

The CBD Explosion – Keeping Out of Harm’s Way

Ken Mackie, MD
Gill Center and the Department of
Psychological and Brain Sciences
Indiana University
Bloomington, IN USA
kmackie@indiana.edu



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Financial Disclosures

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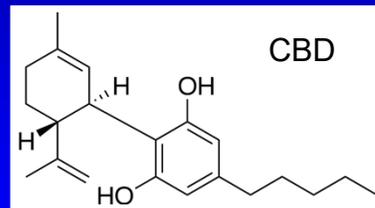
Learning Objectives

- Describe the pharmacological effects of CBD in various (human) physiological systems
- Discuss how CBD may interact with other drugs

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What Is Cannabidiol (CBD)?

- Phytocannabinoid produced by various *Cannabis* species
- Many years “poor cousin” to THC
- Last 10 years: marked interest
- Talk outline:
 - What is CBD?
 - What can it do?
 - Desired effects
 - Undesired effects



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THC vs CBD synthesis

THC and CBD (and terpenes) are synthesized in trichomes



<https://www.researchgate.net/publication/317185536>

Different enzymes

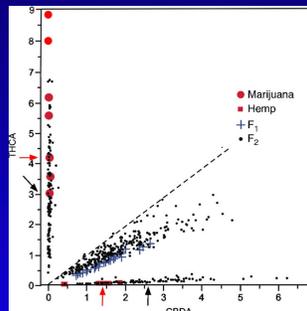
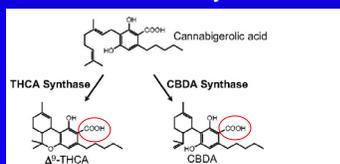
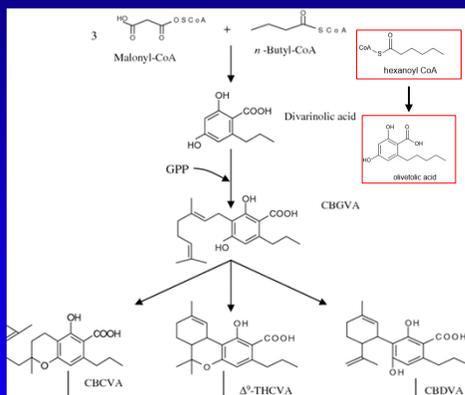


Fig. 1 Delta9-tetrahydrocannabinolic acid (THCA) versus cannabidiolic acid (CBDA) content as a % of dry weight (DW) in mature pistillate inflorescences of *Cannabis sativa* derived from a marijuana parent and siblings, a hemp parent and siblings, the F1 parent and siblings, and the F2 cohort. Red arrows point to the hemp and marijuana parents; black arrows point to mean THCA content and CBDA content for marijuana-like and hemp-like F2s, respectively. The dashed line indicates the expected ratio of THCA to CBDA if the two main cannabinoid synthase enzymes were equally competitive for their common precursor, cannabigerolic acid. (New Phytologist (2015) 208: 1241–1250)

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Phytocannabinoid biosynthetic pathways



Phytochem Rev (2008) 7:615–639

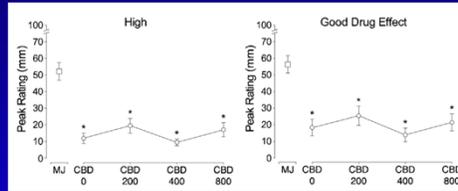
“Varin” compounds

- Attracted much interest for possible differences from THC and CBD
- Differ from THC, CBD
- C3 vs C5 on the “3” position (SE corner)
- Same synthetic pathways, C4 (vs C6) alcohol as substrate (polyketide synthase is promiscuous for substrates)

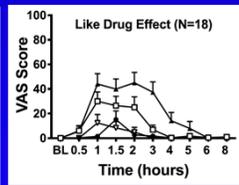
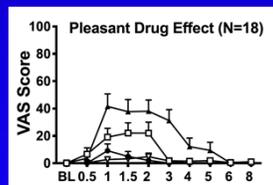
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Is CBD “Psychoactive”?

- CBD is often considered “non-psychoactive”
- CBD does not elicit the same subjective sensations as THC
- However, CBD can clearly be distinguished from placebo following ingestion



Drug and Alcohol Dependence 172 (2017) 9–13



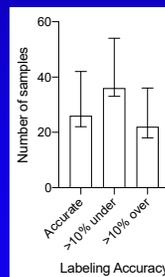
- 100mg CBD (Vaped)
- ▲ 100mg CBD/3.7mg THC (Vaped)
- 100mg CBD (Oral)
- ▼ Placebo

Drug and Alcohol Dependence 211 (2020)

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Sources of CBD in the US

- Currently, more cost effective to purify CBD from cannabis than to make through chemical synthesis
 - CBD can be made in bacteria, algae, yeast, etc (clone enzymes)
- Epidiolex® (Greenwich Biosciences)
 - CBD in ethanol, sesame oil, sucralose, and strawberry flavor
- Many non-prescription CBD preparations available
 - CBD-rich
 - “Full spectrum” (terpenes and non-THC cannabinoids)
 - Issues of labeling
 - Contamination
 - THC
 - Heavy metals
 - Pesticides



JAMA 318:1708, 2017

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CBD as a Therapeutic

- Human therapeutic applications of CBD
 - Anti-epileptic
 - Decreased opioid craving
 - Anxiety
 - Schizophrenia (mixed)
 - Countering detrimental effects of THC (mixed)
- Pain
- Anti-inflammatory
- Anti-depressant

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CBD Efficacy in Epilepsy

- Patient > Pharma
- Charlotte Figi
 - Six-year-old female with Dravet syndrome, intractable seizures
 - Improved markedly treated with CBD-rich cannabis extracts
 - Received much publicity (2013 Sanjay Gupta, etc)
 - Several anecdotal report of CBD oil efficacy
 - Efficacy varied based on initial geographical location
 - GW Pharma became involved
 - Epidiolex trials
 - Dravet and Lennox-Gastaut
 - Tuberous sclerosis

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CBD Efficacy in Epilepsy (cont.)

- CBD significantly decreased seizures in Dravet and Lennox-Gastaut syndromes
 - LGS: 42%/37%/17% decrease in drop seizures at 20 mg/kg⁻¹ / 10mg/kg⁻¹ / placebo
 - LGS: 39%/36%/14% >50% decrease in seizures/month
 - Dravet: 39%/13% decrease in up to 20 mg/kg⁻¹ / placebo
 - Dravet: 62%/34% improvement caregiver QoL
- Safety
 - Drug/drug interactions (later)
 - Elevated transaminases (~10%)
 - Diarrhea (20%)
 - Somnolence (36%)

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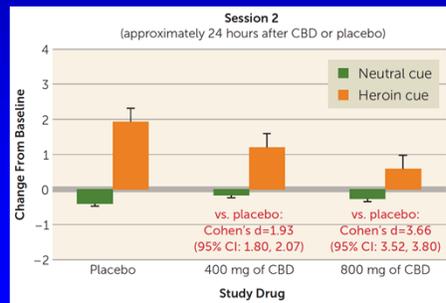
CBD Efficacy in Epilepsy (cont.)

- Thoughts on CBD in epilepsy
 - Very large doses (10-20 mg/kg)
 - Added onto multiple drugs – polypharmacy
 - Impression that CBD may be more efficacious for generalized (vs focal) seizure disorders
 - Patients are often developmentally delayed – subtle cognitive effects might be missed
 - Unknown mechanism of action
 - Does CBD slow progression of underlying disease or just suppress seizures?
 - Adults and other epilepsies?

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CBD Heroin-Induced Craving

- Craving important in driving relapse
- Preclinical data suggest CBD might decrease relapse
- Small randomized/double blind study on oral CBD on heroin cue-induced craving
- Former heroin users
- 400-800 mg CBD/day
- Caveats:
 - Lab-based study
 - Improve “real life” abstinence rates?



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CBD and Anxiety

- CBD treatment is anxiolytic in many preclinical models
- Example, ICR mice and boa constrictor
- Mouse appropriately views snake as threat
- CBD treatment decreases freezing and other non-productive “anxiety” measures

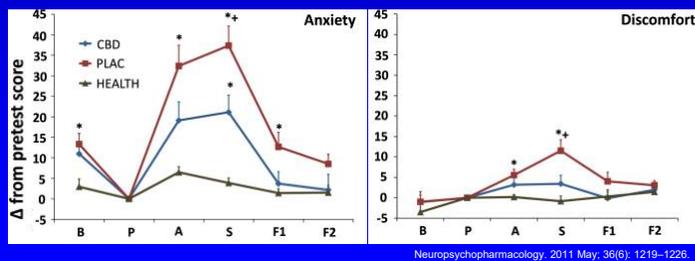


<http://repti-film.weebly.com/epicrates-cenchria.html>

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CBD and Anxiety (cont.)

- Human studies
- Simulated public speaking task, socially anxious subjects
- 600 mg CBD 1-2 hours before test
- Significant improvement in anticipatory (A), speech (S), and immediately afterwards (F1)
- Animal work suggests mediation by serotonin 5-HT_{1A} agonism



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Molecular targets for CBD

- 5HT_{1A} (allosteric?) agonist
- 5-HT_{2A} agonist, 5-HT_{2C} antagonist (allosteric?)
- GPR55 antagonist
- CB₁ negative allosteric modulator
- GPR18 antagonist
- Nav_{1.7} antagonist
- PPAR_γ agonist
- Fatty acid amide hydrolase (FAAH) (increase endocannabinoids)
- Etc

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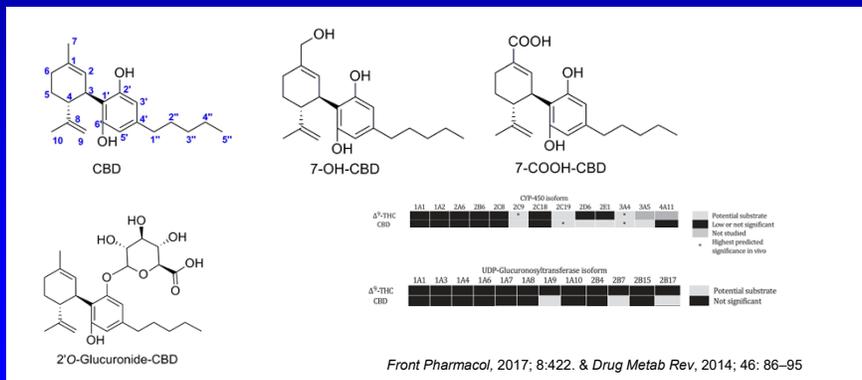
CBD: Absorption and Metabolism

- Route of administration
 - Oral, topical, tincture, inhaled, etc
- Oral
 - Low bioavailability (~6%) (poor absorption and 1st pass)
 - Enhanced ~4x w/fatty meal
 - Many attempts to increase oral bioavailability
- Topical
 - Decent absorption, formulation dependent
- Vaped
 - Excellent bioavailability

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CBD: Absorption and Metabolism (cont.)

- Metabolism (Phase I, CYP3A4 and CYP2C19, Phase II UGT)
- Analogous to THC metabolism (oxidation at 7 position)
- 7-OH-CBD retains activity in epilepsy models

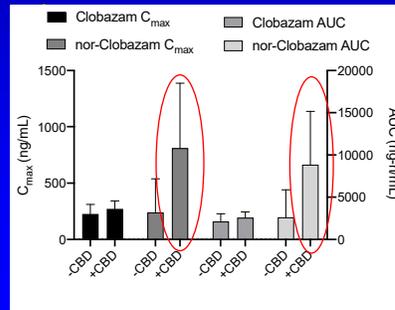
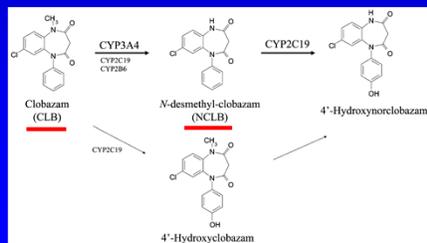


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CBD Inhibition of Clobazam Metabolism

- Clobazam is a common anti-epileptic used in Dravet and Lennox-Gastaut syndromes
 - In patients receiving CBD+CBZ, CBZ levels can increase ~1.5x and n-CBZ levels ~4x
 - Is CBD efficacy due to increased CBZ and n-CBZ?
 - Probably not*

*Epilepsy & Behavior 98 (2019) 201–206



Clin Pharmacol in Drug Develop 2019, 8: 1009

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CBD: Reported Drug Interactions

- | | |
|-------------------------------------|------------------------|
| • Clobazam ¹ | Multiply documented |
| • Tacrolimus ² | Case report |
| • Evero- and sirolimus ³ | Series of case reports |
| • Coumadin ⁴ | Case report |
| • Methadone ⁵ | Case report |
| • Clopidogrel ⁶ | Preclinical (CYP2C19) |
| • Brivaracetam ⁷ | Case report |

N.B. All at high dose CBD

¹Epilepsia 2015 56: 1246–1251

²Am J Transplant 2019 19(10):2944-2948

³Pediatr Neurol 2020 Apr;105:59-61.

⁴Epilepsy Behav Case Rep 2017 Oct 12;9:10-11

⁵PEDIATRICS 1456, June 2020:e20193256

⁶Drug Metab Pharmacokinet 2013 28(4):332-338

⁷Epilepsia 2019 60(7):e74-e77.

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CBD Summary

- Synthesized in the Cannabis plant to various levels
- Lacks THC psychoactivity, but can have subjective effects
- Efficacy in some seizure disorders, possibility for anxiety
- More work needs to be done to determine efficacy for other indications
- Much potential for drug-drug interactions, particularly at the doses used for treating drug-resistant epilepsies

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Further Reading

- *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome*, NEJM 376:2011, 2017
- *Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome*, NEJM 378:1888, 2018
- *Cannabidiol as a potential treatment for psychosis*, Ther Adv Psychopharmacol 9:16, 2019
- *Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy*, Cannabis and Cannabinoid Research 1.1, 2016
- *A Novel Self-Emulsifying Drug Delivery System (SEDDS) Based on VESIsorb® Formulation Technology Improving the Oral Bioavailability of Cannabidiol in Healthy Subjects*, Molecules 24: 2967, 2019
- *Cannabinoids and Epilepsy*, Neurotherapeutics 12:747, 2015
- *Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabiniol by human hepatic microsomes*, Life Sci 80:1415, 2007
- *Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol During Public Speaking in Real Life*, Front Pharmacol 8:259, 2017
- *Cannabinoids in the Treatment of Epilepsy: Current Status and Future Prospects*, Neuropsychiatric Disease and Treatment 16:381, 2020

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CBD Regulatory Framework

Justin Macy, PharmD, JD | Digital Health Senior Manager
Niamh Lewis, JD | Digital Health Regulatory Expert

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Financial Disclosures

We declare that neither we, nor any immediate family members, have a current affiliation or financial arrangement with any potential sponsor and/or organization that may have a direct interest in the subject matter of this continuing pharmacy education program within the last 12 months.

We do declare that we are NABP employees.

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Controlled Substances Act – Schedule I

Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation, which contains any quantity of the following hallucinogenic substances, or which contains any of their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation . . .

(10) Marihuana

(17) Tetrahydrocannabinols



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2018 Farm Bill

- Defined “hemp” as:
 - “the plant *Cannabis sativa* L. and **any part of that plant, including** the seeds thereof and **all derivatives, extracts, cannabinoids . . . with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent** on a dry weight basis.”
- Amended the Controlled Substances Act definition of “marihuana” to exclude “hemp”
- CBD’s relationship with legality? ***It’s complicated.***
 - CBD products still need to comply with the Federal Food, Drug, and Cosmetic Act; the Federal Trade Commission Act; and state laws.



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Federal Food, Drug, and Cosmetic Act

A “dietary supplement” does not include a product containing an article that has been either:

1. approved as a new drug; or
2. authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public – ***unless the product was first marketed as a dietary supplement or as a food.***



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The Approval of Epidiolex®

Intended for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older.



Timeline

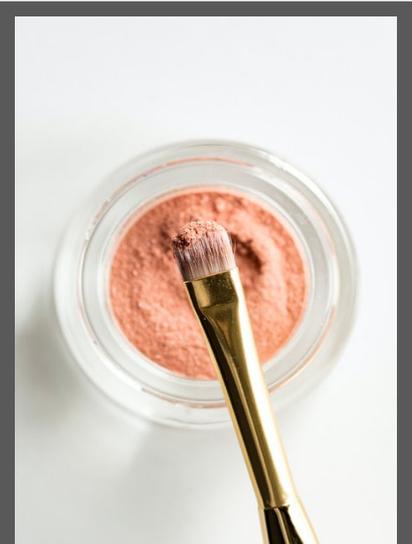
2006: CBD was authorized for investigation as a new drug by GW Pharmaceuticals

June 2018: FDA approved GW Pharmaceuticals’ New Drug Application for Epidiolex

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 <p>NABP National Association of Boards of Pharmacy</p> <h3>CBD in Food and Dietary Supplements</h3> <p>“ It is currently illegal to market CBD by adding it to a food or labeling it as a dietary supplement. ”</p>	 <p>U.S. FOOD & DRUG ADMINISTRATION</p> <h3>Can THC or CBD products be sold as dietary supplements?</h3> <p>No. Based on available evidence, FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act [21 U.S.C. § 321(ff)(3)(B)]. Under that provision, if a substance (such as THC or CBD) is an active ingredient in a drug product that has been approved under section 505 of the FD&C Act [21 U.S.C. § 355], or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are excluded from the definition of a dietary supplement. FDA considers a substance to be “authorized for investigation as a new drug” if it is the subject of an Investigational New Drug application (IND) that has gone into effect. Under FDA’s regulations (21 CFR 312.2), unless a clinical investigation meets the limited criteria in that regulation, an IND is required for all clinical investigations of products that are subject to section 505 of the FD&C Act.</p> <p>There is an exception to section 201(ff)(3)(B) if the substance was “marketed as” a dietary supplement or as a conventional food before the drug was approved or before the new drug investigations were authorized, as applicable. However, based on available evidence, FDA has concluded that this is not the case for THC or CBD.</p> <p><small>https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#dietarysupplements</small></p>
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 <p>NABP National Association of Boards of Pharmacy</p> 	<h3>CBD in Cosmetics</h3> <ul style="list-style-type: none">• “Certain cosmetic ingredients are prohibited or restricted by regulation, but currently that is not the case for any cannabis or cannabis-derived ingredients. Ingredients not specifically addressed by regulation must nonetheless comply with all applicable requirements, and no ingredient – including a cannabis or cannabis-derived ingredient – can be used in a cosmetic if it causes the product to be adulterated or misbranded in any way.”• “If a product is intended to <i>affect the structure or function of the body</i>, or to <i>diagnose, cure, mitigate, treat or prevent disease</i>, it is a drug, or possibly both a cosmetic and a drug, even if it affects the appearance.”
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CBD in Animal Food

- “Is it legal, in interstate commerce, to sell a food (including any animal food or feed) to which THC or CBD has been added?”

Answer: No.

- FDA has issued many warning letters to companies that manufacturer or sell ingestible products for animals.



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FDA Warning Letters

- **Since the passage of the 2018 Farm Bill:** FDA has issued at least 26 warning letters to companies that manufacture or sell CBD.
- FDA has issued warning letters to companies that manufacture or sell topical CBD – if those products are marketed with claims to diagnose, treat, cure, or prevent any disease.

“ Although you intend to market CBD Inflammation Relief, CBD Headache Relief, and CBD Sleep Support as dietary supplements, FDA has concluded that based on available evidence that CBD products cannot be dietary supplements because they do not meet the dietary supplement definition under section 201(ff) of the Act [21 U.S.C. § 321(ff)]. Further, FDA has concluded, based on available evidence, that CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) and (ii) of the Act [21 U.S.C. § 321(ff)(3)(B)(i) and (ii)]. Under those provisions, if an article (such as CBD) is an active ingredient in a drug product that has been approved under section 505 of the Act [21 U.S.C. § 355], or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are outside the definition of a dietary supplement.¹ There is an exception if the substance was “marketed as” a dietary supplement or as a conventional food before the new drug investigations were authorized; however, based on available evidence, FDA has concluded that this is not the case for CBD. FDA is not aware of any evidence that would call into question its current conclusion that CBD products are excluded from the dietary substance definition under section 201(ff)(3)(B)(i) and (ii) of the Act [21 U.S.C. § 321(ff)(3)(B)(i) and (ii)], but you may present FDA with any evidence bearing on this issue. For more information on FDA’s regulation of CBD products, see our webpage at <https://www.fda.gov/news-events/public-health-focus/fdaregulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>. ”

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State Law Examples

Although hemp-derived CBD is no longer federally controlled, some states have stricter requirements. Examples:

- **Idaho:** “[U]nless an oil extract contains no THC and is excluded from the definition of ‘marijuana’ under Idaho Code §37-2701(t) . . . such oil is a controlled substance in Idaho.”
- **Iowa:** “Because CBD is derived from parts of the cannabis plant that are included in definition of marijuana, CBD is considered marijuana under Iowa law. . . . Consequently, any product containing any amount of CBD or any amount of THC is classified as a Schedule I controlled substance under Iowa law.”



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State Law Examples (cont.)

- **South Dakota:** According to the South Dakota attorney general, with the exception of Epidiolex (an FDA-approved prescription-only drug), “[c]urrent South Dakota law makes industrial hemp illegal and all forms of CBD oil illegal.”
- **Hawaii:** “CBD may not be added to food, beverages or cosmetics, sold without a prescription, or marketed as a ‘dietary supplement.’”
- **Louisiana:** CBD retailers (including online retailers) need to obtain a permit and have a physical place of business in the state.



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Federally, CBD is permitted in which of the following?

1. Supplements
2. Foods
3. Cosmetics
4. Animal foods

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True or False: FDA only takes regulatory action when CBD products are marketed with claims to treat serious diseases.

1. True
2. False

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Questions?

Justin Macy | jmacy@nabp.pharmacy

Niamh Lewis | nlewis@nabp.pharmacy

Digital Health Team | custserv@safe.pharmacy

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