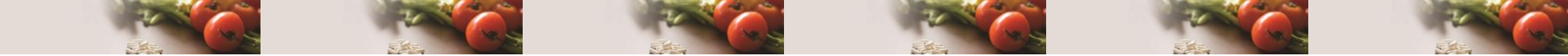


Current FDA Regulation of Hemp/CBD in Foods and Dietary Supplements

Holly J. Bayne
Founder & Principal
Law Office of Bayne & Associates
March 31, 2022

FDLI

FDA's Current Enforcement Policy

"Under current law, it's unlawful to sell a food or dietary supplement with CBD in interstate commerce."

Speech by Lowell Schiller, JD, FDA Principal Associate Commissioner for Policy, Office of Policy, National Industrial Hemp Council 2019 Hemp Business Summit

SUNSOIL
FLOR DE MARÍA
FINE CHOCOLATE
EXHALE
FULL SPECTRUM CBD OIL
goldbee
CBD Softgels
five
ORIGINAL MILK CHOCOLATE
JUST CBD
UNOIA
CBD VEGAN GUMMIES
R+R MEDICINALS
CBD WELLNESS GUMMIES
MEDTERRA
LIPOSOMAL HEMP+
good night
CHARLOTTE'S WEB
MEDTERRA
CBD GUMMIES SLEEP TIGHT
aprch
CBD Sparkling Water
Vthrive
CBD+ SLEEP BLEND
Garden of Life
Dr. Formulated
CBD 50mg
WHOLE HEMP EXTRACT
HOLMES ORGANICS
saha
JOY ORGANICS
CBD OIL
CBD
GUMMIES WILD BERRY
TOMMY CHONG'S HEMP
Smokiez
JAMBERRY CBD GUMMIEZ
pure encapsulations
Hemp CBD VESIsorb

FDA Rationale: CBD is a “Drug”

- In 2018, FDA approved Epidiolex® *cannabidiol oral solution, a purified drug substance,* under § 505 of FDC Act for childhood seizures (Greenwich Biosciences, Inc.)
  - Active ingredient, CBD, naturally occurs in *Cannabis sativa*
  - *Cannabidiol oral solution* is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100mg/mL

Dietary Supplement Exclusionary Clause

- Under § 201(ff)(3)(B)(i),(ii),"dietary supplement" definition does not include an "article":
  - (i) approved by FDA as a new drug under § 505; or
  - (ii) authorized for drug investigation under an IND for which substantial clinical investigations have been instituted and made public,

    unless first marketed as dietary supplement or food.

Prohibition Against Adding "Drugs" to Food

Under § 301(ll) of FDC Act, it is prohibited act to introduce into interstate commerce any "food" to which has been added a "drug" approved under § 505 or "drug" for which substantial clinical investigations have been instituted and made public unless such "drug" was first marketed as food.

FDA Rulemaking Discretion

- Under both §§ 201(ff)(B)(3)(i),(ii) and 301(ll) of FDC Act, FDA has discretion to issue regulations via notice and comment rulemaking finding such “article” or “food” to be lawful
- No rulemaking to date and no indication FDA intends to initiate such rulemaking

“Full Spectrum Hemp Extract” Excluded

- Charlotte’s Web, Inc. filed NDIN (May 2021) for “Full Spectrum Hemp Extract” (CW FSHE); 9.75 mg CBD per 0.15 mL; 2x per day = 19.5 mg CBD per day
- FDA Response:
  - CW FSHE is a “CBD product” excluded from dietary supplement definition; “carefully designed for consistent CBD levels”; raw material provides “robust” CBD levels
  - Notification failed to show NDI will reasonably be expected to be safe under § 413(a)(2); adulterated under § 402(f)(1)(B)

“Hemp Oil” NDIN Rejected by FDA

- Enzolytics, Inc. filed NDIN (Nov. 2019)
  - Hemp oil from *Cannabis Sativa L.: “purified proteins and fatty acid molecules”; also, “hemp oil”; “hemp seed oil”*
- FDA Response:
  - Failed to demonstrate “hemp oil” does not contain CBD; per earlier filing 25.5% CBD
  - CBD product excluded from DS definition
  - No comment on whether adequate basis of safety

FDA's CBD Safety Concerns

- CBD has potential to cause:
  - liver injury
  - male reproductive toxicity, or damage to fertility in males or male offspring of women who have been exposed (animal data)
  - drug interactions
  - unknown effects from cumulative exposure

CBD is Unapproved Food Additive

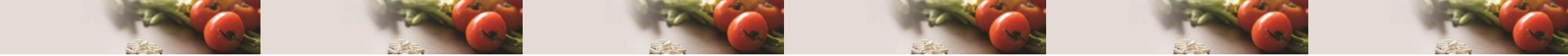
- Independent of “drug” status, FDA views CBD as unapproved food additive
- Existing data do not support GRAS status of CBD or hemp extract containing CBD
- Permitted as GRAS human food ingredients under specified conditions of use: *hulled hemp seed*, *hemp seed protein powder* and *hemp seed oil*

FDA/FTC Warning Letters

- Nov. 2019: 15 CBD Warning Letters (CDER)
  - Infant teething pain/earaches, autism, ADHD, Parkinson's, Alzheimer's and other disease claims
- Dec. 2020: 5 CBD Warning Letters
  - COVID and related disease claims
  - Cited claims for CBDA (cannabidiolic acid) and CBG (cannabigerol) and anti-inflammatory effects
- March 2021: 4 CBD Warning Letters (2 for OTC drugs)
- March 2022: 3 CBD Warning Letters

FDA View of Delta-8 THC?

- FDA received104 AERs between 12/1/2020 and 2/28/2022
- Poison Control Centers rec'd 2,362 exposure cases between 1/1/21 and 2/28/22 (41% involved patients less than 18 years of age)



Current FDA Regulation of Hemp/CBD in Foods and Dietary Supplements

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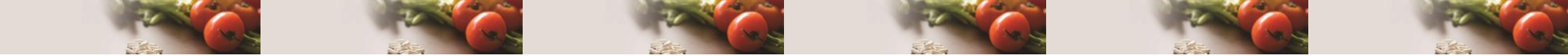

State Law Compliance Challenges

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March 31, 2022

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The “Patchwork” of State Law

- Federal inaction + State action = Patchwork of requirements
- Current challenge: 50-state compliance
- Heterogeneity and changing State requirements demands constant vigilance

Navigating the Patchwork: Considerations

1. What type of product is it?
2. Is the product legal to produce, distribute, or sell in the jurisdiction?
3. What requirements are applicable (e.g., sourcing, testing, labeling)?
4. Does compliance give rise to conflict?

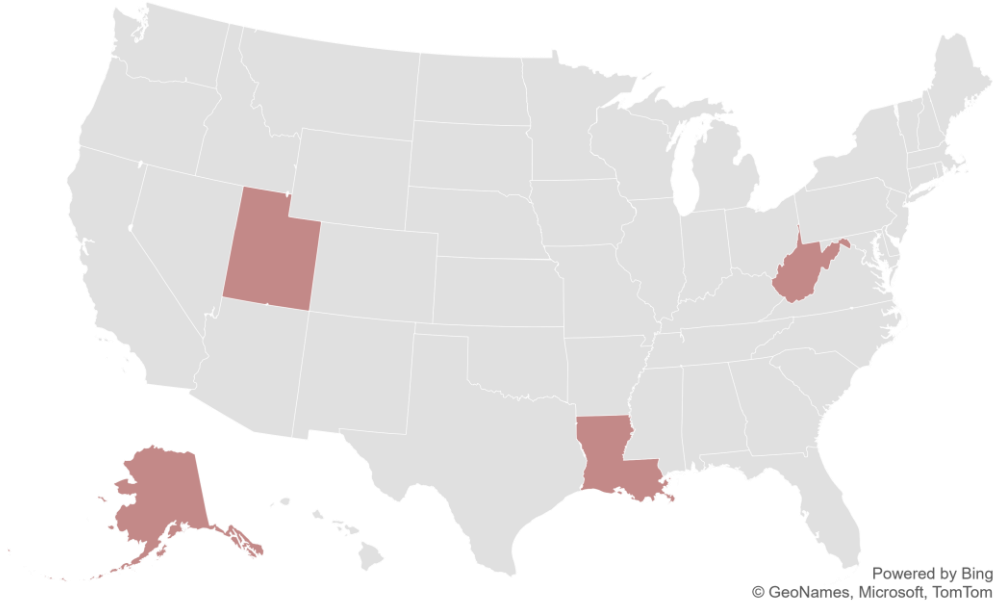
Marketability Issues

- Conventional Foods
  - **UT**: “Cannabinoid product” may not be added to conventional food product
  - **CA**: Only permissible if manufactured in-state (guidance)
  - **HI**: Only GRAS hemp ingredients permitted in foods
  - **Numerous States**: Cite to FDA position

- Dietary supplements
  - **LA**: “Consumable hemp product” may not be marketed as “dietary.”

Marketability Issues (II)

- Premarket Submission Required



Marketability Issues (III)

- Delta-8 THC
  - **ND**: Licensees may not "sell hemp or hemp products…created using the isomerization of cannabinoids to create isomers of [THC], including delta-8, delta-9, and delta-10."
  - **NY**: "Cannabinoid hemp products" may not contain "synthetic cannabinoids, or cannabinoids created through isomerization, including Δ8-tetrahydrocannabinol and Δ10-tetrahydrocannabinol."
  - *But see* **Louisiana**

Formulation Issues

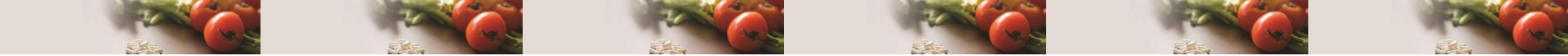
- THC Calculation
  - **KS**
  - **IN**
- Product Limitations
  - **OR**
  - **NY**
  - **AK**
  - **ID**

OAR 845-026-0400
Table 3

INDUSTRIAL HEMP PRODUCT THC CONCENTRATION AND SERVING SIZE LIMITS			
Type of Industrial Hemp Product	Maximum Amount of Total Delta-9-THC Per Serving	Maximum Amount of Total Delta-9-THC per Container	Maximum Concentration of Total Delta-9-THC
Hemp Edibles	2 mg	20 mg	0.3%
Hemp Topicals	N/A	N/A	0.3%
Hemp Transdermal Patches	2 mg	20 mg	0.3%
Hemp Tinctures	N/A	100 mg	0.3%
Usable Hemp	N/A	N/A	0.3%
Industrial Hemp Concentrates or Extracts	N/A	N/A	0.3%
Cannabinoid Hemp Products Other than Hemp Edibles, Topicals, Tinctures, or Transdermal Patches	2 mg	20 mg	0.3%

Labeling Issues

- Is a single label possible?
  - **UT**: Review/approval of product labels
  - **AK**: THC-content warnings
  - **IA**: Must be plainly IDed as “consumable hemp product”
  - **NY**: NF/SF Panel, no imitation candy labels or cartoons
  - Differing QR code, bar code, web address requirements
  - Required disclaimer language



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Food & Dietary Supplement Safety

CBD as a Dietary Supplement

Safety Reporting

March 2022

FDLI

Obligation to Manage Adverse Events
Dietary Supplements & OTC Drugs

- **Drug Consumer Protection Act (2006) – Public Law 109-462**

- Adverse events meeting the FDA defined criteria for **serious** must be reported within 15 days to the FDA.
- Although mandatory reporting is limited to serious adverse events, the manufacturer is obligated to document and assess **every** allegation of an adverse event associated with a dietary supplement to determine whether or not it meets the “serious” criteria.
- All records related to any adverse event report must be kept for no less than six years.
- Exemptions to the rules for small companies have expired.

FDA Concerns About Prescription Product Safety

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- *To assess a known serious risk related to the use of the drug*
- *To assess signals of serious risk related to the use of the drug*
- *To identify an unexpected serious risk when available data indicates the potential for a serious risk*

Rx Safety vs NDI / GRAS

Extract from FDA Response to IND (DS –> Rx)

It is important that you understand that neither a finding that a substance is GRAS for one or more food uses nor the filing of an NDI notification for the use of a substance as a dietary ingredient in a dietary supplement can be relied upon for a determination of safety for the use of that substance as an active ingredient in a drug product. In addition, summaries of proprietary studies that exist as part of opinions or notifications issued by regulatory agencies, such as FDA (e.g., summary basis of approval or GRAS designations) cannot be relied upon because summaries do not constitute full reports of investigations under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (see also 21 CR 314.430(e)(2)). However, the Sponsor may obtain a right of reference to these studies or rely on the study findings if they have been published in scientific literature.

It’s not that Easy to See Trends

- Product line may contain many SKU’s
- Reports from consumers are voluntary;
  consumer products have no mandatory oversight
- Consumers may not recognize an “unintended effect”
- Data generated will containing numerous “lay” terms
- Company focus on regulatory compliance versus product characterization

Example – Spontaneous AE Log

Case number	Case created date	Date first received	Case type	Information type
2018-US-007282	2018-05-01 7:56	2018-05-01 12:00	Spontaneous AE	Confirmed AE
2018-US-007338	2018-05-02 6:21	2018-05-02 12:00	Spontaneous AE	Confirmed AE
2018-US-007400	2018-05-02 11:13	2018-05-02 12:00	Spontaneous AE	Confirmed AE
2018-US-007413	2018-05-02 12:05	2018-05-02 12:00	Spontaneous AE	Confirmed AE
2018-US-007488	2018-05-03 9:44	2018-05-03 12:00	Spontaneous AE	Confirmed AE

- Extract from third party log
- File has **29 columns** and **1223 rows of data**

Example – Spontaneous AE Log

Verbatim (all)	Verbatim (most important)	Reportability (case)	Problem type	Product type	Serious	Expected
Unevaluable event	Unevaluable event	Non-reportable	Adverse event	Dietary Supplement	No	No
Application site itching; Application site rash	Application site rash	Non-reportable	Adverse event	Monograph Pharmaceutical	No	No
Condition aggravated	Condition aggravated	Non-reportable	Adverse event	Dietary Supplement	No	No
Stomach cramps; Diarrhea	Stomach cramps	Non-reportable	Adverse event	Dietary Supplement	No	No

- Lots of duplicate data to sort through
- Expectedness column is always “No”
- **Is there a hidden message?**

Seeing the Trends - *Importance of Coding*

- **1223** reported adverse events coded MedDRA System Organ Class
- *List distilled to 768 unique case with GI Disorders* emerging as most common *374 (48.7%)*

MedDRA SOC	Number of Reports
GI Disorders	355
GI Disorders Or Immune System Disorders	1
GI Disorders Or Immune System Disorders Or Skin And Subcutaneous Tissue Disorders	2
GI Disorders Or Infections And Infestations	1
GI Disorders Or Nervous System Disorders	4
GI Disorders Or Psychiatric Disorders	1
GI Disorders Or Respiratory, Thoracic And Mediastinal Disorders	8
GI Disorders Or Vascular Disorders	2
Grand Total	374

FDA Concerns About Product Safety

	Placebo (n=227)	EPIDIOLEX 10 mg/kg/day (n=75)	EPIDIOLEX 20 mg/kg/day (n=238)
Hepatic Disorders			
Transaminases elevated	3	8	16
Gastrointestinal Disorders			
Decreased appetite	5	16	22
Diarrhea	9	9	20
Nervous System Disorders			
Somnolence	8	23	25
Fatigue, malaise, asthenia	4	11	12
Insomnia, sleep disorder, poor-quality sleep	4	11	5
Infections			
Infection, all	31	41	40
Rash	3	7	13

FDA Concerns About Product Safety

COMBINED INCIDENCE OF SOMNOLENCE AND SEDATION (INCLUDING LETHARGY)

		LGS & Dravet syndrome clinical trials	TSC clinical trial
OVERALL	**PLACEBO** overall	11%	17%
	EPIDIOLEX overall	32%	19%
BY DOSE	**EPIDIOLEX** 10 mg/kg/day	27%	
	EPIDIOLEX 20 mg/kg/day	34%	
	EPIDIOLEX 25 mg/kg/day		19%
USE OF CLOBAZAM	**EPIDIOLEX** without clobazam	16%	14%
	EPIDIOLEX with concomitant clobazam	46%	33%

CPG’s containing CBD

- Will the FDA safety profile of IND / NDA products impact CPG products?
- Are current safety gathering and reporting tools ”good enough” to meet FDA expectations?
- Impact of current RWE / DCT safety data?

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