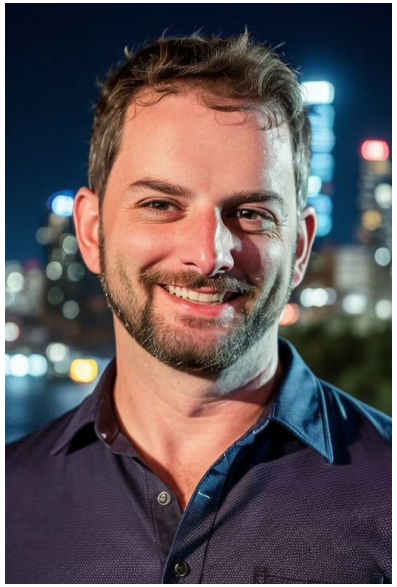
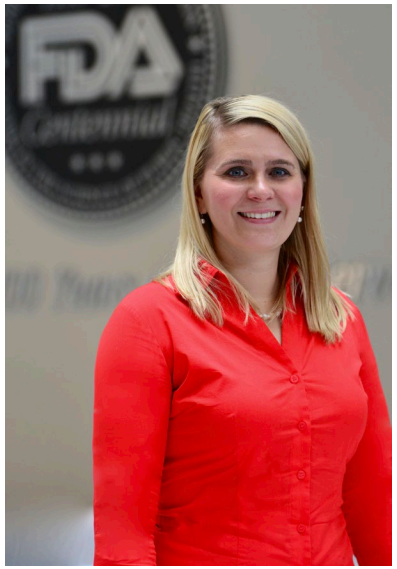
U.S. FOOD & DRUG ADMINISTRATION

FDA Drug Topics: Cannabis Products and the Potential Impact on Patients



Steven Galati, M.D.
Physician
Controlled Substance Staff
Office of the Center Director



Cassandra Taylor, Ph.D.
Public Health Advisor
Office of the Center Director
CDER, FDA

Scott Janiczak, PharmD, MPH
Research Officer
Office of Pharmacovigilance & Epidemiology
Office of Surveillance & Epidemiology

Learning Objectives

- Identify cannabis products on the market and how they are different from FDA regulated drugs, as well as the various ways products are manufactured and how their quality controls differ.

- Explain the potential risks associated with cannabis use, brief review of scientific evidence, and how to initiate a discussion with patients.

- Discuss how to submit a voluntary adverse event report or consumer complaint to FDA and identify important elements that should be included to constitute a high-quality submission.

Previous Webinar

- Cannabis and Cannabis-Derived Products – For Healthcare Practitioners
  - Presented on March 28th, 2023
  - Provided a general understanding of the *Cannabis sativa* L. plant and how products are generally produced utilizing cannabis raw materials
  - Explained why manufacturing controls surrounding cannabis and cannabis-derived products are an integral part of protecting the public health
  - Provided attendees with greater knowledge of the many products available on the marketplace, a discussion on potential benefits and risks, ways to report adverse events associated with these products to FDA, as well as suggestions on how to create a safe space to discuss patient use of these products.

- Link above provides instructions for learners to complete home study activities, complete evaluation, and print certificate for CE
  - Initial release date: May 10, 2023
  - Expiration date: May 10, 2026

- YouTube link: FDA Drug Topics Cannabis and Cannabis Derived Products – For Healthcare Practitioners - March 2023 (youtube.com)

BACKGROUND INFORMATION

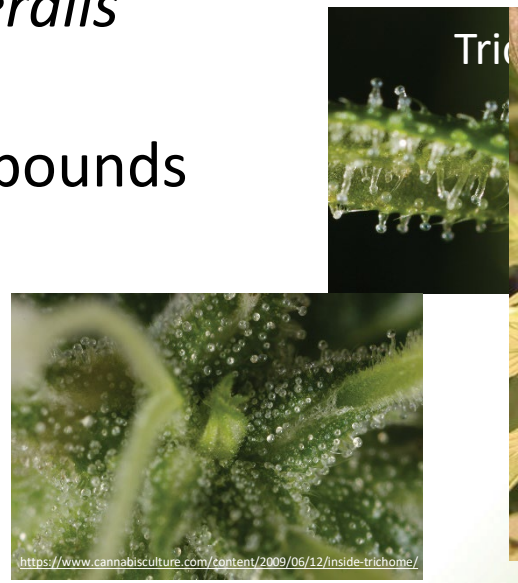
What is Cannabis?

- Cannabis is a genus of flowering plant that generally includes three species: *Cannabis sativa, indica* and *ruderalis*

- Plant contains hundreds of compounds
  - More than 120 cannabinoids
  - More than 100 terpenes
  - Other phytochemicals present

- Commonly known compounds
  - Cannabidiol (CBD)
  - Delta-9 tetrahydrocannabinol (Δ9-THC)

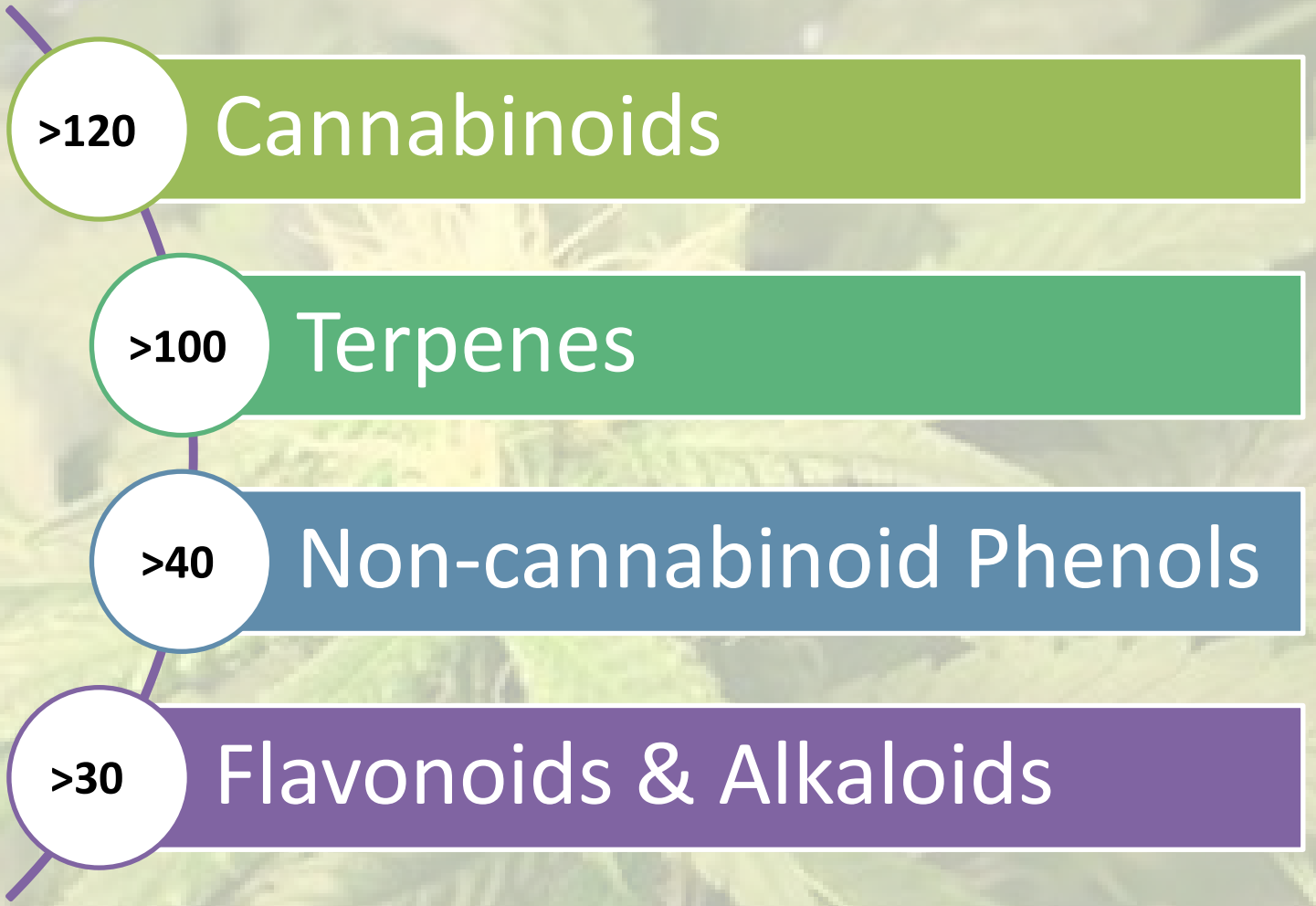
- Unknown number of cultivars (chemovars)
  - Human cultivation for specific traits
  - To create new varieties



Source: POLITICO, C. Rivero published 10/21/2019

Major Constituents from Cannabis Plant

More than 500 constituents have been reported



Radwan, M.M.; Chandra, S.; Gul, S.; ElSohly, M.A. Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis. Molecules **2021**, 26, 2774. https://doi.org/10.3390/molecules26092774

What is Cannabis?

Term: “Marihuana” or “Marijuana”

- Parts of the *Cannabis sativa* plant have been controlled under the Controlled Substances Act (CSA) since 1970
- Under the drug class "Marihuana" (commonly referred to as "marijuana") [21 U.S.C. 802(16)]
- "Marihuana" is currently listed in Schedule I of the CSA due to its high potential for abuse, which is attributable in large part to the psychoactive effects of THC, and the absence of a currently accepted medical use of the plant in the U.S.

> 0.3% delta-9 THC > by dry weight

Term: “Hemp”

- Agriculture Improvement Act of 2018, Pub. L. 115-334, (the 2018 Farm Bill) was signed into law on Dec. 20, 2018
- Removed hemp from regulation by the Drug Enforcement Administration (DEA) under Schedule I of the CSA
- The Farm Bill defined hemp as *Cannabis sativa* L. with a delta-9 THC concentration of not more than 0.3 percent (on a dry weight basis)
- Cannabis plants and derivatives that contain **no more than 0.3 percent delta-9 THC on a dry weight basis** are no longer controlled substances under federal law

Image Source: Canva Pro

LANDSCAPE

Market landscapes in the United States

1. **Federal-level**
   - Highly regulated for human drugs and controlled substances
   - Food, Drug and Cosmetic Act (FDCA), Controlled Substances Act (CSA) & 2018 Agricultural Improvement Act (Farm Bill)

2. **State-level (medical and adult-use programs)**
   - Regulated
   - Patchworks of state laws & enforcement entities
     - Common themes and best practices across states
     - Testing, child-resistant packaging and THC limits – generally common across programs
     - Not in place for hemp-derived products

3. **Hemp-derived/intoxicating cannabinoids**
   - Largely unregulated
   - Very little state oversight

Cannabis Drug Development

Four human drug products approved by FDA; with re-scheduling drug control actions upon approval:

1. Marinol (dronabinol) (1985): nausea from cancer chemotherapy; anorexia associated with AIDS → **Schedule III (under the Controlled Substances Act)**

2. Cesamet (nabilone) (1985 (2006)): nausea from cancer chemotherapy → **Schedule II**

3. Syndros (dronabinol) (2016)*: nausea from cancer chemotherapy; anorexia associated with AIDS → **Schedule II**

4. Epidiolex (CBD) (2018): for childhood seizures & Tuberous Sclerosis Complex → Originally Schedule V but now **No longer controlled**

Photo: https://prescriptiongiant.com/product/cesamet-generic-nabilone/

Photo: https://www.syndros.com/what-is-syndros/how-to-use

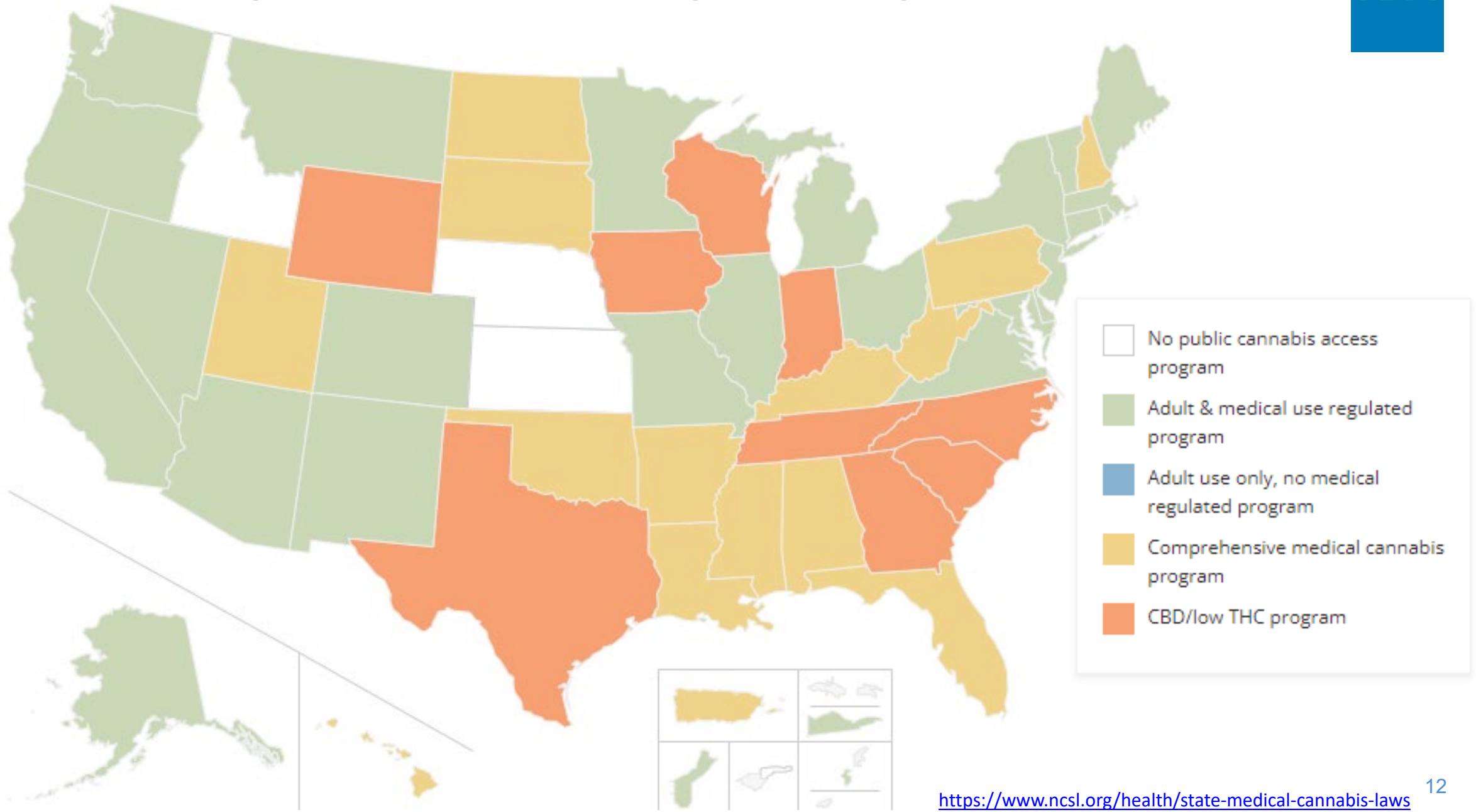
Photo: https://www.epidiolex.com/about-epidiolex/story

* Not currently marketed

Cannabis Use at State-level

- Per the National Conference of State Legislators (NCSL)
  - "Medical-Use"
    - As of April 24, 2023: 38 states, 3 territories and the District of Columbia allow medical use of cannabis products by qualified individuals
  - "Non-Medical/Adult-Use":
    - As of Nov. 8, 2023: 24 states, 3 territories and the District of Columbia have enacted measures to regulate cannabis for adult non-medical use
  - "Low THC, high cannabidiol (CBD)":
    - As of Aug. 2024: 9 states allow use of these products for medical reasons in limited situations or as a legal defense

State Regulated Cannabis Programs, August 2024



https://www.ncsl.org/health/state-medical-cannabis-laws

State-level Programs

- These products are not lawful under the FDCA
- Products have not been evaluated by FDA and have not undergone clinical trials
- Quality control requirements allow for state-level actions and oversight
- Products may contain compounds that cause intoxicating effects
- Each state program regulates cultivation, manufacturing, and sales of their products
- Products are sold in state-licensed cannabis dispensaries and sanctioned points-of-sale
- Purchases require a government-issued photo ID at point-of-sale
- Age-gating is used at point-of-sale to protect children

State-level: Medical and Adult-Use

Medical Programs

- Access requires registration with state
- Patients need a “qualifying medical condition” accepted by their state program
- Program access largely depends on experience and evaluation of state authorizing HCPs
- Product formulations, doses, and strengths vary greatly from state-to-state
- Products have not been shown to be safe and effective under the FDCA for any clinical indications

Adult-Use

- Access not does require registration with state
- No “qualifying medical condition” is required
- Do not need to see HCPs to gain access
- Wide variety of products often containing compounds that may cause intoxicating effects
- Limits on amount of cannabis adults may possess

SEED-TO-SALE

Generalized Tracking Process

1
Plant tag introduced: Cultivars, Growers, Harvest

2
Manufacturing Info: Firm, location, formulations

3
Final product formulation tag introduced & testing

4
Products distributed to sale locations

5
Regulators track sales, inventory, AEs, testing

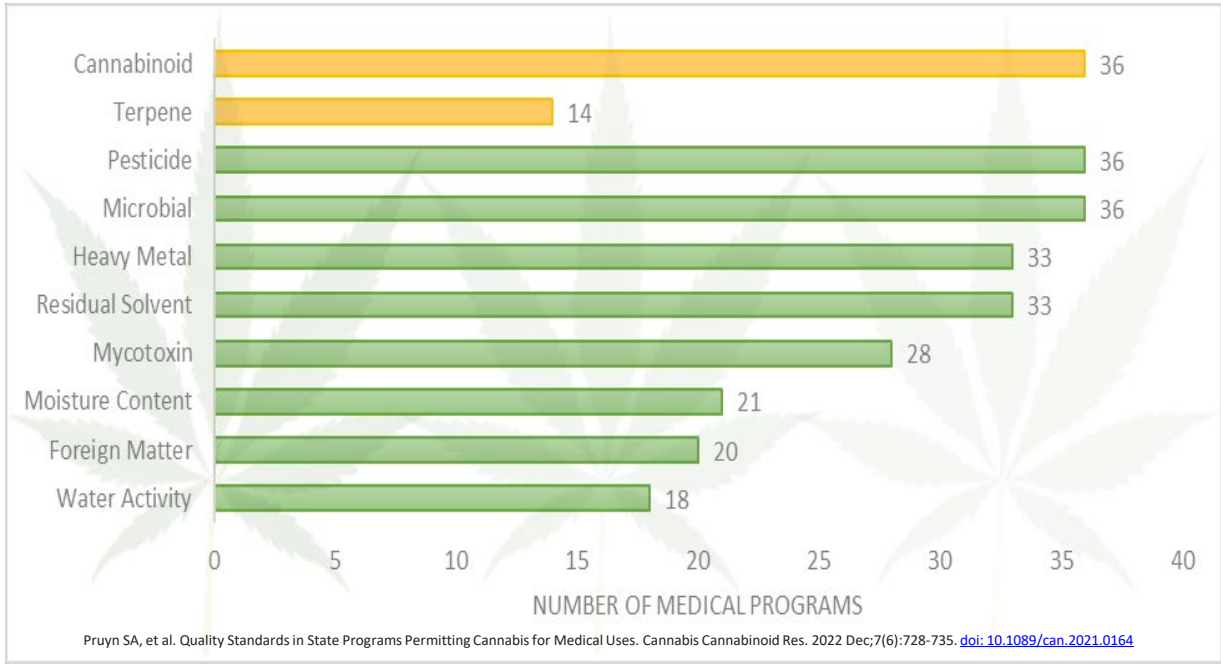
Image Source: Canva Pro

Quality Control

- Medical and Adult-use programs are **intrastate** markets for products
  - Example: Maryland products are manufactured, regulated and sold only in Maryland dispensaries

  - Every state has different quality controls:
    - Cultivation requirements
    - Manufacturing requirements
    - Testing requirements
    - Seed-to-sale systems

  - State programs can take actions:
    - Quality control issues
    - Recalls
    - Adverse Events
    - Other actions



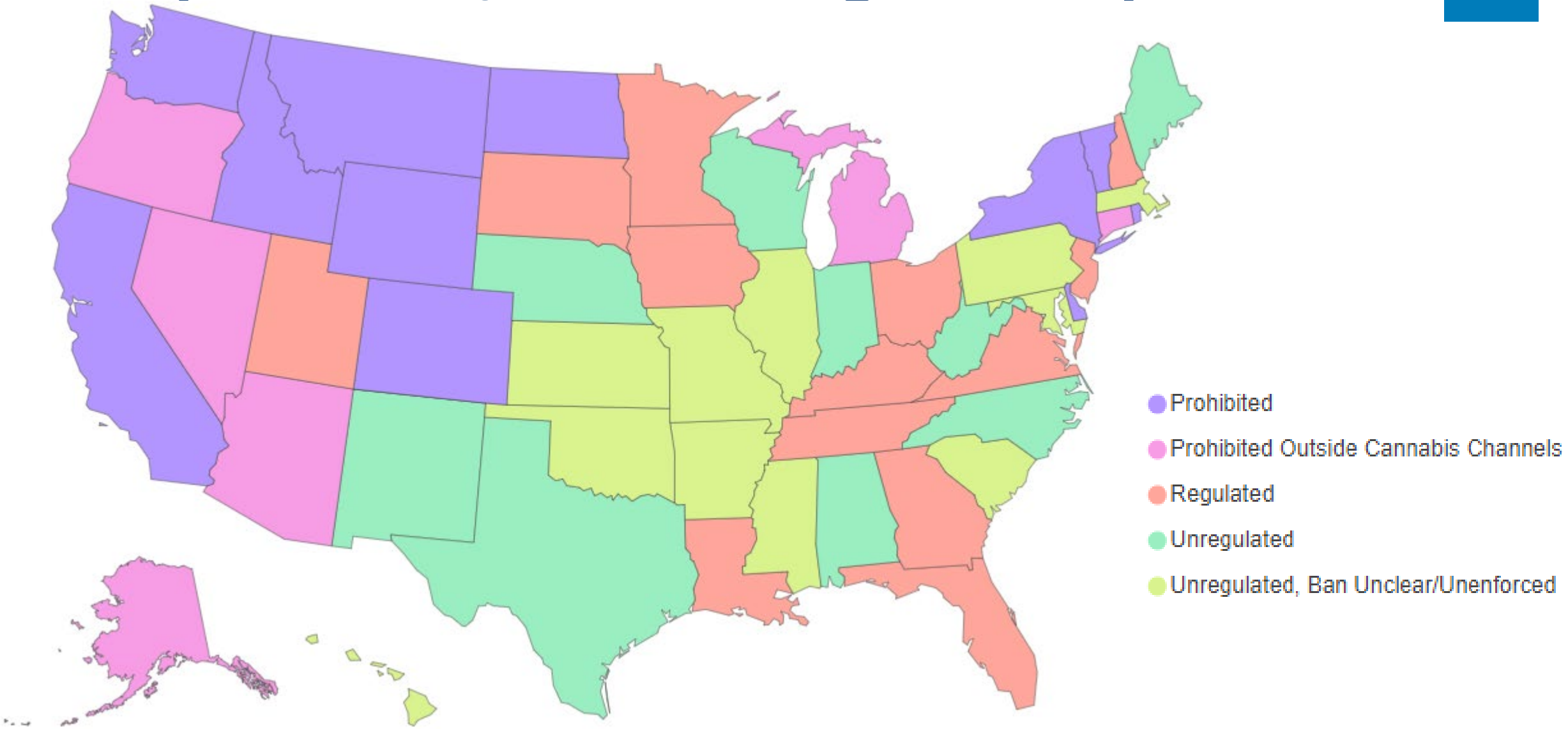
Pruyn SA, et al. Quality Standards in State Programs Permitting Cannabis for Medical Uses. Cannabis Cannabinoid Res. 2022 Dec;7(6):728-735. doi: 10.1089/can.2021.0164

- Hemp-derived/intoxicating products are **interstate** markets
  - Largely unregulated and lack quality controls
  - Manufacturing process may occur across multiple states & in unsanitary conditions
  - Sales occur online across multiple states and in unregulated locations (e.g., gas station, convenience store)
  - Lack the seed-to-sale systems making regulatory actions difficult

Hemp-Derived/Intoxicating Marketplace

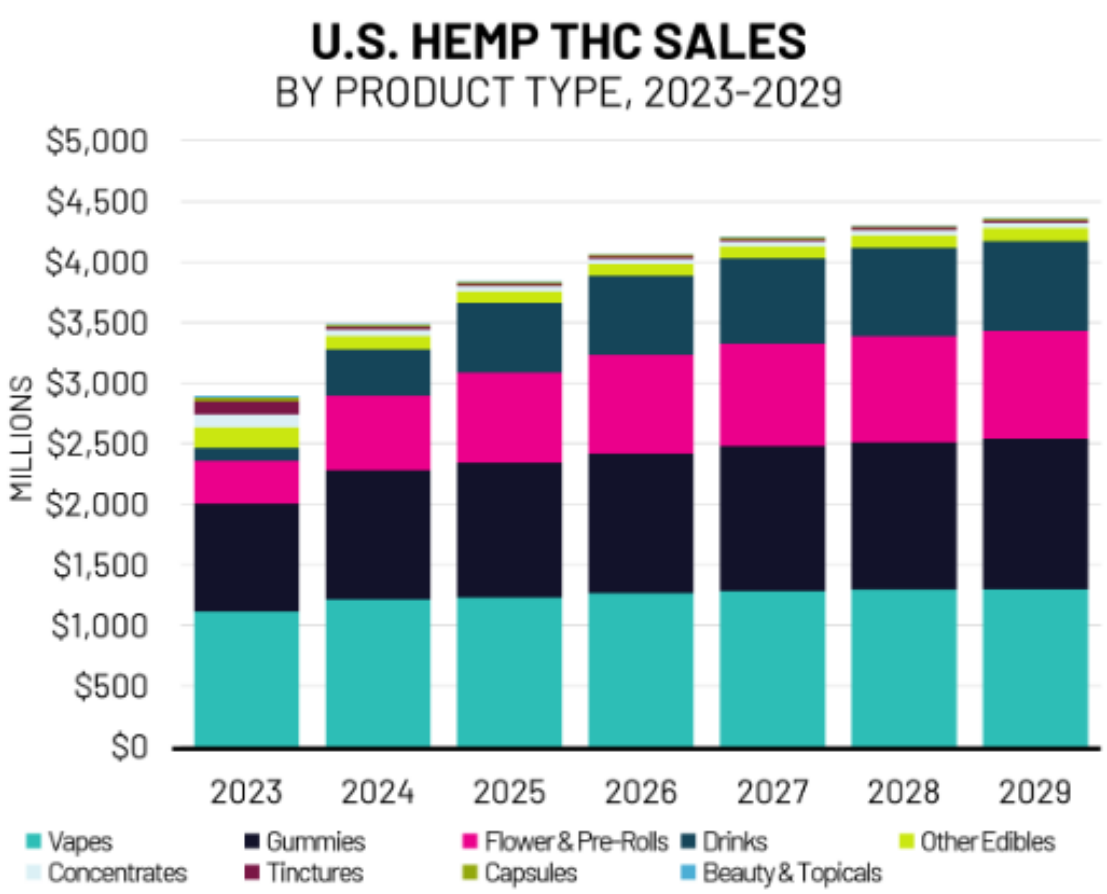
- These products are not lawful under the FDCA
- Largely unregulated and state oversight challenging due to interstate commerce
- Products may contain compounds converted from hemp-derived CBD and chemical synthesis
- Products may contain high concentrations and high doses of multiple compounds
- Synthesized compounds may also exist in these products (e.g., hidden ingredients)
- Manufacturing controls largely do not exist (e.g., unsanitary conditions)
- Products are sold at unregulated point-of-sale (e.g., gas station, convenience store, online)
- Age-gating is not always used at point-of-sale

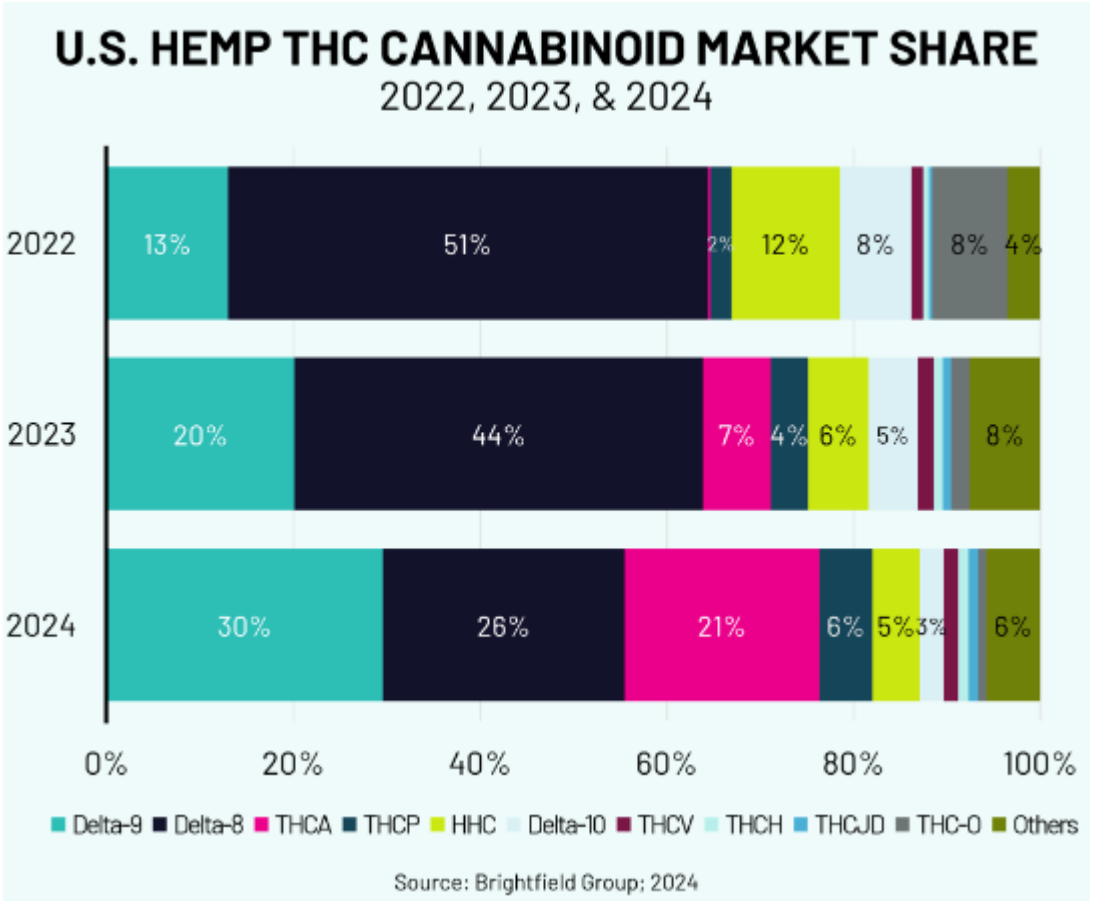
Hemp-Derived/Intoxicating Marketplace



Source: Brightfield Group 2024

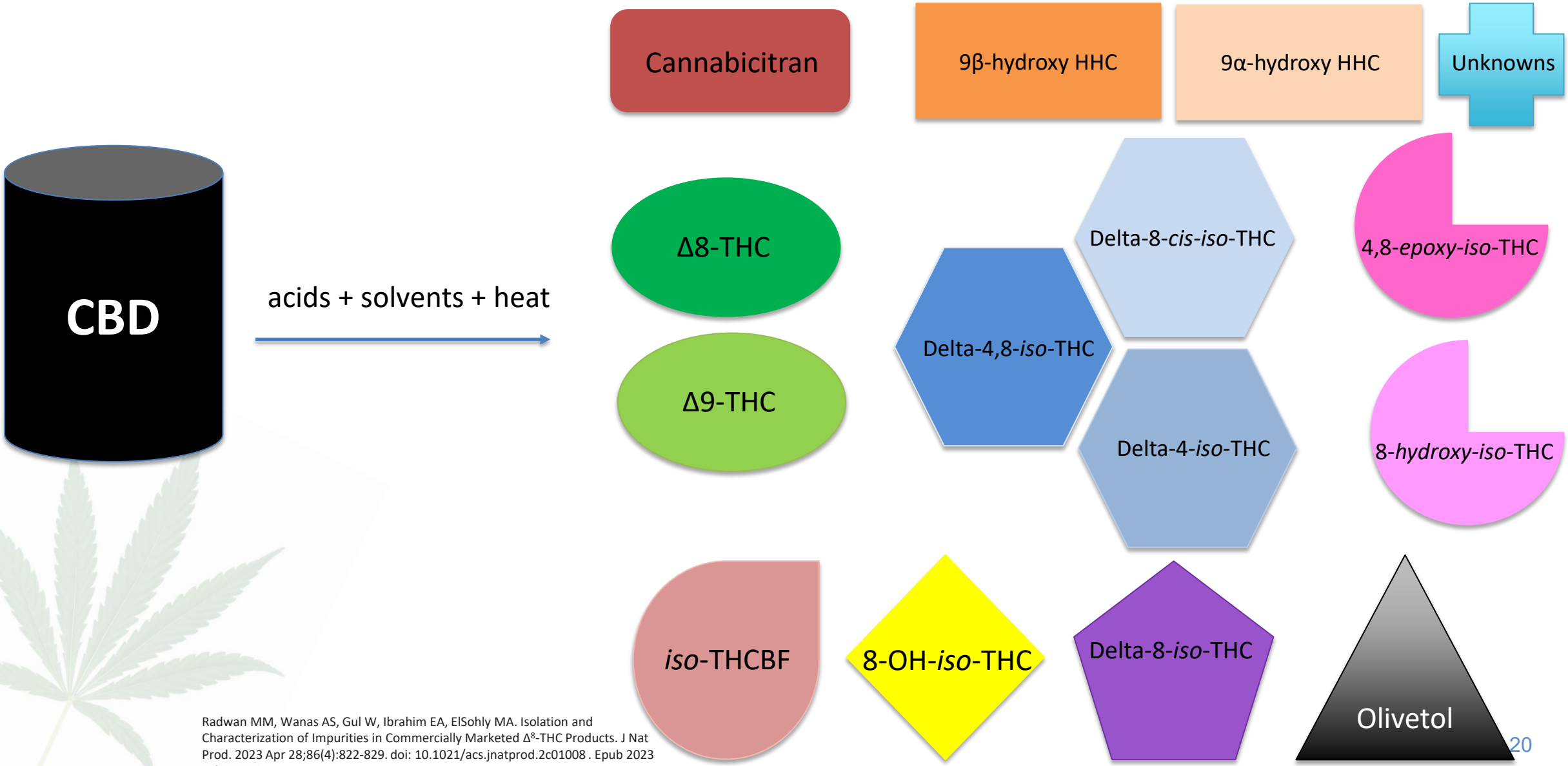
Hemp-Derived/Intoxicating Marketplace





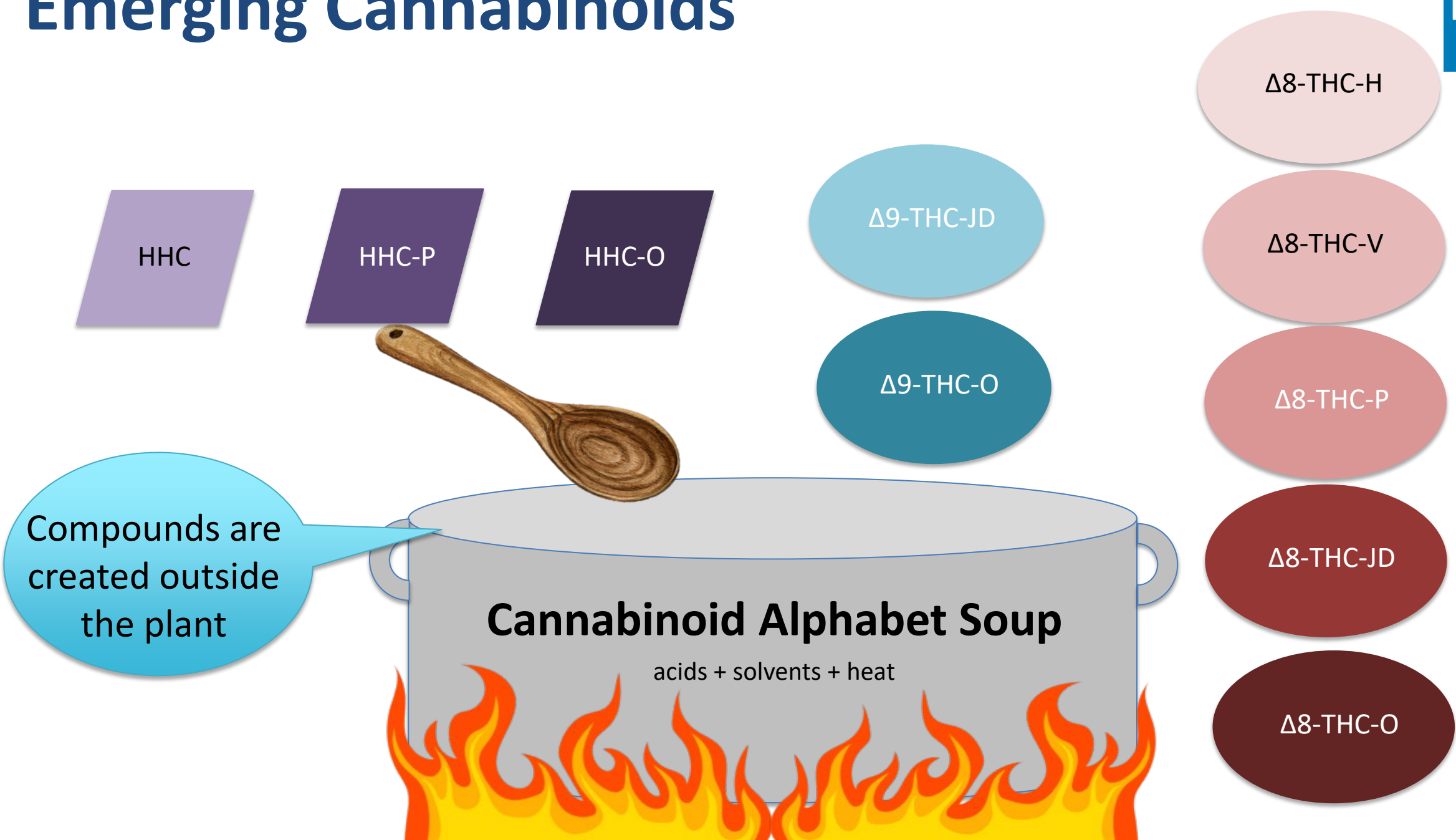
Source: Brightfield Group 2024

Chemical Conversion Examples

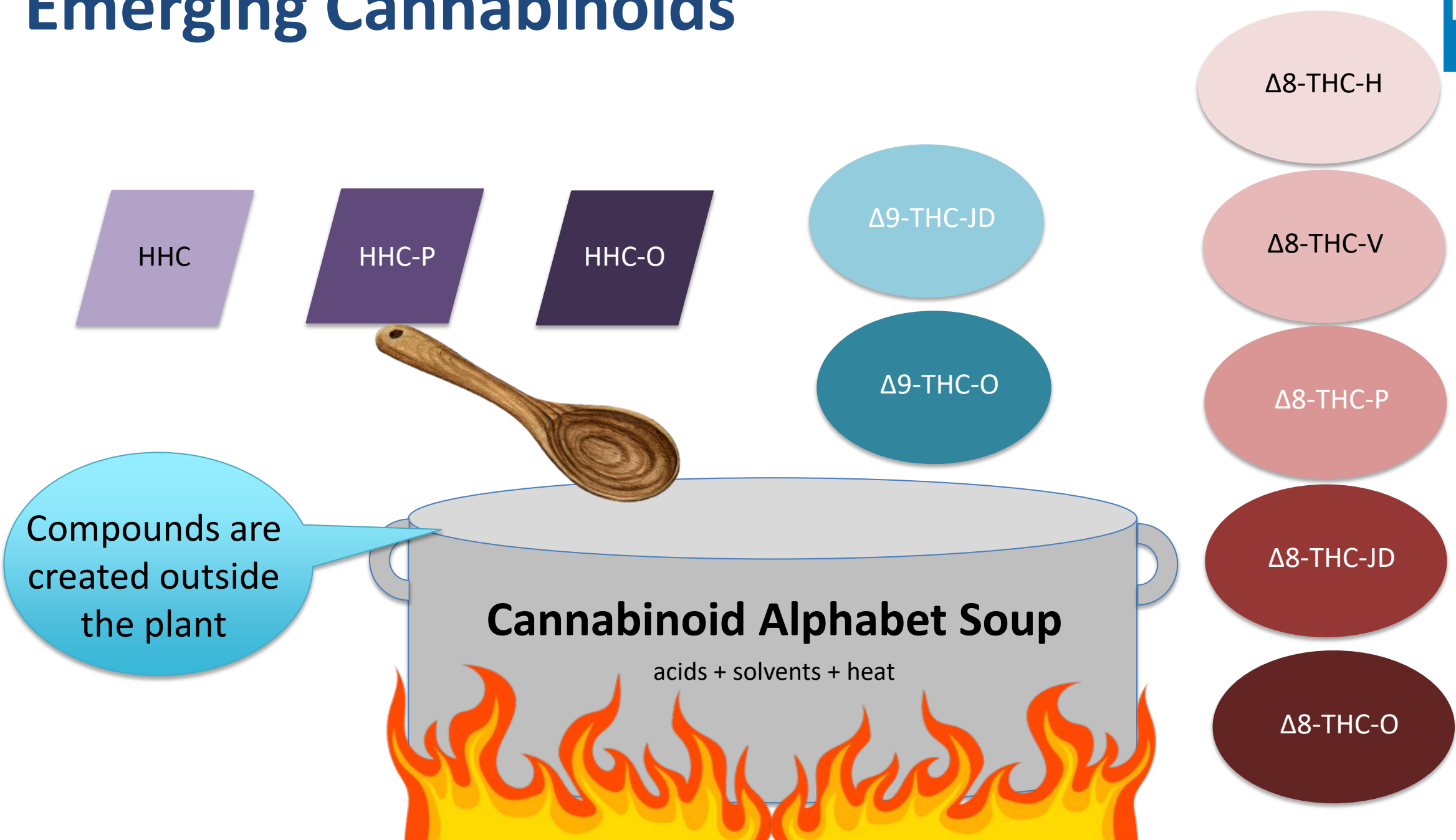


Radwan MM, Wanas AS, Gul W, Ibrahim EA, ElSohly MA. Isolation and Characterization of Impurities in Commercially Marketed Δ^8-THC Products. J Nat Prod. 2023 Apr 28;86(4):822-829. doi: 10.1021/acs.jnatprod.2c01008 . Epub 2023 Feb 24. PMID: 36827690.

Emerging Cannabinoids



Emerging Cannabinoids



Misinformation

- Inaccurate or misleading labels and purported claims
  - Potential for impurities (e.g., solvents, heavy metals, pesticides) & other adulterants
- Consumer confusion that products are regulated or approved
- Lack of high-quality data to support purported claims
  - Confounding results from uncontrolled studies or surveys
  - Numerous variables and often lacking proper control group
  - Gold standard: randomized controlled trials
- Falsification of product certificates of analysis (COAs)
- Misrepresentation on the need for an Investigational New Drug Application (IND)
  - When researchers need to submit an IND:
    - Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must **seek an exemption** from that legal requirement.

Image Source: Canva Pro

Misinformation

JAMA. 2017 Nov 7; 318(17): 1708–1709. PMCID: PMC5818782
Published online 2017 Nov 7. doi: 10.1001/jama.2017.11909 PMID: 29114823

Labeling Accuracy of Cannabidiol Extracts Sold Online

Marcel O. Bonn-Miller, PhD,[✉1] Mallory J. E. Loflin, PhD,[2] Brian F. Thomas, PhD,[3] Jahan P. Marcu, PhD,[4] Travis Hyke, MS,[5] and Ryan Vandrey, PhD[6]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818782/

AJPH
A PUBLICATION OF THE AMERICAN PUBLIC HEALTH ASSOCIATION
https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2020.305768

Crowdfunding Cannabidiol (CBD) for Cancer: Hype and Misinformation on GoFundMe

Marco Zenone BA, Jeremy Snyder PhD, and Timothy Caulfield LLM

Accepted: May 06, 2020 Published Online: October 01, 2020

For Release

FTC Announces Crackdown on Deceptively Marketed CBD Products

Companies made unsupported claims that their oils, balms, gummies, coffee, and other goods could treat serious diseases such as cancer and diabetes

December 17, 2020

https://www.ftc.gov/news-events/news/press-releases/2020/12/ftc-announces-crackdown-deceptively-marketed-cbd-products

Misinformation

How To Pick Out Fraudulent and Misleading COAs: Q&A with Kia Mikesh of Adams Independent Testing

Kia Mikesh, the CEO of Adams Independent Testing, discusses the prevalence of misleading certificates of analysis in the hemp industry, how to identify them and how to mitigate the issues that come with them.

Theresa Bennett
May 8, 2020

https://www.cannabisbusinesstimes.com/hemp/news/15691686/how-to-pick-out-fraudulent-and-misleading-coas-qa-with-kia-mikesh-of-adams-independent-testing

CANNABIS WATCH

'It's very easy to get fooled': Two cannabis rivals are raising awareness about fake-products scams

Rivals Kiva Confections and Wana Brands team up to launch anti-scam campaign to help consumers

By Steve Gelsi Follow

Last Updated: Nov. 21, 2023 at 7:37 a.m. ET

First Published: Nov. 20, 2023 at 2:30 p.m. ET

https://www.marketwatch.com/story/its-very-easy-to-get-fooled-two-cannabis-rivals-are-raising-awareness-about-fake-products-scams-9657e630

Misinformation

- Excerpt from *Marketing Claims and Risk Product Contamination section*:

- "…**false or misleading claims of therapeutic efficacy**…"
- "…**inaccurate labeling is not uncommon**"
- **"significantly diverged from the concentration determined by independent laboratories** (Bonn-Miller et al., 2017; Pavlovic et al., 2018; Vandrey et al., 2015; White, 2019)"
- "CBD concentration was **not consistent across batches** of same product…(White, 2019)"
- "…companies advertise products are laboratory-tested for CBD content, these **claims often lack verification** because CBD products are not currently listed in the U.S. Pharmacopeia"

CLINICAL INFORMATION

Clinical

- The two most prominent cannabinoids from cannabis (*Cannabis sativa* L.) are Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD)
  - Δ9-THC is the primary intoxicating component - "high"

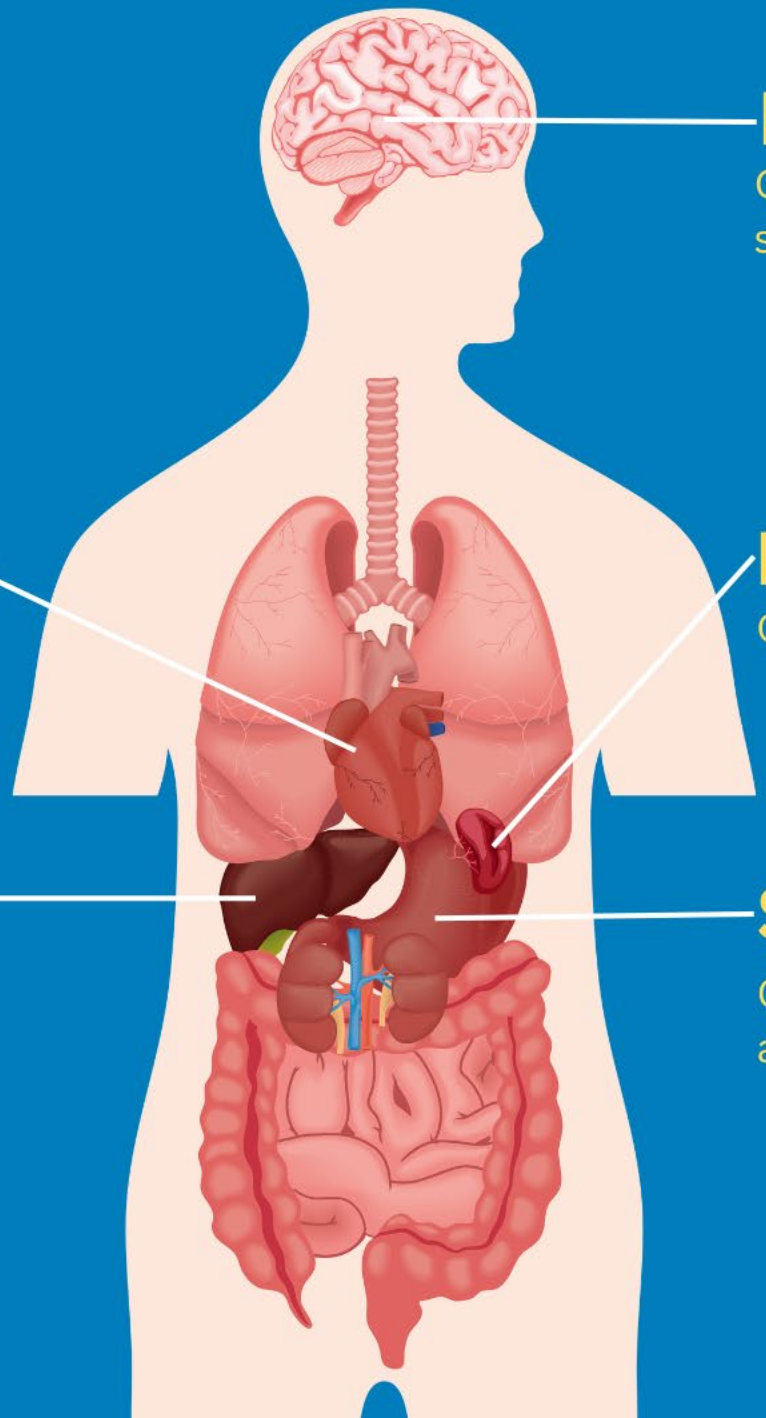
- Many patients self-administer Δ9-THC and or CBD marketplace products for perceived clinical benefits (e.g., pain, sleep, anxiety)
  - Important for practitioners to be aware of a patient's use and risks

- Hemp products are often perceived as harmless and typically marketed for the CBD component (does not exceed 0.3% Δ9-THC by weight)
  - CBD has potential drug interactions and clinical effects
  - Δ9-THC component, if taken in large enough quantities, may still have a relevant clinical or intoxicating effects

Clinical

- Endocannabinoid Receptors
  - CB1
    - Main clinical site for Δ9-THC activity as agonist
    - Clinical effects of euphoria, psychosis, pain relief, sedation, tachycardia, motor and memory impairment and increased appetite (Hill, 2022)
    - Mainly location is brain region such as prefrontal-limbic region, hippocampus, amygdala (An, 2020)
  - CB2
    - Main site for CBD (although Δ9-THC does have action) as negative allosteric modulator
    - Numerous locations including peripheral immunological tissue (Orsolini, 2019)

Δ9-THC & CBD
Key Clinical Effects



Brain
CB1 - Euphoria, pain relief, psychosis, sedation, appetite, memory impairment

Heart
CB1 - Tachycardia, hypotension

Immune System
CB2 - Immune modulation

Liver
CBD - Elevated Transaminase
Δ9-THC & CBD - numerous potential drug interactions

Stomach
CB1 - Reduces motility/peristalis, antiemetic (central acting)

Approved Active Human Drug Formulations

Brand-name (Drug)	Indication	Dose	Key Precautions
Epidiolex (Cannabidiol) Oral Solution	Treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older. **Not a controlled substance**.	Starts at 2.5mg/kg twice per day and up to 10mg/kg/day to 25 mg/kg/day.	Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment and use caution with concomitant use with valproate Epidiolex approval information
Marinol (synthetic D9-THC – dronabinol)	Treatment of anorexia associated with weight loss in patients with AIDS. Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. **A Schedule III controlled substance**	Supplied as capsules in strengths of 2.5 mg, 5 mg, and 10 mg	Watch for Neuropsychiatric Adverse Reactions such as psychiatric effects and cognitive or motor impairment, hemodynamic changes, substance use and paradoxical vomiting. Marinol approval information
Cesamet (Nabilone)	A **synthetic analogue** of Δ9-THC is approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. **A Schedule II controlled Substance**	Supplied as 1 mg capsules	Similar information to synthetic D9-THC formulations. Nabilone is more potent than dronabinol Nabilone approval information

Clinical Pharmacology

- Pharmacokinetics:
  - Metabolism of a drug in the body
  - Absorption, bioavailability, distribution, metabolism and excretion
  - Relates to an organ dysfunction, DDI
- Pharmacodynamics:
  - Actions of the drug in the body
  - Receptor binding, second messenger systems

Clinical - Pharmacology

- Pharmacokinetics
  - CBD:
    - Peak plasma concentrations typically 1-2 hours after ingestion
    - Extensive first-pass metabolism
    - Primary metabolism – CYP2C19 and CYP3A4
  - Δ9-THC (oral):
    - Extensive first pass metabolism
    - Peak Plasma time 0.5 to 4 hours with a half-life 5.6 hours and 44-59 hours for metabolite
    - Subjective and other cognitive effects peak around 1.5-3 hours with a duration around 6.8 hours (Vandrey, 2017) **Note: User may believe they did not achieve the desired effect and re-dose**
    - Primary metabolism – CYP2C9 and CYP3A4
  - Δ9-THC (inhalation):
    - Avoids first pass metabolism
    - Peak Plasma time 3-10 minutes with higher concentrations than oral admin
    - Impairment greatest within 1 hour and declines by 2-4 hours (Lucas, 2018)

Pharmacokinetics (PK) based Cannabidiol Drug Interactions

Precipitant	Mechanism	Object (Substrate)	Clinical Impact	Prevention or Management
CBD	CYP1A2 inhibition IC_{50} = 21 µM	Caffeine Theophylline Tizanidine	Caffeine Cmax ↑ by 15% Caffeine AUC ↑ by 95%	Consider a dose ↓ of CYP1A2, CYP2B6, CYP2C8 or CYP2C9 substrates as clinically appropriate in case of AEs.
CBD	CYP2B6 inhibition IC_{50} = 2.91µM	**Bupropion** Efavirenz	**In vitro data**	
CBD	CYP2C8 inhibition IC_{50} = 3.23 µM	Amodiaquine Buprenorphine	In vitro data	
CBD	CYP2C9 inhibition IC_{50} = 2.46 µM	D9-THC Phenytoin[1] **Warfarin[1]**	A case report showed nonlinear increase in warfarin, dose reduction required by 30% (Grayson 2017)	
CBD	CYP2C19 inhibition IC_{50} = 3.21 µM	Clobazam **Diazepam**	N-CLB exposures ↑ by 3-fold[2] 7-OH-CBD Cmax ↑ 73% 7-OH-CBD AUC ↑ 47%	Consider a dose ↓ of CYP2C19 substrates.

[1]Multiple CYPs are involved in the metabolism of the drug with major contribution form CYP2C9
[2]N-desmethy clobazam (N-CLB) is a substrate of CYP2C19

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf

Pharmacokinetics (PK) based Cannabidiol Drug Interactions

Precipitant	Mechanism	Object (Substrate)	Clinical Impact	Prevention or Management
CBD	CYP3A4 inhibition IC_{50} = 1.42 µM	**Sildenafil**	Sildenafil has case reports of MI with smoked cannabis (McLeod, 2002)	Consider dose reductions or monitor for CYP3A4 substrates
CBD	UGT1A9 inhibition	Diflunisal Propofol Fenofibrate	In vitro studies predicted a DDI	Consider a dose↓ of UGT1A9 substrates as clinically appropriate in case of AEs.
CBD	UGT2B7 inhibition	Gemfibrozil **Lamotrigine** Morphine	**In vitro** studies predicted a DDI	Consider a dose ↓ of UGT2B7 substrates as clinically appropriate in case of AEs.
CBD	P-gp inhibition	Sirolimus Tacrolimus Digoxin	↑ in exposures of orally administered P-gp substrates may be observed	TDM Dose ↓ of P-gp substrates
CBD	Intestinal P-gp inhibition + CYP3A4 inhibition	Everolimus	2.5-fold ↑ exposures	TDM Dose ↓ of everolimus

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf

Pharmacokinetics (PK) based Cannabidiol Drug Interactions

Precipitant	Mechanism	Object (Substrate)	Clinical Impact	Prevention or Management
Fluconazole	CYP2C19 inhibition	CBD	CBD Cmax ↑ by 24% CBD AUC ↑ by 22% 7-OH-CBD Cmax ↓ by 41% 7-OH-CBD AUC ↓ by 28% 7-COOH-CBD Cmax ↓ by 48% 7-COOH-CBD AUC ↓ by 33%	Lower dose of CBD or hold during fluconazole treatment
Itraconazole Ketoconazole	CYP3A4 inhibition	CBD	Case study showed CBD and THC nearly doubled by ketoconazole (Stott, 2013)	Lower dose of CBD or hold during itraconazole/ketoconazole treatment
Rifamycin	CYP3A4 and CYP2C19 induction	CBD	CBD Cmax ↓ by 34% CBD AUC ↓ by 32% 7-OH-CBD Cmax↓ by 67% 7-OH-CBD AUC ↓ by 63% 7-COOH-CBD Cmax - 7-COOH-CBD AUC ↓ 48%	Clinical impact of CBD exposures is not known. Consider CBD dose increase up to 2-fold if CBD required (Dravet's syndrome).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf

Pharmacodynamics (PD) based Cannabidiol Drug Interactions

Precipitant	Mechanism	Object (Substrate)	Clinical Impact	Prevention or Management
CBD	Combined liver inflammatory effects.	**Valproate**	Valproate Cmax ↓ by 17% Valproate AUC ↓ by 21% 2-propyl-4-pentanoic acid ↓ by 28% - 33% CBD Cmax ↓ 26% 6-OH-CBD AUC ↓ 27% 7-OH-CBD AUC ↑ 22% 7-COOH-CBD Cmax ↑ 25% 7-COOH-CBD AUC ↑ 32% ↑ Liver enzymes	Discontinuation or reduction of CBD
CBD	Combined CNS effects	CNS depressants and alcohol	May ↑ Risk of sedation and somnolence	Caution with other CNS depressants
CBD	Decreased renal clearance	**Lithium**	Case report showed lithium level doubled (Singh, 2020)	Consider lowered lithium dose

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf

Delta-9 THC Drug Interactions

Pharmacokinetics (PK)				
Precipitant	**Mechanism**	**Object (Substrate)**	**Clinical Impact**	**Prevention or Management**
Amiodarone Fluconazole	CYP2C9 inhibition	THC		Monitor for potentially increased THC-related adverse reactions
Ketoconazole Itraconazole Clarithromycin Ritonavir Erythromycin Grapefruit juice	CYP3A4 inhibition	THC	Ketoconazole nearly doubled CBD and THC levels (Stott, 2013)	
THC	Protein binding	**Warfarin**, cyclosporine, amphotericin B	Based on in vitro data	Monitor patients for increased adverse reactions, monitor INR
THC (smoked only)	CYP1A2 induction	Theophylline, **Olanzapine**, **clozapine**	Increased clearance of substrate	Educate patients, watch for change in efficacy, check drug levels

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018651s033lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/205525Orig1s013lbl.pdf

Delta-9 THC Drug Interactions

Pharmacodynamics (PD)
• Additive CNS effects (e.g., dizziness, confusion, sedation, somnolence) may occur when THC is taken concomitantly with drugs that have similar effects on the central nervous system such as CNS depressants. • Additive cardiac effects (e.g., hypotension, hypertension, syncope, tachycardia) may occur when THC is taken concomitantly with drugs that have similar effects on the cardiovascular system.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018651s033lbl.pdf

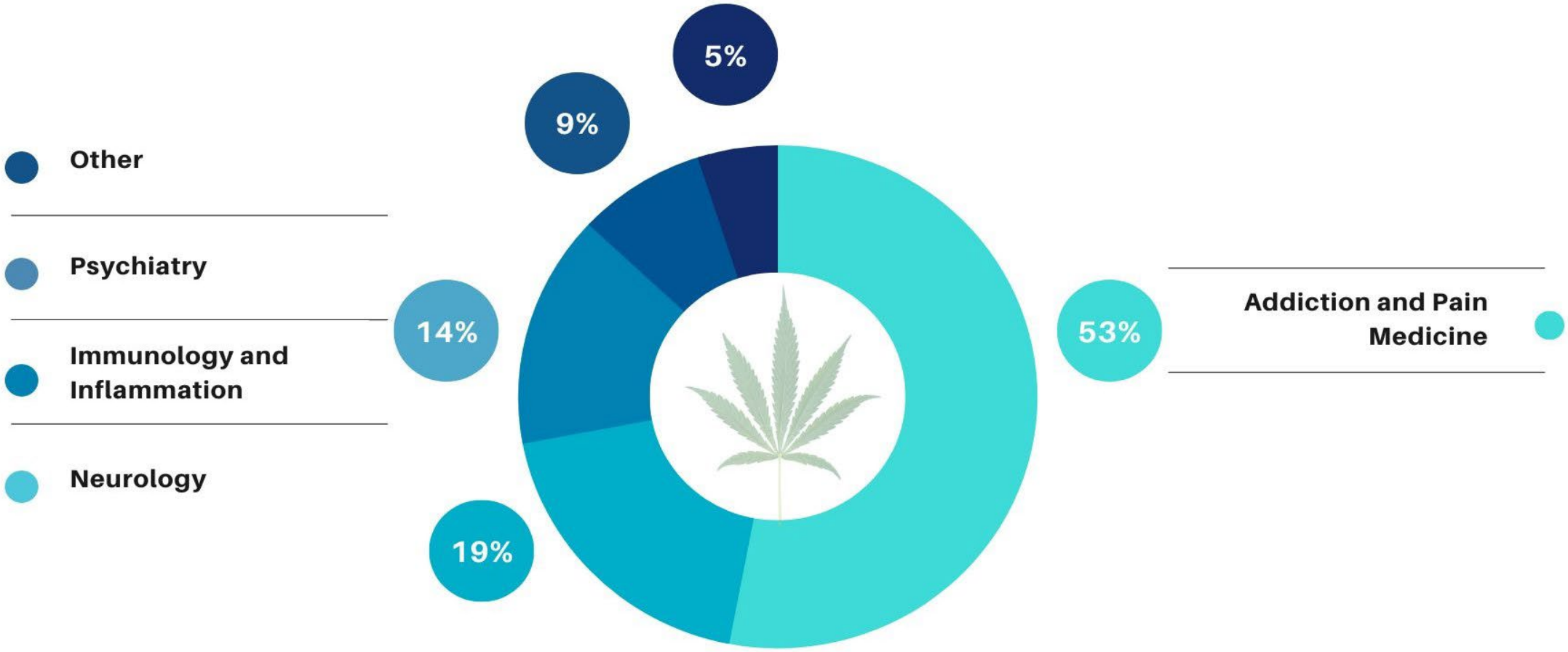
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/205525Orig1s013lbl.pdf

Clinical Evidence

- State level annual reports show most common condition patients are authorized cannabis for use for are in pain-related disorders followed by PTSD
  - However, often patients are self-medicating without a prescription in state approved programs for disorders such as pain, sleep, psychiatric disorders, Crohn's disease
  - Largest amount of literature in pain-related conditions

- Most professional organizations such as the American Psychiatric Association, American Academy of Neurology, International Association for the Study of Pain, do not endorse the use of cannabis for any conditions due to lack of sufficient, high quality, clinical evidence

Cannabis Clinical Research Areas



Taylor and Pruyn, 2023

Clinical Evidence

- Review of the literature shows overall mixed to negative results for most conditions
  - Pain conditions:
    - Most studied
    - Systematic reviews, meta-analyses and proposed guidelines show a possible modest effect, however, the adverse reactions may outweigh benefit (Whiting 2015, Dykukha 2021, McDonagh 2022, Bell, 2024)
  - Psychiatric disorders:
    - The preponderance of available literature does not support medical cannabis for any psychiatric condition and appears most authors/guidelines recommend against cannabis use for psychiatric conditions (Hindley et al. 2020, O'Neil et al. 2017; Shishko et al. 2018; Hindocha et al. 2020; Jugl et al. 2021)
  - Other Disorders:
    - Inflammatory Bowel Disorder and sleep disorders – small studies and/or observational data

Clinical Safety

- CBD:
  - Epidiolex label states AEs > 10% and placebo include somnolence, diarrhea, transaminase elevations, fatigue, rash, poor sleep quality
  - Note if patient taking a drug with any hepatotoxicity

- Δ9-THC:
  - Euphoria, psychosis, sedation, tachycardia, motor and memory impairment and increased appetite (Hill 2022)
  - Evidence shows association with earlier onset psychosis, relationship with frequency of use and development of psychosis and exacerbation of psychosis with pre-existing psychotic disorders (D'Souza 2005, Robinson 2023, Groening 2024)
  - Impairs memory and coordination (Morgan 2018)
  - Withdrawal reactions – e.g., irritability, anxiety, sleep difficulty, tremor, headache, sweating

Information obtained from FDA approved drug labels unless referenced

Other Cannabinoids of Interest

- Numerous cannabinoids exist and have limited clinical information available without characterized safety profiles

- **Delta-8 THC:**
  - Naturally occurring at very low quantities
  - Intoxicating effects similar to Δ9-THC but less potent (roughly 30%)

- **Hexahydrocannabinol (HHC):**
  - Considered semi-synthetic, commonly sprayed onto or mixed with cannabis products

- **Tetrahydrocannabiphorol (THCP):**
  - Very potent ~ 33x affinity of CB1r compared to Δ9-THC (Caprari 2024)
  - Naturally occurring but typically produced synthetically and marketed as "CBD derived"

- **Tetrahydrocannabinol-O-acetate (THC-O):**
  - Users report it being twice as potent as Δ9-THC, longer in onset and duration, and it is marketed as possessing a more “psychedelic” quality compared to Δ9-THC

CBD, THC, or Marijuana Risks During Pregnancy or Breastfeeding

- FDA strongly advises against the use of unapproved cannabidiol (CBD), tetrahydrocannabinol (THC), and marijuana in any form during pregnancy or while breastfeeding due to possible risks
  - The U.S. Surgeon General and American College of Obstetricians and Gynecologists (ACOG) recommends not using cannabis during pregnancy

- Cannabis products claiming, or promoted, as approved treatments for relief of pain, anxiety, or morning sickness have not been shown safe or effective through scientific studies
  - FDA has approved one prescription drug with CBD as an active ingredient. This drug is approved to treat rare, severe forms of seizure disorders in children
  - FDA has not approved cannabis (marijuana) for any use

- Patients should talk with a health care professional before taking any cannabis products (CBD, THC, or marijuana), medicines, vitamins, or herbs while pregnant or breastfeeding

- Additional FDA Resources:
  - Medicine and Pregnancy
  - Beyond Morning Sickness: Hyperemesis Gravidarum

Approach to the Patient

- Many patients may not reveal (or even know to discuss) their use of cannabinoids
- Screening high risk patients (such as patients with psychiatric or forensic histories) is considered good clinical practice (Connor, 2021)
- Numerous resources are available for both practitioners and patients → provided at the end of this presentation and take-home handout

Image Source: Canva Pro

Basic Approach to Patient Conversation:

START

Screen high-risk patients (e.g., pain, psychiatric) with open-ended questions in a nonjudgemental exploration

INQUIRE

Reasons for use and patient's perspective (e.g., self-medicating)

- "What benefits do you find from taking (product)?"
- Duration/amount: "How often have you used (product) in past week/month/year?"

IDENTIFY

Source of product (e.g., what brand)

- "Where do you buy (product) and do you have the label?"

DISCUSS

Potential or active concerns (e.g., AEs, safety risk, DDI) and determine if a substance use disorder present (e.g., interfering with function, amounts, and frequency)

- Highlight available approved treatments if patient using to self-medicate a disorder

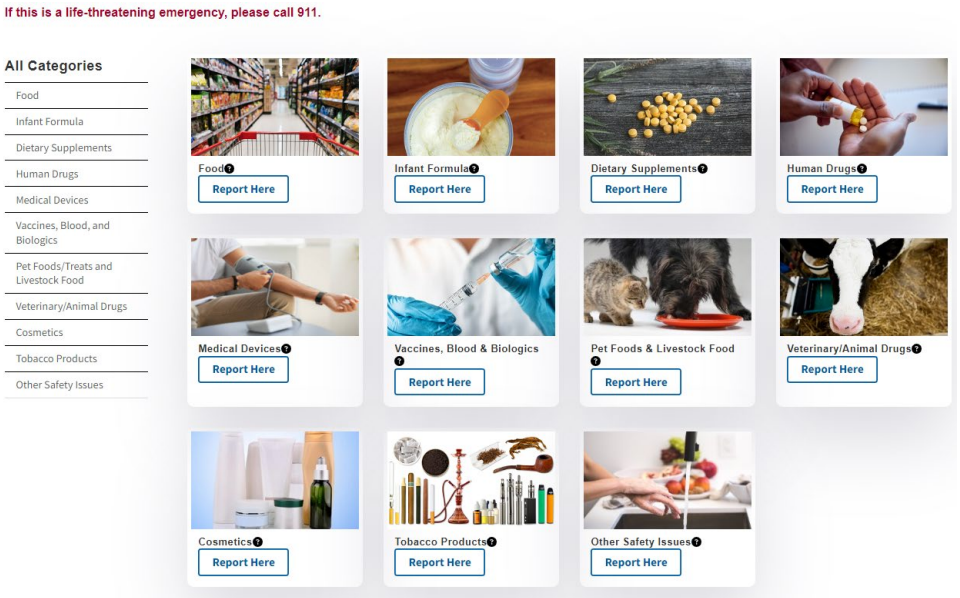
Image Source: Canva Pro

ADVERSE EVENT REPORTING

Reporting Safety Concerns to FDA

Food and Drug Administration
MedWatch

Link to MedWatch



Report a Problem through SmartHub

Link to Safety Reporting Portal

How to Report to MedWatch

- Online (www.fda.gov/medwatch)
  - Use the interactive form at FDA Form 3500
  - FDA encourages **online reporting** because it is quickest and most direct route

- Download the form above
  - Mail
  - Fax 1–800–332–0178

- Call FDA
  - 1-800-FDA-1088
  - Monday - Friday 8AM – 4:30 PM EST

MedWatch Reporting

We encourage you to submit reports involving:

- Adverse events/experiences
- Product quality problems
- Other product safety issues

Required information:

- Patient identifier
- Description of event or problem
- Product name
- Reporter first and last name

Components of a High-Quality Report

- Description of adverse event
- Suspected product information (e.g., manufacturer, product name, formulation, lot number, place of purchase, product pictures or website, dosage, dates of therapy, reason for use)
- Concomitant medication information
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information

What Does FDA Do With The Reports

- Reviewers evaluate reported information
  - Safety information of interest to reviewers during surveillance includes:
    - Serious adverse events (death, life-threatening, hospitalization, disability, congenital anomaly, other/required intervention)
    - Unexpected adverse events
    - Product specific concerns
    - Drug interactions
    - Adverse events reported in a specific patient population
    - Trends
- Analysis assists in determining actions related to potential safety issue(s)

SUMMARY & RESOURCES

Summary and Conclusions

- FDA has a well-defined role to play in the **regulation and development of products** containing cannabis and cannabis-derived compounds, **including enforcement action**, and FDA will continue to protect and promote the public health with respect to these products.

- FDA continues to focus on supporting scientific and rigorous testing and approval of drugs derived from cannabis and supporting **robust scientific research** into understanding **therapeutic uses and safety** of non-drug cannabis products.

- FDA is actively exploring potential **regulatory pathways** for the **lawful marketing** of appropriate cannabis-derived products.

- FDA has **only approved** one cannabis-derived and three cannabis-related drug products.

- You **can help** identify potential signals by reporting adverse events to MedWatch.

Free Resources for HCPs

- SAMHSA Resources:
  - 200 page Counseling Manual – "Brief Counseling for Marijuana Dependence"
  - Overview of Motivational Interviewing – "Using Motivational Interviewing in Substance Use Disorder Treatment"
  - Infographic to Hang in Office – "Marijuana: The Risks Are Real"
  - Information on Risks of Use – "Learn About Marijuana Risks"
  - 60-second Videos from SAMHSA
    - "Marijuana Use while Pregnant or Breastfeeding" – avoiding marijuana can give baby a healthier start in life
    - "Build a Brain" – visuals on how marijuana can impact adult memory, brain development, & concentration
    - "Virtual Assistant" – marijuana risks through lighthearted conversation, appealing to young adult audience
- CDC Resources:
  - Addiction (Marijuana or Cannabis Use Disorder)
  - Marijuana and Public Health

Handout Available for Download

Key Webinar Points - FDA Drug Topics: Cannabis Products and the Potential Impact on Patients

Background:

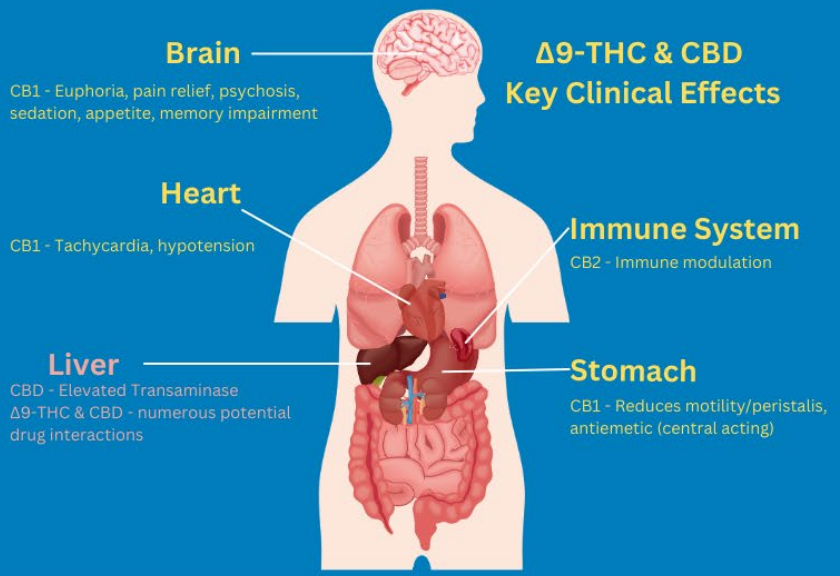
- > 500 compounds in *Cannabis sativa* L. plant
  - Δ9- tetrahydrocannabinol (Δ9-THC) is intoxicating
  - cannabidiol (CBD) alone is not intoxicating
- State-regulated products vary widely (medical & adult-use)
- Hemp products largely unregulated & widely available (e.g., gas stations, online)
- Products can be manufactured from plant parts or from chemicals
- Labeling may be misleading (e.g., hidden ingredients)

Δ9-THC Pharmacodynamics & Pharmacokinetics:

- Orally peaks around 1-3 hr; Duration ~7hr
  - User may believe desired effects did not occur & may re-dose
- Inhalation peaks ~3-10 min; Impairment greatest in first hr; Duration ~2-4 hr
  - Much faster onset than oral with higher maximum plasma levels leading to more deleterious effects.

Clinical:

- Patients use cannabis or cannabis-derived products to self-medicate for pain, PTSD, sleep disorders, IBS, etc.
- Outside FDA approved drugs - general lack of high-quality evidence to support the above medical conditions
- Educate patients about risks including DDI, adverse events, abuse potential, & withdrawal syndromes (if chronic use)



Approach to Patient Conversation:

- Start: Screen high risk patients (e.g., pain, psychiatric) using open-ended questions
- Inquire: Reasons for use of cannabis products
  - "What benefits do you find from taking (product)?"
  - Duration/amount - "How often have you used (product) in past month/year?"
- Identify:
  - Source of product "Where do you buy (product) and do you have the label?"
- Discuss:
  - Potential or active concerns (e.g., AEs, substance use disorder, side effects, DDI)
  - Highlight available approved treatments

Key Pharmacodynamic Interactions

Precipitant	Mechanism	Substrate	Clinical Impacts
CBD	Combined liver inflammatory effects	Valproate	Discontinuation or reduction of CBD
CBD	Decreased renal clearance	Lithium	Consider lower lithium dose, frequent monitoring while dosing
Δ9-THC	Additive CNS effects	Alcohol, benzos, opioids	Avoid concomitant use, educate patient, monitor for CNS adverse effects
Δ9-THC	Additive cardiac effects	Stimulants	Avoid concomitant use, educate patients, monitor for cardiac effects (e.g., tachycardia, hypertension)

Key Pharmacokinetic Interactions

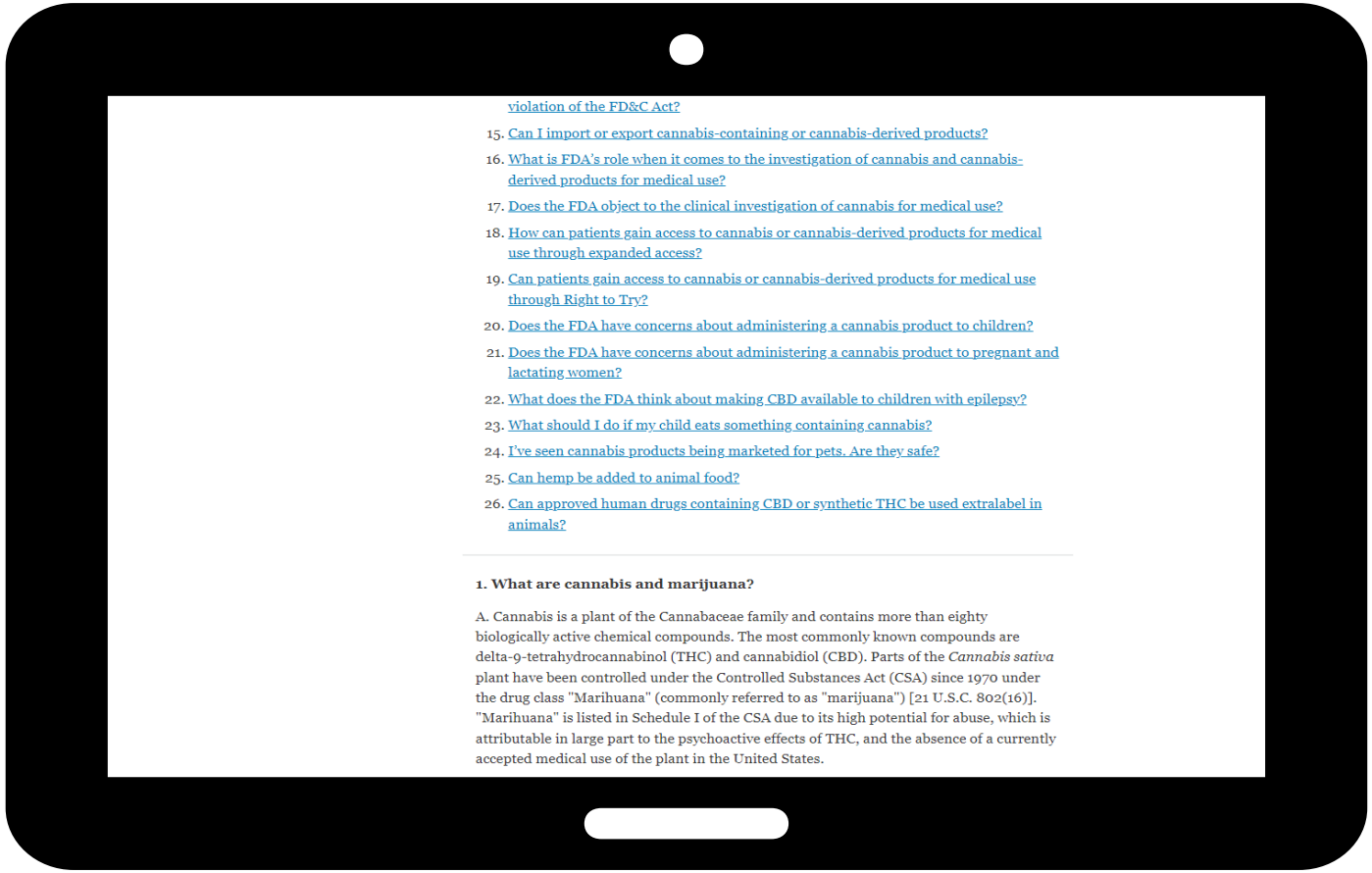
Precipitant	Mechanism	Substrate	Clinical Impacts
CBD/Δ9-THC	CYP3A4	↑ Sildenafil	Case reports of MI when combined with cannabis
CBD/Δ9-THC	CYP2C9-inhibit/protein binding	↑ Warfarin	Case reports of increased INR
CBD	CYP2C19 inhibit	↑ Diazepam, clobazam	Consider lower doses of the substrate
Smoked Cannabis	CYP1A2 induction	↓ Olanzapine, clozapine	Educate, watch for change in efficacy, check drug levels
Fluconazole	CYP2C19 inhibit	↑ CBD	Educate about possible adverse effects and/or stop CBD
Amiodarone	CYP2C9 inhibit	↑ THC	Educate about possible adverse effects/stop THC
Ketoconazole Macrolides	CYP3A4 inhibit	↑ CBD and THC	Educate about possible adverse effect and/or stop CBD

FDA Resources

FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)

On this page:

- FDA New Releases and Statements
- Consumer Information
- FDA Remarks and Testimony
- Science & Research
- Other Regulatory Resources
- Questions and Answers



References

- FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)
- FDA and Cannabis: Research and Drug Approval Process
- FDA Regulation and Quality Considerations for Cannabis and Cannabis-Derived Compounds – Chronicles article and Podcast
- FDA's 50 Years of Experience with Cannabis Research Helping to Support Tomorrow's Cannabis Drug Development
- What You Should Know About Using Cannabis, Including CBD, When Pregnant or Breastfeeding
- Delta-8 THC Has Serious Health Risks

Thank You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