured in prepared food,
 - or subjected to labelling standards like alcohol

Lack of federal regulatory standards coupled with aggressive commercialization in some states may be compounding public health risks

<https://www.wsj.com/articles/if-weed-is-medicine-so-is-budweiser-11547770981>



Consumer protection concerns



Mislabeling:
THC & CBD



Stability



Dosing



Variability



Adverse Event
Reporting

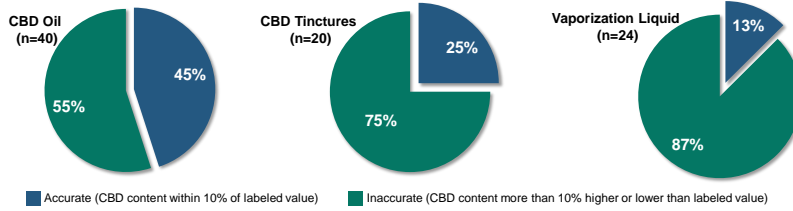


Contamination



Cannabidiol Extracts May Be Inaccurately Labeled

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



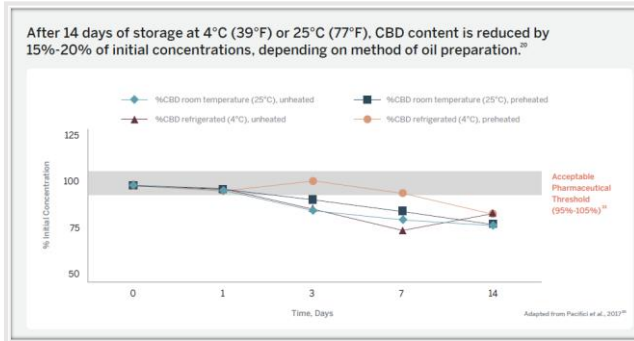
- Of 84 products analyzed, nearly 70% were inaccurately labeled with respect to CBD and 21.4% contained THC¹
- Due to variable CBD and THC content, the authors conclude that these products should be avoided for pediatric patients²

*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.



Stability

- FDA has authority to inspect and evaluate, even after production
- Retail CBD products do not have requirements for stability testing



...And how much THC does it take to get high?

- GW2015-1: 5mg THC: CNS side effects in 2/6 subjects

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



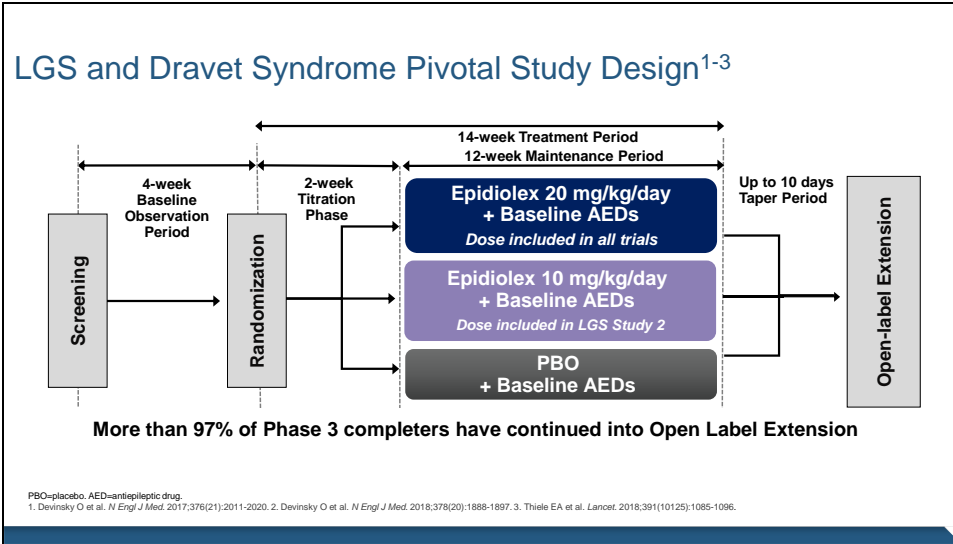
The average marijuana joint in Colorado contains **63 mg of THC** but only about **17 mg** enters the body from smoking the whole joint.

Therapeutic Potential of Cannabinoids: An Emerging Science

Elise Conlee, PhD

Randomized Controlled Clinical Trial
Data: Cannabidiol Oral Solution
(Epidiolex[®])

FDA Approved June 2018



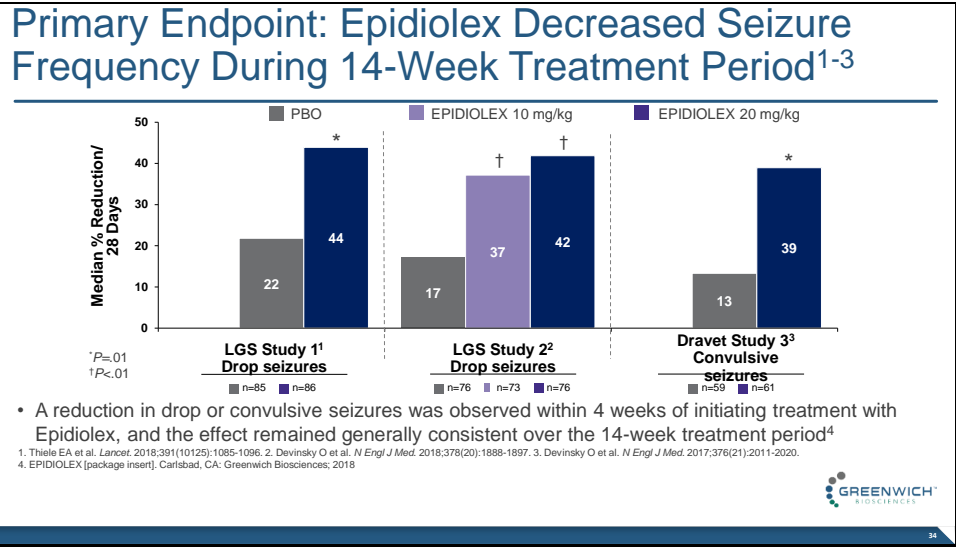
Patient Characteristics 1-4

Variable	LGS Study 1 (N=171)	LGS Study 2 (N=225)	Dravet Study 3 (N=120)
Age,* %			
2-5 years	13.5	11.6	29.2
6-11 years	31.0	32.4	39.2
12-17 years	21.6	26.2	31.7
18-55 years	33.9	29.8	N/A
Seizure types at baseline, %			
Generalized tonic-clonic	59.6	49.8	89.2
Tonic	79.9	76.4	24.2
Atonic	62.0	58.2	13.3
Clonic	11.1	7.1	20.8
Primary seizure types at baseline, median/28 days (range)			
Convulsive seizures	—	—	13.0 (3.7-1716.7)
Drop seizures	73.8 (10.3-3174.6)	85.0 (8.7-7494.0)	—

*Age range for Dravet Study 3 is reported as 2-5, 6-12, and 13-18 years.

1. Devinsky O et al. *N Engl J Med*. 2017;376(21):2011-2020 2. Devinsky O et al. *N Engl J Med*. 2018;378(20):1888-1897 3. Thiele EA et al. *Lancet*. 2018;391(10125):1085-1096 4. Greenwich Biosciences. Data on file.





Discontinuation Rates Due to Adverse Reactions in Controlled Trials

Patients discontinued, %	PBO	Epidiolex 10 mg/kg/day	Epidiolex 20 mg/kg/day
Any adverse reaction	1.3	2.7	11.8
Transaminase elevation	0.4	1.3	5.9
Somnolence, sedation, and lethargy	0	0	3

- The most frequent cause of discontinuations was transaminase elevation

Epidiolex (package insert). Carlsbad, CA: Greenwich Biosciences; 2016.



Dosing and Practical Use

Epidiolex® (cannabidiol) Indications and Dosing

INDICATIONS AND USAGE

Epidiolex® (cannabidiol) is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

DOSAGE & ADMINISTRATION

Starting dose		Maintenance Dose	Maximum Recommended Dose
Week 1	Week 2		Week 3 and On
2.5 mg/kg taken twice daily	Increase dosage to maintenance dose of 5 mg/kg twice daily		If tolerated and required, increase dose weekly by 2.5 mg/kg (5 mg/kg/day) to max recommended dose of 10 mg/kg twice daily
5 mg/kg/day	10 mg/kg/day		20 mg/kg/day

- * Food may affect Epidiolex levels.
- Dose adjustment is recommended in patients with moderate or severe hepatic impairment. A slower dose titration may also be necessary for these patients.
- Administration of 20mg/kg/day resulted in somewhat greater reductions in seizure rates than 10mg/kg/day, but with an increase in adverse events.
