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Navigating Drug Preclusion Gaps for Food and Dietary Supplements Containing CBD and Other Cannabinoids

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Moderated by **Robert Durkin**, Of Counsel, Arnall Golden Gregory LLP

Navigating Drug Preclusion Gaps for Food and Dietary Supplements Containing CBD and Other Cannabinoids

The 2018 'Farm Bill'

- Signed into law on December 20, 2018
- Definition of cannabis
  - Hemp
  - Marijuana
- Explicitly preserved agency's authority to regulate hemp and hemp derived products under their jurisdiction:
  - UDSA
  - DEA
  - FDA

Navigating Drug Preclusion Gaps for Food and Dietary Supplements Containing CBD and Other Cannabinoids

The 'exclusionary' or 'race to market' clauses:

Together, 201(ff)(3) and 301(ll) prohibit an article from legally being included in a dietary supplement or added to a food:

- if the article is approved under 21 U.S.C. § 355 (section 505 of the Act); or

- if the article has been authorized for investigation as a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.

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The 'exclusionary' or 'race to market' clauses:

There are two statutory exceptions to exclusion found in 301(ll) and 211(ff)(3):

- if the article was marketed in food or dietary supplement before the drug was approved or before the authorization; or

- the Secretary, at the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the Act.

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The ‘exclusionary’ or ‘race to market’ clauses:

The article:

“FDA has approved Epidiolex, which contains a purified form of the drug substance CBD.”

“EPIDIOLEX® (cannabidiol) oral solution

Initial U.S. Approval: 2018”

“Cannabidiol, the active ingredient in EPIDIOLEX”

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The ‘exclusionary’ or ‘race to market’ clauses:

Possible paths forward

- Someone wins the race and shows that the article was marketed in food or dietary supplement before the drug was approved or before the authorization;
- The Secretary, at the Secretary’s discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the Act; or
- Legislative intervention.

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The 'exclusionary' or 'race to market' clauses:

Possible discussion points

- Concerns with interpretation / application of clauses
  - Meaning of 'article'?
  - Meaning of 'approved'?
  - Inherent disadvantages for those in the natural products space.
- Which possible solution for the 'CBD situation' is best?
  - Regulation
  - Legislation (such as HR 8179, with consideration of FDA's comments)
- GRAS and issue of 'natural' or 'synthetic'.
- What are the implications for other components of hemp?
- Implications for other DIs if hemp/CBD get treated in a unique manner?

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This presentation is intended to provide general information on various regulatory and legal issues. It is NOT intended to serve as legal advice or counsel on any particular situation or circumstance.

EAS Consulting Group

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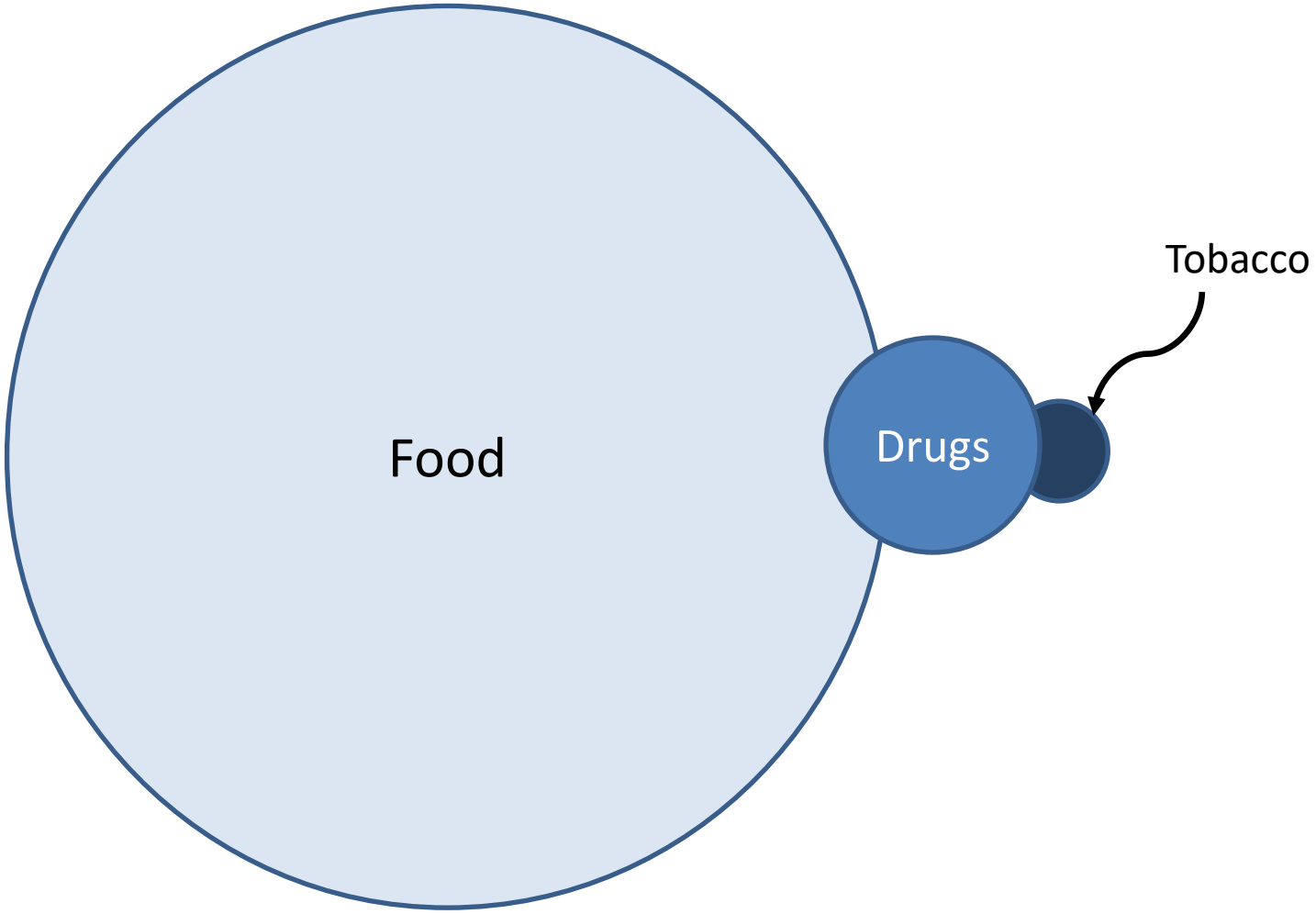
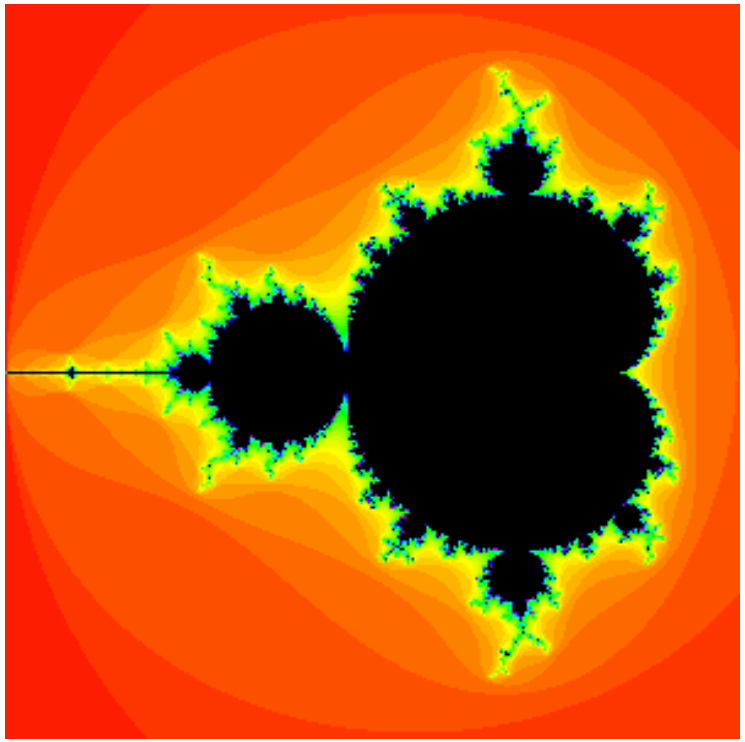
First a Food, Always a Food…

(3)(B) Does not include an *article* approved as a new drug…or investigated as a new drug…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.

FDC Act § 201(ff)(3)(B) or § 402(f)

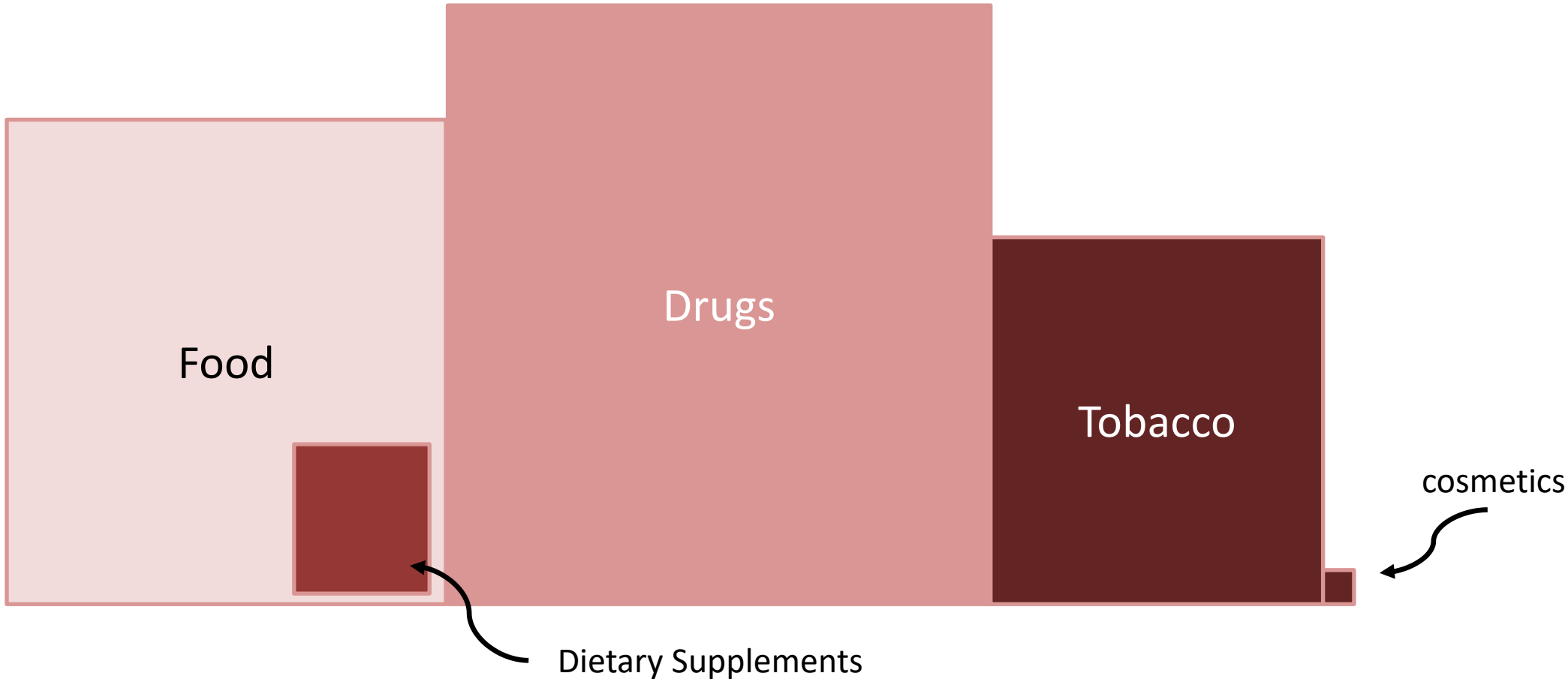
Articles Found in Regulated Products



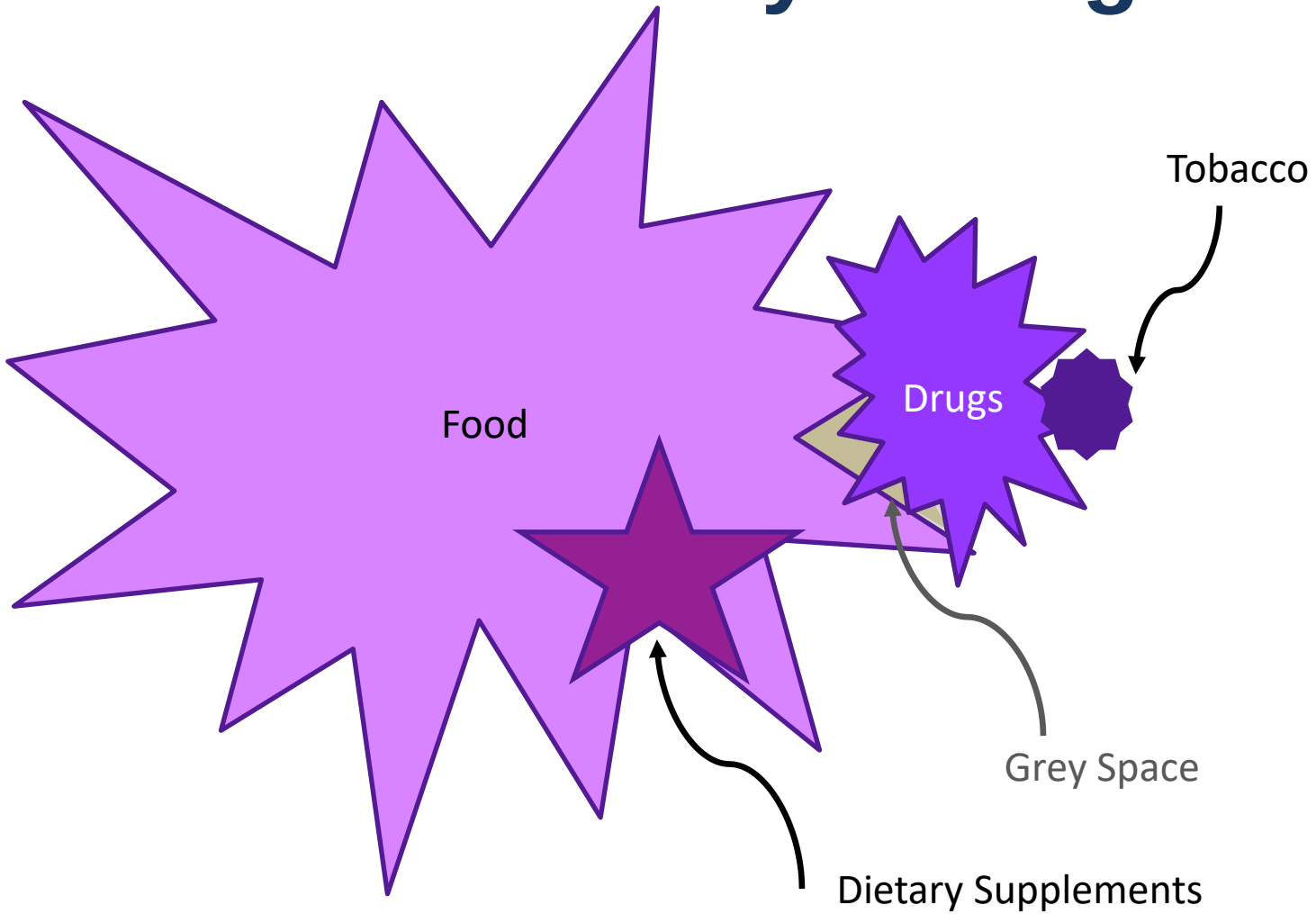


Mandelbrot Set

Classes of FDA Regulated Products



Venn Reality of Regulated Products



Benoit Mandelbrot

Polling Question #1

Will FDA and/or Congress make allowance for cannabidiol (CBD) purified from hemp to be used legally in food and/or dietary supplements?

A. Yes
B. No
C. I cannot answer. I have inside information.

Drug Definition

"Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."

-and-

"articles (other than food) intended to affect the structure or any function of the body of man or other animals"

FD&C Act § 201(g)(1)

Hemp Definition

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

Farm Bill 2018 § 297(A)

Full-Spectrum Extract

Cannabis industry in-use definition:

A range of cannabis extracts begotten by various extraction methods with a defining characteristic the presence of *some* quantity of delta-9 tetrahydrocannabinol (d9-THC).

Full-Spectrum Extract

Botanical industry definition:

An extract comprising the complete range of soluble constituents native to the plant. Full-spectrum extracts require careful design of manufacturing processes to justify use of the term, such as repeated extraction of the same biomass using different solvents ranging from hydrophilic to hydrophobic or polar to non-polar.

AHPA Standardization of Botanical Products – White Paper (2003)

Broad-Spectrum Extract

Cannabis industry in-use definition:

A full spectrum extract that contains less than 0.3 percent (0.3 wt. %) d9-THC *or* possesses undetectable levels of d9-THC.

Broad-Spectrum Extract

Botanical industry definition:

An extract comprising a wide range of the constituents native to the plant. Broad spectrum extracts are made using relatively non-selective solvents and manufacturing processes so that both relatively hydrophilic and relatively hydrophobic types of botanical constituents are captured.

AHPA Standardization of Botanical Products – White Paper (2003)

Isolate

A purified single chemical constituent, such as cannabidiol (CBD), that has been isolated from an herb or other organism.

Distillate

A semi-purified chemical constituent, such as delta-9 tetrahydrocannabinol (d9-THC), that is commingled with other chemical constituents that possess similar boiling points to the semi-purified constituent. Distillates are typically produced by first extracting an herb or other organism followed by distilling the resultant extract.

Polling Question #2

Should FDA seek to officially define industry phrases, such as “full-spectrum,” “broad-spectrum,” “isolate” or “distillate” in relation to hemp?

A. Yes
B. No
C. Maybe, depends on what else happens first.

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Thank you

Dietary Supplement Definition

"(1) Means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: vitamin, mineral,…

-and-

(2) Means a product that is intended for ingestion.

-and-

(3) (B) Does not include an article approved as a new drug…or investigated as a new drug…

FDC Act § 201(ff)

Navigating Drug Preclusion Gaps for Food and Dietary Supplements Containing CBD and Other Cannabinoids

Megan Olsen, Council for Responsible Nutrition

FDLI

What is an “article”?

- A dietary supplement does “not include an ***article*** that is approved as a new drug . . . or 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.” FDCA 201(ff)(3)(B)

How does FDA define “article”?

- *Pharmanex v. Shalala*
  - Challenge to warning letter for red yeast rice supplement containing monacolin k, which FDA determined was chemically identical to lovastatin (active ingredient in a prescription drug)
  - Tenth Circuit held that “article” could refer to the individual active ingredients of approved drugs not just the finished drug product – *Pharmanex v. Shalala,* 221 F.3d 1151(10th Cir. 2000)

Pharmanex v. Shalala

- FDA did recognize that naturally occurring levels of monacolin k (lovastatin) were ok (history of traditional use)
- According to FDA, Cholestin had been engineered specifically to increase lovastatin levels and was marketed to pharmacists based on its similarities to approved drug

Application to CBD

- Range of CBD products, from CBD isolate to full-spectrum hemp extract with CBD
- Is hemp extract with CBD the same article as CBD isolate found in Epidiolex?

Hemp Extract with CBD

- Argument that hemp extract with CBD is not the same “article” as CBD isolate
  - CBD isolate removed from plant constituents
  - Extracts should be considered in entirety
- Preclusion should not apply where a finished extract contains CBD, but the extract bears a similar phytochemical profile as that of the plant

Safety Consequences of Regulatory Gaps

Jensen N. Jose

Center for Science in the Public Interest

FDLI

Consumer Perception/Safety

Many consumers are:

- Interested in CBD products
- Unsure about safety
- Receiving mixed messages

What Consumers See When Shopping

Per Regulatory Requirement, product contains a total delta-9-tetrahydrocannabinol concentration that does not exceed 0.3% on a dry-weight basis.

THE VITAMIN SHOPPE

Search

Live Chat | Sign In/Register | Reorder

Broad Spectrum		Full Spectrum
Non-detectable levels of THC	VS.	Contains trace amounts of THC
Contains a minimum of 2 or more naturally occurring cannabinoids, terpenes, and fatty acids		Includes a range of 80-120 cannabinoids, terpenes, bioflavonoids, flavonoids, & fatty acids

All CBD starts as crude oil directly from the hemp plant. The oil is then refined to remove THC and other unwanted components. The full and broad spectrum classifications refer to the amount of cannabinoids still present in the product after the refining process.

In addition to some THC, full-spectrum CBD products typically also contain plant compounds such as flavonoids and terpenes.

Why take your CBD with a side of these other compounds? Combining CBD, THC, and these other natural compounds creates what's known as the "entourage effect," says Titus. "The synergistic application of all the plant materials works better than just an isolated compound."

Yep, that means that products labeled "full-spectrum CBD" may also contain some THC, the psychoactive ingredient in cannabis associated with the high sensation marijuana causes. Don't worry, though, FDA regulations require that CBD and other hemp products contain less than 0.3 percent THC, which will not get you high.

What Consumers See at FDA

What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD

• • •

- It is currently illegal to market CBD by adding it to a food or labeling it as a dietary supplement.

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

• • •

2. How does the 2018 Farm Bill define hemp? What does it mean for FDA-regulated products?

A. At the federal level, the Agriculture Improvement Act of 2018, Pub. L. 115-334, (the 2018 Farm Bill) was signed into law on Dec. 20, 2018. Among other things, this new law changes certain federal authorities relating to the production and marketing of hemp, defined as "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." These changes include removing hemp from the CSA, which means that cannabis plants and derivatives that contain no more than 0.3 percent THC on a dry weight basis are no longer controlled substances under federal law.

• • •

9. Can THC or CBD products be sold as dietary supplements?

A. No. Based on available evidence, FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act [21 U.S.C. §

FDA Responds to Three GRAS Notices for Hemp Seed-Derived Ingredients for Use in Human Food

• • •

Foods containing hemp seed and hemp seed-derived ingredients are currently marketed in the US. Hemp seeds are the seeds of the hemp plant, *Cannabis sativa*. Although hemp is from the same species as cannabis (marijuana), the seeds themselves do not naturally contain tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis. The hemp seed-derived ingredients that are the subject of these GRAS notices contain only trace amounts of THC and CBD, which the seeds may pick up during harvesting and processing when they are in contact with other parts of the plant. Consumption of these hemp seed-derived ingredients is not capable of making consumers "high".

Supplement Market is the "Wild West"

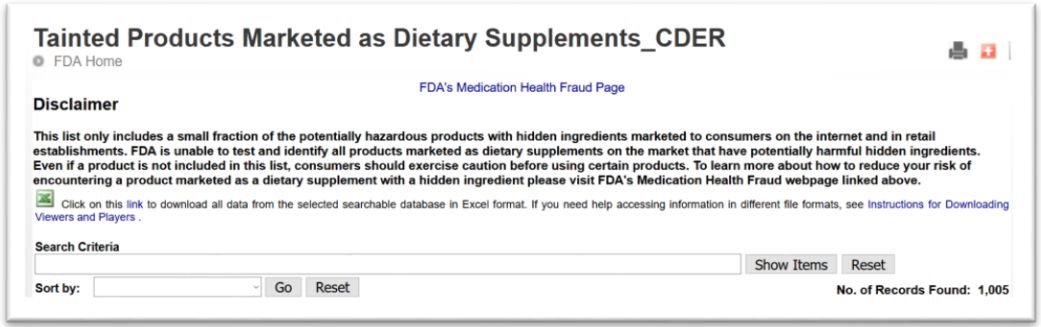
- Adulterated/Misbranded supplements
- Disease/Treatment and unsubstantiated Claims

Dietary supplements already cause an estimated 23,000 emergency room visits per year.

Adverse-event reports submitted to the FDA describe 2,100 incidents over a period of a year caused by supplements involving serious outcomes.

Adulteration/Misbranded Supplements

- FDA's database contains 1,005 records of tainted supplements
  - Only "a small fraction of the potentially hazardous products"
- FDA is unable to test and identify all products and urges consumers to exercise caution
- FDA has identified emerging trends in tainted weight loss, body building, and sexual enhancement supplements



Tainted Products Marketed as Dietary Supplements_CDER

FDA Home

FDA's Medication Health Fraud Page

Disclaimer

This list only includes a small fraction of the potentially hazardous products with hidden ingredients marketed to consumers on the internet and in retail establishments. FDA is unable to test and identify all products marketed as dietary supplements on the market that have potentially harmful hidden ingredients. Even if a product is not included in this list, consumers should exercise caution before using certain products. To learn more about how to reduce your risk of encountering a product marketed as a dietary supplement with a hidden ingredient please visit FDA's Medication Health Fraud webpage linked above.

Click on this link to download all data from the selected searchable database in Excel format. If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players .

Search Criteria

Show Items Reset

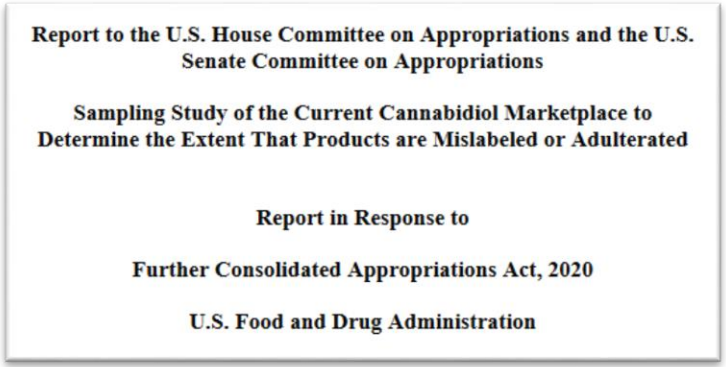
Sort by: Go Reset

No. of Records Found: 1,005

https://www.fda.gov/media/109066/download

Adulteration/Misbranded – CBD

- Of the CBD products the FDA tested, 49% contained some THC, 18% of products contained significantly less than the amount indicated, and 37% contained significantly more than indicated.
- Ingredients that are not listed on product labels, including synthetic cannabinoids and dangerous contaminants, have been identified in cannabis products in other studies.



Report to the U.S. House Committee on Appropriations and the U.S. Senate Committee on Appropriations

Sampling Study of the Current Cannabidiol Marketplace to Determine the Extent That Products are Mislabeled or Adulterated

Report in Response to

Further Consolidated Appropriations Act, 2020

U.S. Food and Drug Administration

Forensic Sci Int. 2019 Jan;294:e25-e27. doi: 10.1016/j.forsciint.2018.10.019. Epub 2018 Nov 1.

The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids

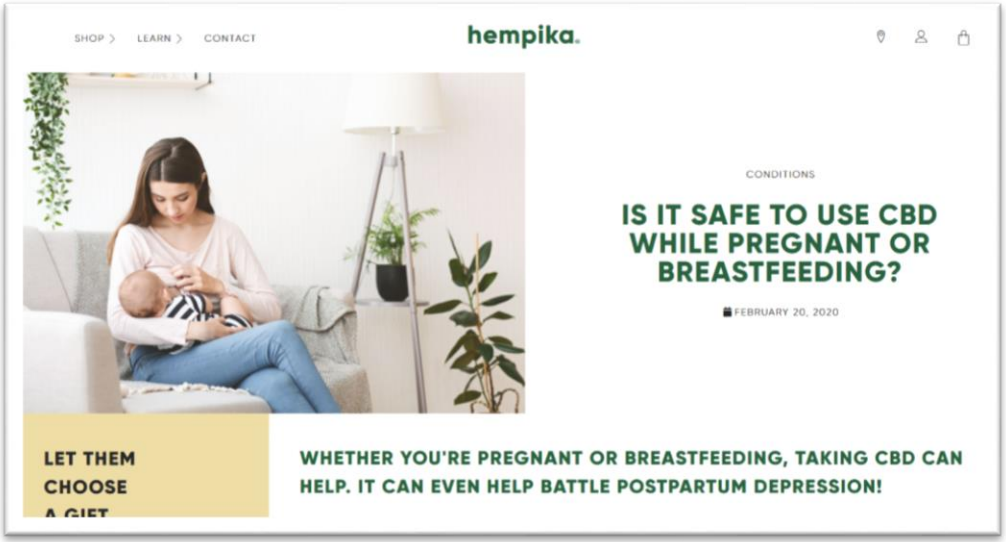
Justin L Poklis [1], Haley A Mulder [2], Michelle R Peace [2]

Affiliations + expand

PMID: 30442388 PMCID: PMC6321772 DOI: 10.1016/j.forsciint.2018.10.019

Disease/Treatment claims

- Maternal Health



"CBD can help mitigate anxiety, postpartum depression, morning sickness, **insomnia**, and **chronic pain**, all of which are potential side effects of being pregnant or of recently giving birth."

Disease/Treatment claims

- Opioid and addiction treatment

Crackdown Urged on Supplements Marketed as Opioid Withdrawal Aids

CSPI Investigation Shows Manufacturers Can't Support Claims

December 8, 2017

FDA NEWS RELEASE

FDA Warns Companies Illegally Selling CBD Products to Treat Medical Conditions, Opioid Addiction

Disease/Treatment Claimns

- Examples of FDA CBD warning letters:
  - COVID-19 (CBD Gaze)
  - Seizures and neurodegenerative diseases (Bella Rose Labs)
  - Breast cancer (KOI CBD LLC)
  - Diabetes (KOI CBD LLC)
  - Pain Relief (KOI CBD LLC)
  - Arthritis (Whole Leaf Organics, LLC)

FDA Principal Associate Commissioner for Policy

- “We don’t know how many dietary supplements are on the market, and we have no systematic way of knowing when a new product is introduced.”
- “We don’t know how many products contain any given ingredient. And if it turns out that there’s a safety problem with a particular ingredient, or a particular ingredient supplier, we don’t have the basic information to quickly identify which products are affected.”
- “We don’t have a reliable way to capture trends in the market so we can anticipate and adapt to new areas of risk.”
- “And we don’t have the visibility we need to be able to effectively prioritize our resources.”
  - Lowell Schiller (Council for Responsible Nutrition Conference - 11/7/2019)

Gaps

- Lack of **premarket review**
  - GRAS loophole
- Lack of **knowledge**
  - No Product registration/listing
- Lack of **oversight** resources
  - Can’t sufficiently monitor for bad actors
- Lack of **enforcement** authorities and resources
  - Rebranding and Reformulating to avoid enforcement
  - Recalls are difficult and no authority of drugs and “non”-dietary supplements
- Lack of **Understanding**

CBD-Specific Actions

- **Guidance**: Publish and finalize strong guidance on temporary enforcement discretion focused on mitigating hazards and protecting vulnerable populations.
- **Publish a comprehensive plan** covering food, supplements, drugs and cosmetics.
- **Funding:** Congress should provide the FDA with **$5 million** to develop regulatory activities, and issue an interim policy enforcement discretion while developing a notification system for hemp-derived ingredients.
  - As described in the *Explanatory Statement for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2021*,

Fixing the Overall Supplement Marketplace

- Strengthen FDA leadership
- Close the GRAS loophole
- Premarket review of dangerous products
- Mandatory product listing and registration
- Adverse Events Reporting
- Require drug-drug interaction warnings
- Improve the safety and quality of prenatal supplements
- Allocate additional resources
- Strengthen enforcement
- Authorize shared enforcement
- Authorize Criminal penalties
- Provide recall authority
- Accurately define dietary supplements

Thank You

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