Part II: What is FDA's Role in the Regulation of CBD?

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Part II: What is FDA's Role in the Regulation of CBD?

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Agenda/Overview

- Introduction/Background
- Regulation of FDA product categories
  - Food
  - Cosmetic
  - Dietary supplement
  - Drug
- Future issues?
- Q&A

Reminder - Agriculture Improvement Act of 2018

- "Hemp" removed from definition of "marihuana" – no longer a controlled substance
  - *Cannabis sativa L.* plant and any part of that plant, including seeds, derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not;
  - Not more than 0.3% THC by dry weight

- CBD may or may not be "marihuana" (a controlled substance) – depends on source
  - CBD not "marihuana" if derived from "hemp", as defined by the 2018 Farm Bill
  - CBD not "marihuana" if derived from other varieties of Cannabis (*Indica, Ruderalis*)

Reminder - Agriculture Improvement Act of 2018 (2)

- Does NOT exempt “hemp” from the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Product must have an appropriate regulatory status
  - Food: Is it generally recognized as safe (GRAS)?
  - Dietary Supplements: Is it subject to a new dietary ingredient notification (NDIN)?

Food Definitions

- "Food"
  - Articles used for food or drink for man or other animals
  - Chewing gum
  - Articles used for components of any such article
- "Food additive"
  - "Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (. . . including any source of radiation . . .)" if such substance is not "generally recognized as safe" (GRAS) for its intended use as determined by qualified experts
    - "Through scientific procedures" (i.e., toxicology testing) or
    - "Based on common use in food" before January 1, 1958

Food Limitation – FD&C Act 301(ll)

- Prohibits distribution of any "food" to which has been added:
  - Approved drug or biologic product; or
  - Drug or biologic "for which substantial clinical investigations have been instituted" and existence of which has been made public
  - Exceptions:
    - Drug/biologic marketed in food before approval or substantial clinical investigations
    - Drug/biologic added to "enhance food safety"
- FDA: this provision bars CBD addition to food
- BUT: provision bars the addition of a "drug" to food
  - Drug is defined by its "intended use"
  - May be an argument that CBD with a legitimate food purpose could be permitted
  - Would not necessarily block other cannabis-derived ingredients
    - But provision does not require an IND to be in place, therefore potentially broader range of publicly-disclosed studies could disqualify other substances

FDA Public Hearing – May 31, 2019

- FDA interested in how to position cannabis-derived compounds as food ingredients
  - At least one presenter was asked if there was any information on “taste, aroma, or nutritive value” of CBD in food (answer: he didn’t know)

- Some presenters recommended linking ingestion amount to product classification (drug, dietary supplement, food)

Authorization of Food Ingredients

- "Food additive" requires pre-market clearance from FDA
  - Applicant's food additive petition with appropriate safety data
  - FDA issues a regulation describing permitted use (then found in 21 CFR)
  - If no food additive regulation, or regulation does not cover the current use, the food is "adulterated" and therefore unlawful

- If ingredient is GRAS, it is <u>not</u> a food additive and no regulation is needed

Criteria for GRAS Status

- Two basic routes are available:
  - Scientific procedures
  - Common use in food prior to 1958
- Under “scientific procedures” toxicological testing must demonstrate safety
  - Safety data must be publicly available (pivotal data must be in peer-reviewed, published scientific literature)
  - Consensus must exist among qualified experts
- No requirement to submit company’s GRAS determination to FDA, but can through FDA’s voluntary GRAS Notification program
  - One company claims it has developed a self-determined GRAS position for its CBD extract; basis has not been made public
- FDA has “no questions” about GRAS Notifications for hulled hemp seeds, hemp seed protein, and hemp seed oil (specific uses in human food)

Cosmetic Definition

- "Cosmetic" means articles (excluding soap):
  - (1) intended to be "rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance," and
  - (2) intended for use as a component of any such articles
- No FDA pre-market review (except for color additives)
- FDA: no specific prohibition on cannabis-derived ingredients (product must still be safe)
  - Do cannabis-derived ingredients provide a cosmetic effect?

Enforcement Example

- Joint FDA/FTC Warning Letter to PotNetwork Holdings, Inc. (March 28, 2019)
  - "Liquid Gold Gummies (Sweet Mix)" and "Liquid Gold Gummies (Sour Mix)" (among other products)
    - Claims about Alzheimer's disease, cancer, arthritis, other diseases
    - FDA: claims cause products to be "drugs"
  - Both labeled as foods: FDA cites FD&C Act 301(ll)

- FTC:
  - Concerned that "one or more of the efficacy claims cited [in the letter] may not be substantiated by competent and reliable scientific evidence"
  - In other words, lack of evidence that products work as claimed

DIETARY SUPPLEMENTS

Do Any CBD Products Qualify As Dietary Supplements?

Christopher Van Gundy, Partner, Sheppard Mullin Richter & Hampton LLP

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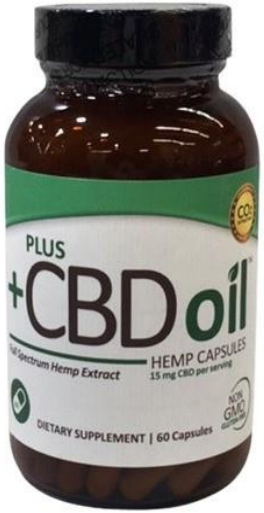
The FDA's Answer

- No. http://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd



FDA Regulation Of Dietary Supplements

- Dietary Supplement Health and Education Act ("DSHEA") of 1994
  - "The law defines dietary supplements in part as products taken by mouth that contain a 'dietary ingredient.' Dietary ingredients include vitamins, minerals, amino acids, and herbs or botanicals, as well as other substances that can be used to supplement the diet."
  - "Dietary supplements come in many forms, including tablets, capsules, powders, energy bars, and liquids. These products are available in stores throughout the United States, as well as on the Internet."
  - "Dietary supplements are not intended to treat, diagnose, cure, or alleviate the effects of diseases."

FDA Regulation Is Minimal

- For products with structure/function claims, the manufacturer, packer or distributor must notify the FDA of same within 30 days *after* first marketing.

- Generally, the manufacturer or distributor does not have to prove the safety of the dietary supplement to FDA's satisfaction.

  - But see new dietary ingredients ("NDI").
  - NDI is a dietary ingredient that was not marketed in the U.S. before October 15, 1994

- Within 75 days *before* introducing an NDI into interstate commerce, a manufacturer or distributor must submit to FDA notification which includes information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling.

The Drug Exclusion Rule

- CBD products cannot be an NDI because, according to FDA, they are excluded from DSHEA altogether pursuant to the “Drug Exclusion Rule.”
  - **21 U.S.C. Section 321(ff)(3)(B)**
- “The term dietary supplement . . . does not include . . . an *article* that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of title 42, or an article 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, 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*.”
- “Emphasis Supplied”

FDA Reasoning For The Exclusion

- *EPIDIOLEX* contains a highly purified form of cannabidiol (CBD) that comes from the cannabis plant; the *active ingredient* is nearly 100% cannabidiol. It is believed to work differently from other prescription seizure medicines, but the exact mechanisms of action (how it works) are unknown.

- The “article” is the “active ingredient,” CBD is the active ingredient, so all CBD “dietary supplements” are excluded from DSHEA

Points To Ponder

- “Active ingredient” is not in the statutory language
- The active ingredient of Epidiolex is a highly purified form of CBD “Isolate.”
  - All terpenes, flavonoids, fats, impurities, THC and other cannabinoids are removed
- No one has proved to FDA’s satisfaction that any CBD product was marketed in the U.S. before substantial clinical investigations of Epidiolex began.

Is FDA Correct In “Excluding” All CBD Products?

- Full Spectrum CBD (Hemp)
  - Impurities, chlorophyll, fibers, fats, water removed
  - Trace amounts of THC
  - Other cannabinoids remain
- Broad Spectrum CBD (Hemp)
  - Full spectrum but all traces of THC removed
- Is The “Article” CBD or the entire extract?

The Red Yeast Case Points The Way?

- *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000)
  - Approved drug lovastatin to control cholesterol
  - Refined and higher concentrations than naturally occurring in red yeast
  - FDA: Excluded!

- The Approved Drug

Natural Levels of Lovastatin Not Excluded

Cholestin

- Cholestin also contained refined, higher concentrations of lovastatin than naturally occurring
- The Court could not decide what "article" meant and so deferred to FDA's interpretation
- Cholestin today at naturally occurring levels – A-OK

"The Pretender"

Evidence of Differing Effects On The Human Body?

- Hemp Extract with CBD ≠ CBD Isolate?
- “Entourage Effect”
- Gallily, Yekhtin, Hanus, *Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol*, 6 Pharmacology & Pharmacy, 75-85 (10 February 2015)
  - “Pure” CBD ceased to have effect at certain dosing
  - Enriched CBD avoided the bell-shaped response
  - Different effects = Different articles?

The Curious Case Of Coffee

- Acrylamide is a chemical that is produced by roasting or frying certain foods, such as coffee
- It is considered a human carcinogen by IARC
- A San Francisco Court found it is present in coffee at levels considered to be carcinogenic
- WHO: Coffee may have anti-cancer properties

My Questions For You

- Are full spectrum and broad spectrum hemp CBD extracts excluded from DSHEA under existing law?
- If not, should FDA exercise its discretion under the Drug Exclusion Rule to permit these substances to be marketed as dietary supplements (assuming they otherwise qualify) under circumstances?
- Is there sufficient safety data to qualify these substances as NDI?

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The FDA's Role in the Regulation of CBD

Drug Products

Presented by

Brian Malkin, *Counsel*, Arent Fox LLP

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Overview

- Introduction/Background
- Drug Products Generally
- Prescription Drug Products
- OTC Drug Products
- FDA Drug Enforcement

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Drug Products Generally

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FDA Position on Cannabis Products

- FDA viewed most cannabis products as Schedule I and took a hands-off approach, even though states developed programs to grow, process, and dispense cannabis for medical uses (and more recently recreational)
- Following 2018 Farm Bill, FDA retained explicit authority to regulate hemp-derived products such as CBD, which were de-scheduled if "hemp"
- USDA Interim Final Rule further defines "hemp"
  (i.e., derived from *Cannabis sativa L.* and NMT 0.3 % Δ9THC) to mean
  - NMT 0.3 % (Δ9THC + (87.7%)THCA)
    - Why? THCA may convert to Δ9THC, the "intoxicating" THC variety and 87.7% THC/weight.
    - But where did the Δ9THC limit come from? Is it possible to grow "hemp" for CBD with these parameters?
- "Marihuana" & Marihuana Extract" are still Schedule I CSA
  - No currently accepted US medical use
  - Lack of accepted safety for use under medical supervision, and
  - High potential for abuse

What about "hemp extract", "hemp flower extract", or "CBD"?

What about synthetic THC and CBD?

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FDA works with DEA to (Re-/De-) Schedule Drugs

Eight-Factor Analysis

- Actual or relative potential for abuse
- Scientific evidence of pharmacologic effects
- Current scientific knowledge regarding the substance
- Historical and current pattern of abuse
- Scope, duration, and significance of abuse
- Risk to public health
  - CDC includes risks of addition, short and long-term effects on brain, cancer, heart attacks and stroke, lung health, and poisoning
- Psychic or physiological dependence liability; and
- If the substance is an immediate precursor of a controlled substance.

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FDA/DEA, 2018 Farm Bill, and State Marijuana Programs

- DEA denied two 2016 petitions to reschedule cannabis and marijuana under CSA because found not safe under medical supervision and high potential for abuse
- 2018 Farm Bill still grants FDA Jurisdiction over cannabis-derived products in interstate commerce.

What does this mean for state medical marijuana programs?

Are medical marijuana programs unsafe and unmedical according to the DEA/FDA?

Does the FDA plan to regulate interstate products in state medical or recreational marijuana programs?

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FDA Position on “Hemp”, CBD, and THC

- Prior to GW Pharma, “hemp” was “hemp (seed) oil” —no CBD
- GW Pharma filed an IND for CBD product derived from *Cannabis sativa L.*, Epidiolex® (IND: 5/17/2014; NDA approved 6/25/2018) to treat certain rare forms of childhood epilepsy, making all CBD products drugs as of IND date
- Hemp seed products can be sold as foods if they do not hemp products with CBD
- “Drug” means including a known drug (e.g., CBD) or by intended use (i.e., drug claims – treat, cure, or mitigate illness or disease)
- Marijuana-derived, THC products remain Schedule I

What about CBD products with NMT 0.3% Δ9THC – does it matter if it comes from hemp or marijuana?

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Prescription Drug Products

Prescription Drug Products

- Marinol® Schedule III Rx drug (capsule) / Syndros® Schedule II Rx drug (oral solution) (Note: DEA determined liquid form had a higher abuse potential.)
  - Synthetic delta-9-THC to relieve nausea/vomiting associated with chemotherapy for cancer patients and to assist with anorexia associated with weight loss in AIDS patients
- Cesamet® Schedule II Rx drug (Note: DEA kept as Schedule II because of use only as an antiemetic.)
  - Synthetic similar to delta-9-THC capsule used to relieve nausea/vomiting associated with cancer chemotherapy
- Epidiolex® Schedule V Rx drug
  - GMP-grade CBD purified from cannabis/marijuana (<0.1% tetrahydrocannabinols (THC primarily) in final product)
  - Low potential for abuse – other examples cough preparations NMT 200 mg codeine per 100 ml (100 g), e.g., Robitussin AC®, Phenergan with Codeine®, and ezogabine
  - Risks include liver safety, sedation, drug interactions, insomnia, diarrhea, infections, and abuse potential
  - Schedule V only applies to Epidiolex and its generic forms, not CBD generally
  - **Should Epidiolex be descheduled as "hemp" post-2018 Farm Bill, because derived from *Cannabis sativa L.* and NMT 0.3% Δ9THC?**

Prescription Drug Products (cont'd)

- Animal drug manufacturers need to obtain research-grade marijuana from NIDA/DEA-approved source(s) and INAD with CVM
- DEA entertaining applications for additional sources of marijuana outside of University of Mississippi but none will be reviewed until regulations are drafted and final
- IND/DEA license requires Schedule I level security at marijuana study sites but product considered to have poor potency and quality (may require irradiation for mold and safety) and NIDA approval


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Over-the-Counter
Drug Products

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Over the Counter Drug Products

- OTC products: Rx-to-OTC NDA or Monograph
- Some OTC drug products, e.g., external analgesics, are tentative final monographs (TFMs)
- FDA permits OTC under TFMs using “enforcement discretion” but “proposed rules” may have “no legal effect”

OTC products need OTC drug claims as specified in OTC NDA or monograph – but what does the inclusion of another “drug” mean? Can another “drug” be an inactive ingredient, e.g., alcohol, and at what threshold?

*Rx to over the counter NDA or Monograph

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Over the Counter Drug Products (cont.)

What is an Active Ingredient?

- Component intended to furnish pharmacological activity or other direct effect in diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the body of man or other animals.

Over the Counter Drug Products (cont.)

Can “Hemp Extract”, “Hemp Flower Extract”, or “CBD” be an inactive ingredient in an OTC Drug?

- OTC productions can only contain suitable inactive ingredients that are:
  - Safe in the amounts administered
  - Do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine the product meets its professed standards of identity, strength, quality and purity
- FDA’s inactive ingredient database does not include “hemp extract”, “hemp flower extract”, or “CBD”

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FDA Drug Enforcement

Warning Letters

- 01Nov2017 – Warning letters for CBD products to prevent, diagnose, treat, or cure cancer – unapproved drug products
  - Examples:
    - “combats tumor and cancer cells”
    - “CBD makes cancer cells commit ‘suicide’ without killing other cells
    - “CBD … [has] anti-proliferative properties that inhibit cell division and growth in certain types of cancer, not allowing the tumor to grow”
- 23July2019 – Curaleaf Inc. warning letter
  - Claims to treat cancer, Alzheimer’s disease, opioid withdrawal, pain and pet anxiety
  - Examples (in addition to cancer ….)
    - “CBD has also been shown to be effective in treating Parkinson’s disease.”
    - “CBD has been linked to the effective treatment of Alzheimer’s disease ….”
    - “CBD is being adopted more and more as a natural alternative to pharmaceutical-grade treatments for depression and anxiety.”
    - “CBD can also be used in conjunction with opioid medications, and a number of studies have demonstrated that CBD can in fact reduce the severity of opioid-related withdrawal and lessen the buildup of tolerance.”
    - “CBD oil is becoming a popular, all-natural source of relief used to address the symptoms of many common conditions, such as chronic pain, anxiety … ADHD.”
    - “ “[V]ets will prescribe puppy Xanax to pet owners which can help in certain instances but is not necessarily a desirable medication to give your dog continually. Whereas CBD oil is natural and offers similar results without the use of chemicals.”
    - “For dogs experiencing pain, spasms, anxiety, nausea or inflammation often associated with cancer treatments, CBD (aka cannabidiol) may be a source of much-needed relief.”

Warning Letters (cont'd)

Examples for "Hemp Infused Body Butter" and "Hemp Oil", "Teeth/TMJ – Essential Oil + CBD Infusion" and "Ears – Essential Oil + CBD Infusion"

- "Instead of synthetic chemical that can have safety concerns, this blend uses the best of nature to help calm the inflammation and pain of teething, while also promoting sleepiness for your little one."
- "This blend also works great for jaw and TMJ dysfunction pain."
- "No matter what age, ear aches are a terrible, no good way to live each day! Our main priority was safety, effectiveness . . . as we formulated this for the entire family including our precious little ones. When the pain is bad, this roller goes to work for soothing pain, inflammation, and to battle against the bacterial/viral critters to blame."
- Increasing evidence suggests that CBD oil is a powerful option for pain . . . anxiety . . . and autism . . . It seems like an attractive and safe option for children."
- "CBD oil may have neuroprotective properties and may protect against neurological conditions, such as Parkinson's and Alzheimer's disease."
- "CBD oil may improve depression, anxiety, and PTSD."
- "CBD may reduce the risk of cancer or help cancer treatment."
- "CBD may reduce the risk of diabetes."

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FDA's Recent Statements on Hemp & CBD Products

- **Amy Abernethy, MD, PhD.** Principal Deputy Commissioner - Office of the Commissioner, Hemp Production and the 2018 Farm Bill Before the Senate Committee on Agriculture, Nutrition and Forestry (7/25/2019)
  - "The passage of the 2018 Farm Bill has led to the misperception that all products made from or containing hemp, including those made with CBD, are now legal to sell in interstate commerce. The result has been that storefronts and online retailers have flooded the market with these products, many with unsubstantiated therapeutic claims."
- **Lowell Schiller, JD,** FDA Principal Associate Commissioner for Policy (part of FDA's CBD Policy Working Group) at 2019 Hemp Business Summit (8/12/2019)
  - CBD has a different risk profile compared to some other cannabinoids, such as THC. For example, it does not provide the same sort of "high" or intoxicating effects as THC and is therefore not expected to be an abused substance.
  - At the same time, we also know that CBD is not a risk-free substance. As with many drugs, there are potential adverse effects – including, in the case of CBD, potential liver toxicity, drug interactions, and drowsiness. Other adverse effects also have been identified. And there may be other risks that emerge with further study.

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Questions?

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Cannabis Vapor Products

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CBD Vapor Products

Is there a regulatory pathway for CBD Vapor Products?

- FDA's Center for Tobacco Products (CTP) has no regulatory authority over CBD vapor products because they do not meet the statutory definition of tobacco products.
- The FDA's reach is limited to tobacco products, which are defined as "any product made or derived from tobacco that is intended for human consumption, including any component, part or accessory of a tobacco product … ."
- Cannabidiol or any cannabinoid derived from hemp or cannabis is outside the scope of the definition in the Tobacco Control Act.

FDA Enforcement

- FDA issued a warning letter to Curaleaf, Inc. (July 22, 2019) for several products including their CBD Disposable Vape Pen.
  - Unapproved drug product based on claims that the vape pen is intended for treatment of chronic pain
  - Claim that CBD is a dietary supplement

FDA's Focus

- The FDA's current focus on nicotine vaping may be forewarning regarding the Agency's view on CBD-based vapor products.

- While the FDA lacks clear authority to regulate CBD vapor products*, the pressure on the Agency to curtail youth access, initiation, and use of these products may force the FDA to act upon its overarching mandate to protect children and the public health at large.

Lung Injury Outbreak

- FDA issued a warning to consumers to stop using vaping products containing THC amid more than 2,000 reports of lung injuries—including 39 deaths—following the use of vaping products.
- The FDA is working closely with the U.S. Centers for Disease Control and Prevention (CDC), and state and local public health partners to investigate these illnesses as quickly as possible.
- Potential link to Vitamin E acetate based on recent study results

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