Current and Future Regulatory Framework of CBD and Hemp Products

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The Controlled Substances Act and the Farm Bill of 2014: CBD Status

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Defining Marijuana

Marijuana (Marihuana) was defined under the Controlled Substances Act as:

"... all parts of the plant *Cannabis sativa L.*, whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination."

21 U.S.C. § 802(16).

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CBD and the Controlled Substances Act

- CBD products derived from the non-psychoactive, non-resin, mature stalks, fibers, or seeds of the *Cannabis sativa* plant do not meet the definition of "marihuana" under the CSA and are not subject to Schedule I controls.

- "[t]he mere presence of cannabinoids is not itself dispositive as to whether a substance is within the scope of the CSA; the dispositive question is whether the substance falls within the CSA definition of marijuana." DEA Internal Directive (May 2018).

- DEA has also stated: "based on the scientific literature, it is not practical to produce extracts that contain more than trace amounts of cannabinoids using only the parts of the cannabis plant that are excluded from the CSA definition of marijuana, such as oil from the seeds." DEA Clarification of the New Drug Code (7350) for Marijuana Extract.

  - Currently, DEA appears to be exercising enforcement discretion.

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2014 Farm Bill

Defined “Industrial Hemp” as:

- “...the plant *Cannabis sativa L.* and any part of such plant, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of **not more than 0.3 percent** on a dry weight basis.” 7 U.S.C. § 5940 (emphasis added).

Limitations: Allowed “Industrial Hemp” to be grown or cultivated if:

1. Done for purposes of research conducted under an agricultural pilot program or academic research; and
2. Permitted by state law.
3. There is no provision to permit the interstate sale of Industrial Hemp across state lines or to commercially produce industrial hemp products.

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2018 Farm Bill - Enacted Dec. 20, 2018

- Plans imposed by the state or by Dept. of Agriculture to regulate "hemp production"
- "Hemp" defined as:
  - *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.
- Repeal of "industrial hemp research" provision at 7 U.S.C. § 5940 one year after Dept. of Ag. Regulatory scheme is established
- Conforming Amendments to the CSA to exclude "hemp" from definition of "marihuana" in section 802(16) of the CSA

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2018 Farm Bill: Main Takeaways (cont.)

- Producers (which could include manufacturers) of hemp (including extracts) will require a license from the state or from the federal government.
  - Please note the definition of hemp includes extracts and the words "***growing or not,***" which is a clear indication that an ingredient supplier cannot ship an extract that is 0.3% or greater of hemp.
    - The term "producer" is used in the Act rather than the term "grown."
- At no time can a hemp extract have a THC content of more than 0.3%.
  - This is the plain language of the Act.
  - The Secretary by regulation and based on the legislative history may decide otherwise and limit to cultivation but it is difficult to see how that can be achieved.
- The restriction on THC content is not simply limited to any plant that is cultivated but any extracts derived therefrom
  - This means that the extraction process must limit the THC content in the finished extract before it is even shipped to the finished product manufacturer for further processing.
  - Processes will need to be in place to ensure the proper disposal of THC in the extract if the THC itself cannot be destroyed by the extraction process.
  - Potential significant issue unless addressed in the regulation by permitting the shipment of low concentrates of extracts as long as the finished product meets the 0.3% requirement.

2018 Farm Bill: Main Takeaways (cont.)

- It will take time for the government to issue regulations and issue licenses.
- We may be in a situation where the USDA and the states will exercise enforcement discretion while the regulations and licensing framework are put in place. USDA intends to issue its first regulations in "fall 2020."
- More stringent state laws prohibiting Industrial Hemp will **NOT** be preempted.
- During the interim period, it will be important to ensure that all extracts and hemp-related products conform to the exemption under the Farm Bill of 2014.
- The Farm Bill of 2018 does not solve the issue with FDA, as it unambiguously gives the FDA authority over hemp products.

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2018 Farm Bill: Transportation Complications

- Idaho state police seized nearly 13,000 pounds of hemp that was produced in Oregon and was en route to Colorado.
- Oregon has an existing industrial hemp program allowing the cultivation of industrial hemp consistent with the 2014 Farm Bill, i.e., "for research purposes." Hemp is considered a controlled substance under Idaho law.
- 2018 Farm Bill provision: Transportation of Hemp and Hemp Products
  - No state or Indian Tribe ***shall prohibit*** the transportation or shipment of hemp or hemp products ***produced in accordance with subtitle G*** of the Agricultural Marketing Act of 1946 (as added by section 10113) through the State or the territory of the Indian Tribe, as applicable.
- Hemp company argued that the transportation of hemp across state lines was protected under the 2018 Farm Bill.
- There are no federally approved state programs that the seized hemp could have been produced "in accordance with." The judge sided with the state and denied Big Sky's motion for a temporary restraining order.

(Big Sky Scientific LLC v. Idaho State Police)

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State Actions

- **Arizona Board of Pharmacy**: On December 5, 2018, the Arizona State Board of Pharmacy agreed to remove a provision that required dietary supplement producers to be registered with the state under the state's drug provisions. Arizona agreed with trade organizations that FDA has broad authority over dietary supplements and that the state will not interfere with rules that contradict that authority.

- **Texas Department of Health:** Halted plans to issue a guidance restricting the sale of CBD-infused food in the state. Texas currently restricts the distribution of CBD to "low-THC cannabis" by patients with intractable epilepsy when prescribed by a registered physician.

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CBD and FDA Enforcement

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FDA Actions

Warning Letters: Key Agency Conclusion –

FDA has concluded based on available evidence that CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(ii) of the FD&C Act. Under that provision, if an article (such as CBD) 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. 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.

– *Warning Letter to Signature Formulations, LLC (July 31, 2018)*

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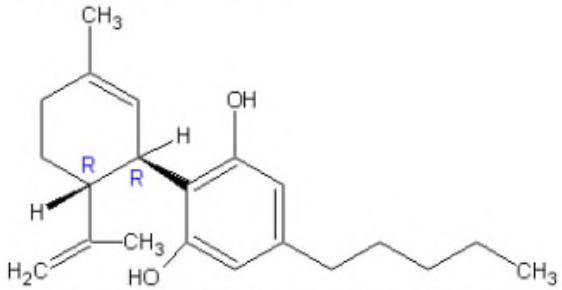
FDA Actions

- Guidance Document: FDA and Marijuana: Questions and Answers
  - "Can products that contain THC or cannabidiol (CBD) be sold as dietary supplements?"
  - FDA Response: "No." (Citing drug exclusion)
- FDA Drug Approval: Epidiolex
- June 25, 2018: FDA approved the first CBD-derived drug, Epidiolex, for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.
- FDA Commissioner Gottlieb emphasized the importance of the drug approval process for "other product developers who want to bring forth marijuana-derived products through appropriate drug development programs." See Press Announcement.

Epidiolex Drug Molecular Structure

Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The chemical structure is:



Cannabidiol, the active ingredient in EPIDIOLEX, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant.

Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents.

EPIDIOLEX (cannabidiol) oral solution is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL. Inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. EPIDIOLEX contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

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Food, Drug, and Cosmetic Act (FD&C Act) – Drug Exclusion

- Section 201(ff) of FD&C Act (21 U.S.C. § 321 (ff)(3)(B): Definition of Dietary Supplement) does not include "an article":
  - Approved as a new drug, antibiotic, or licensed biologic; or
  - Authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public; and
  - which *was not* before such approval or investigation….marketed as a dietary supplement or as a food…."
- Therefore, even if an article was clinically investigated, if it was marketed as a food or a dietary supplement prior to those investigations, it still meets the definition of a dietary supplement.

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FD&C Act – Drug Exclusion (Cont.)

- Section 301(ll) of FD&C Act (21 U.S.C. § 321 (ll)(3)(B)) precludes a "drug" from being added to "food."
  - Does not use the term "article" but "drug."
    - Arguably, the word *drug* is broader than the word *article* and could potentially exclude a non-standardized hemp extract because it contains a naturally occurring drug constituent.
  - Excludes an FDA-approved new drug, antibiotic, or biological if it was marketed in food prior to the commencement of substantial clinical investigations.
  - The FDA at its discretion can approve its use in food, but it is unclear whether § 301(ll) applies to dietary supplements.
  - Thus, a pathway may exist for food that does not exist for dietary supplements, depending on how courts interprets § 301.

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FD&C Act – Drug Exclusion (Cont.)

- Neither § 201(ff) nor § 301(ll) applies to cosmetic products.
  - Cosmetic product may be marketed with CBD as long as -no medicinal or structure/function claims are made for the product.
  - If combined with a permitted OTC-monographed topical drug ingredient, no medicinal claims or structure/function claims can be made for CBD or any other part of the hemp plant.

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FD&C Act – Drug Exclusion (Cont.)

- CBD is one of many different cannabinoids present in the cannabis plant. CBD oils or extracts are often purified to isolate CBD from other naturally occurring cannabinoids and plant content.
- Drug exclusion applied to the same "active moiety." 21 C.F.R. § 316.3(b)(2).
- Distinguishable active moiety → drug exclusion does not apply
  - Non-standardized full-spectrum hemp extracts with only the THC, fiber, and water removed are in the best position.
  - Standardized extracts pose issues that FDA will be forced to address at some point.
    - At this time, the more heavily standardized the extract, the more likely FDA will consider the active moiety to be CBD.

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FD&C Act – Drug Exclusion (Cont.)

- Upon the signing of the Farm Bill of 2018, FDA reiterated its position that CBD is not currently-permitted in food or dietary supplements.
- Statements of the Commissioner indicate that FDA may be willing to consider the presence of CBD in food or dietary ingredients.
  - Unclear what FDA would be considering:
    - FDA may decide to permit non-standardized extracts of CBD, which would be consistent with our prior discussions with FDA.
    - FDA may permit a significantly lower level of CBD than what is approved for use as a drug.
    - FDA may conclude that it is not safe.
    - FDA would only consider the addition of cannabis that has a concentration of less than 0.3%.
    - FDA made it clear that the FD&C Act would permit FDA to authorize an ingredient for use in food and dietary supplements even if it is approved for use in food.
      - Likely will require a Citizen Petition process.
      - Company seeking authorization will be required to prove safety.

FDA Actions: Public Hearing

- **April 2, 2019**: Commissioner Gottlieb announced FDA's new steps to advance the agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products. In doing so, he announced the development of an FDA working group on CBD, which intends to start sharing information/findings "as early as Summer 2019."
- **May 31, 2019**: FDA will hold a public hearing on CBD. Requests to make oral presentations or to submit comments are due by ***May 10, 2019***. The hearing and request for comments focus on three primary areas:
  - Health and safety risks
  - Manufacturing and product quality
  - Marketing/labeling/sales

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Hemp and CBD Products: Key Differences and Considerations

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Other Types of Hemp-Based Products

- Hemp Seed Oil
- Hemp Protein Products
- Hemp Plant Extracts (non-resin, non-standardized extracts or oils of the mature hemp stalk (i.e., not standardized for CBD content))

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Key Differences from CBD

- Maintains natural constituent ratios (i.e., content of CBD is not isolated and concentrated above natural ratios to other cannabinoids).
- CBD, other cannabinoids, and hemp plant components in the end product are naturally occurring.
- Non-standardized hemp has been historically available in the food supply in the form of butters and oils, and as a source of protein.

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Potential Regulatory Issues Implicated by Key Differences

- Clinical investigations of CBD investigational drugs do not apply to non-standardized hemp extracts and oils, because of material differences in product make-up.
- History of marketing of non-standardized hemp products in food/supplements pre-dates clinical investigations. Therefore, based on the legal standard in Section 201(ff), non-standardized hemp extract products can still be marketed as supplements, even if there are applicable clinical investigations.
- Even if these hemp products were considered new dietary ingredients, they would be exempt from notification requirements, because of the history of use in the food supply.

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FDA Risk Factors: Key Considerations

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FDA Risk Factors

1. **Claims**

   Warning letters to CBD manufacturers have included egregious disease claims, e.g., "anti-tumor," causes "cancer cells to commit suicide," "arthritis relief."

2. **Dosage Form**

   Dietary supplements cannot be marketed as conventional food and must be ingested. Cosmetics are topically applied with limited claims (no structure/function claims).

3. **Manufacturing Operations**

   Comply with CGMPs.

4. **Consider Applicable State Laws**

5. **Imported Products**

   Carry a higher risk of detection.

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The Category Review: CBD

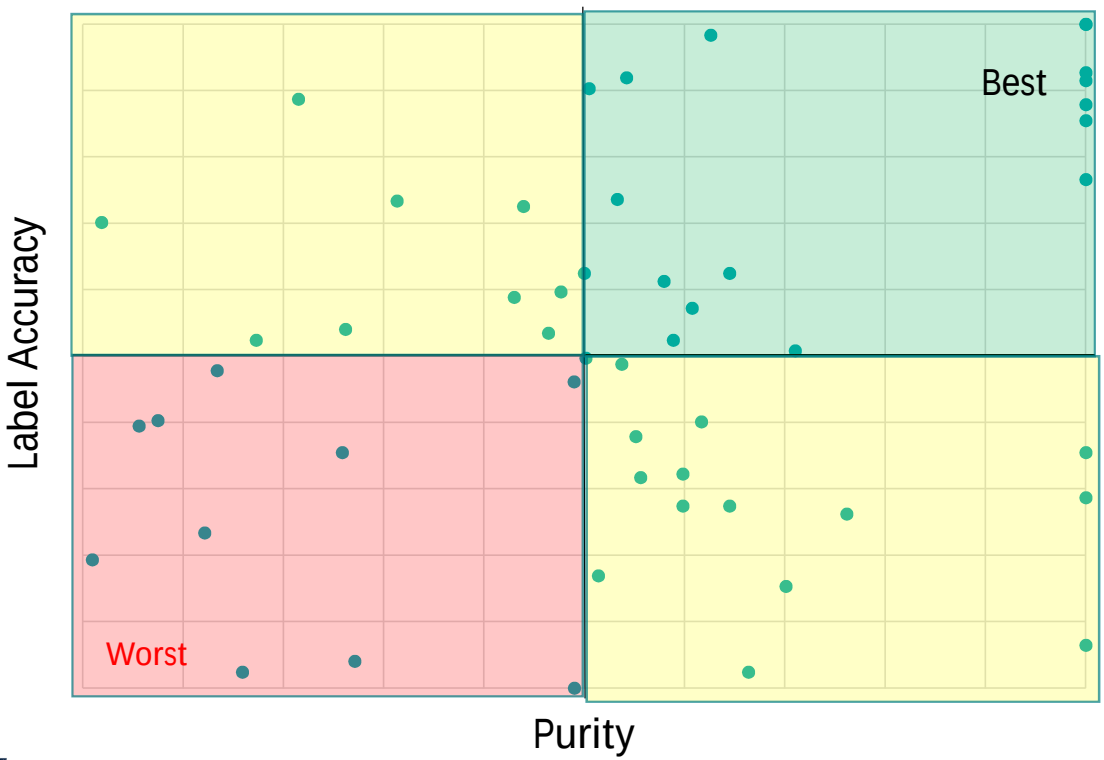
Ellipse has tested over 200 CBD products for over 300 contaminants and toxins

Test	Concern	EA's LOQ	% Detected	90th percentile
Arsenic	Cancer	4ppb	31%	52ppb
Cadmium	Cancer	4ppb	17%	18ppb
Mercury	Brain Dmg	4ppb	24%	4ppb
Lead	Brain Dmg	4ppb	48%	61ppb
Pesticides	Cancer	10ppb	23%	161ppb
Phthalates	Cancer	100ppb	47%	2037ppb
Total THC	Illegal	1ppm	41%	
CBD (>20% off claimed)	Legal Risk	1ppm	40%	--

The **90th percentile** tells you the value for which 90% of the data points are smaller and 10% are bigger.

Benchmarked Brand Performance

Based on 200+ products tested for over 300 analytes including CBD and THC



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Questions?

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