Legal and Practical Issues in the Evolving World of Cannabis Regulation

CBD Regulatory Update

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Speakers

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CBD Regulatory Update

- We Are Still Waiting
- What About Other Cannabinoids?
- May 31, 2019 FDA Public Hearing
- CHPA Citizens' Petition
- Jan. 15, 2020 FDA Remarks To Congress

CBD Regulatory Update

- Oct. 1, 2020 FDA Statement
  - "The agency is committed to protecting the public health while also taking steps to improve the efficiency of regulatory pathways for the lawful marketing of appropriate cannabis and cannabis-derived products."
  - "FDA's existing authorities over foods, dietary supplements, human and veterinary drugs, and cosmetics apply to hemp and CBD products . . . . "
  - Most CBD products are technically not compliant with applicable FDA law

May 31, 2019 Public Hearing

- Acting FDA Commissioner, Norman “Ned” Sharpless, MD
- Following passage of the 2018 Farm Bill, “under current law, CBD and THC cannot lawfully be added to a food or marketed as a dietary supplement.”
- “Potential pathway for CBD products”
- “this lack of research, and therefore evidence, to support CBD’s broader use in FDA-regulated products . . . has resulted in unique complexities for its regulation . . . .”
  - How much CBD is safe to consume in a day?
  - How will it interact with other drugs?
  - Pregnancy?

May 31, 2019 Public Hearing

- Public Docket Re-Opened Mar. 11, 2020
- Public and Stakeholders can submit “high quality data” on the safety and potential benefits of CBD
- Confidentiality Mechanism for Stakeholders
- Seeking data (particularly clinical studies) re:
  - The impacts of long-term sustained or cumulative exposure to CBD
  - Driving impairment/alcohol interaction
  - Transdermal penetration
  - Effects of different routes of administration
  - Differences between “full,” “broad spectrum” and CBD isolates
- Questions: at what dosage, and for what extended period of time?

Nov. 14, 2019 CHPA Citizens' Petition

- Consumer Healthcare Products Association
- Use existing statutory authority to swiftly issue regulations that establish a clear pathway for manufacturers to lawfully market CBD
  - Submit New Dietary Ingredient Notification
  - Don't use drug claims
  - Use GMP's
- NDIN's would provide FDA with much-needed data
  - Evidence for reasonable expectation of safety

Jan. 15, 2020 FDA Remarks To Congress

- Douglas C. Throckmorton
- Center for Drug Evaluation and Research
- Takeaways:
  - "Because the [2018] Farm Bill explicitly preserved FDA's authorities over hemp and other low-THC cannabis products, including cannabidiol (CBD), these products must meet any applicable FDA requirements and standards . . . . "
  - "At present, any food containing CBD or purported CBD dietary supplement product in interstate commerce is in violation of the FD&C Act . . . . "
  - "FDA continues to believe the drug approval process represents the best way to ensure that safe and effective new medicines, including any drugs derived from cannabis, are available to patients in need of appropriate medical therapy."

Jan. 15, 2020 Remarks To Congress

- “There are also many unanswered questions about the science, safety, and quality of products containing CBD.”
- Potential Risks In Using CBD
  - Liver injury
  - Drug Interactions
  - Male Reproductive Toxicity
- The Shadow of Epidiolex
  - Concentration Levels
    - 5 mg/kg = 227 mg/day
    - 20 mg to 40 mg/day
- Other Cannabinoids?

Legal and Practical Issues in the Evolving World of Cannabis Regulation

CBD Regulatory Updates

Brian J. Malkin, Partner, McDermott Will & Emery

McDermott Will & Emery

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FDA's Report to Congress

- Issued 3/6/2020
- Mandated by Consolidated Appropriations Act of 2020 (H.R. 1158), directing $2 million to FDA for "research, policy evaluation, market surveillance, and issuance of an enforcement discretion policy and appropriate regulatory activity" for hemp-derived CBD" and a report on its progress including:
  - (1) a policy of enforcement discretion and
  - (2) a process in which hemp-derived CBD will be evaluated for use in products
- Summarized the regulatory landscape surrounding CBD drugs, dietary supplements, foods, cosmetics, and vape products

FDA's Report to Congress (cont'd)

- Identified next steps, including potentially adopting a risk-based enforcement policy
- **Reopened the public hearing docket** to facilitate information sharing **indefinitely**
- Identified issues surrounding potential differences between "full spectrum" or "broad spectrum" hemp extracts and CBD isolates
- Notified that FDA's CBD sampling report is forthcoming

FDA's Report to Congress (cont'd)

- **Key Questions FDA Still Wants Answered**
  1. What happens if you use CBD daily for sustained periods of time?
  2. What level of intake triggers the known risks associated with CBD?
  3. How do different methods of exposure affect intake (e.g., oral consumption, topical, smoking or vaping)?
  4. What is the effect of CBD on the developing brain (such as children who take CBD)?
  5. What are the effects of CBD on an unborn child or breastfed newborn?
  6. How does CBD interact with herbs and botanicals?
  7. Does CBD cause male reproductive toxicity in humans, as has been reported in studies of animals?
  8. Are there differing safety concerns for use in certain animal species, breeds, or classes?
  9. Are any residues formed in edible tissues of food producing animals?

FDA's Report to Congress (cont'd)

- FDA says it recognizes the …
  - "[V]ast proliferation of CBD consumer products"
  - "[S]ignificant interest in the development of therapies and other consumer products derived from cannabis and its components, including CBD"
  - "[T]he potential opportunities that CBD may offer"; and
  - "[L]imited FDA [enforcement] resources."

FDA's Report to Congress (cont'd)

- Reading between the lines …
  - FDA knows the ship has sailed to reign in CBD products, so it needs to focus its resources on what it can do, e.g., warning letters for drug claims
  - FDA remains concerned about CBD's potential safety risks including:
    - Liver injury
    - Drowsiness
    - Potential for drug interactions
    - Potential male reproductive toxicity risks (at any level)
    - Sustained or cumulative exposure
    - Vulnerable populations like children, pregnant/lactating women, elderly, and unborn children.

FDA's Report to Congress (cont'd)

- Reading between the lines … (cont'd)
  - Not GRAS for foods or dietary supplements
  - Would require notice/comment rulemaking to permit CBD added to any food or dietary supplement
  - Cosmetics may be OK but companies must evaluate safety since topical information known
  - Drug (human and animal) pathway has Epidiolex as an example

FDA's Report on Marketed CBD Products

- Issued 7/8/2020
- Explained previous CBD information-gathering activities, raised concerns about actual CBD content matching the labeled amount and other cannabinoids in the products (such as THC) or contaminants (such as heavy metals and pesticides)
- From 2014 to 2018, FDA tested 78 CBD products: 88% contained cannabinoids, 86% contained CBD, and many contained THC and/or other cannabinoids. FDA referred two products to the Drug Enforcement Agency (one product for containing 16 mg/g THC and one product for containing MMB-FUBINACA (a Schedule I synthetic cannabinoid) at 1.9 mg/gummy). Of the 23 products FDA analyzed in 2014, 35% accurately declared the amount of CBD in the product

FDA's Report on Marketed CBD Products (cont'd)

- In 2019, FDA tested 34 CBD products for certain elements and 31 of those for cannabinoid content. The results of elemental testing did not raise significant public health concerns. Of the tested products labeled to declare the amount of CBD, only one third contained CBD within 20% of the labeled amount. 40% of products that did not declare the CBD amount contained no CBD. About half of the products tested for cannabinoids contained THC
- FDA also tested hemp and/or CBD-containing cosmetic products for CBD, THC, and other cannabinoids, 41 of which were labeled as containing CBD. All 41 did contain CBD and 12 contained THC, although none were labeled as containing THC. Of the 14 products that declared specific amounts of CBD on the label, only four contained within 20% of the declared amount

FDA's Report on Marketed CBD Products (cont'd)

- FDA indicated that it intends to undertake a more extensive CBD product sampling effort, with near-term results informing the long-term sampling plan. The agency is currently analyzing 200 CBD and hemp products marketed online. FDA has completed testing of 147 of those for cannabinoids, 49% of which contained THC. Two products labeled as containing CBD did not. Of the 102 product labels that declared a specific amount of CBD, only 45% contained CBD within 20% of the labeled amount. FDA also analyzed 133 products for arsenic, cadmium, mercury, and lead. All but one, which FDA is still evaluating, did not contain these elements at levels that represent a health concern
- FDA acknowledged that the "products tested are from a limited sample size and cannot be used to draw definitive conclusions." Looking ahead, FDA's reports on its long-term sampling efforts, which aim to include a representative, random sample of the entire CBD marketplace, may provide further insight into FDA's perspective on the CBD sector

FDA Guidance Regarding CBD Clinical Research

- Issued 7/21/2020 ("Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research, Draft Guidance for Industry")
- Research for cannabis or cannabis-derived compounds requires an approved investigational new drug application ("IND") with cannabis from a DEA-registered source (for years only the National Institute on Drug Abuse ("NIDA") Drug Supply Program, in contract with the University of Mississippi) if over the 0.3 percent delta-9 THC limit
- **But for "hemp" products under the 0.3 percent delta-9 THC limit, researchers may obtain cannabis from other sources to conduct research**

FDA Guidance Regarding Clinical Research (cont'd)

- Quality Considerations
  - Quality considerations for an IND will require:
    - Curent Good Manufacturing Practices
    - Quantitative Data Regarding Phytochemicals Including Cannabinoids, Terpenes, and Flavonoids
    - Adequate characterization of cannabis and cannabis-derived compounds to ensure batch-to-batch consistency
    - Quality tests for microorganisms and impurities
    - Applicable CSA drug scheduling considerations
    - Combination product considerations

FDA Guidance Regarding Clinical Research (cont'd)

- IND Application
  - FDA recommends that companies provide qualitative laboratory data, detailed testing methods, including testing methods to evaluate the level of delta-9 THC, in particular for phase 2 and 3 studies and marketing applications, which may differ depending on dosage form
- But new drug application ("NDA") applicants should not rely on published literature in place of a full toxicology program to support development of a botanical drug product for phase 3 trials and beyond

FDA Guidance Looking Ahead

- On July 22, 2020, FDA also submitted a draft guidance titled "Cannabidiol Enforcement Policy" to the White House Office of Management and Budget ("OMB") for review
- FDA is required to submit draft guidances to OMB's Office of Information and Regulatory Affairs (OIRA) at least 30 days before issuance. FDA and other executive agency regulations, budgets, major policies, guidance documents, and agency spend plans are developed in conjunction with, and approved by the OMB. Guidance documents and regulations not approved by OMB often will not go forward

FDA Guidance Looking Ahead (cont'd)

- Substantive aspects of OMB's review and comment on FDA or other agency guidance documents are protected from public disclosure under the government's "deliberative process privilege," which facilitates free exchange between government decision makers before the announcement of a policy
- FDA has yet to issue any official statements providing additional details regarding the draft guidance, but the cannabis industry has been eagerly anticipating this guidance on FDA's enforcement position regarding CBD products

CBD and Gender Differences

- On 11/19/2020 FDA held a conference: “Scientific Conference: CBD and Other Cannabinoids: Sex and Gender Differences in Use and Responses”
- Reiterated more is unknown than known about the CBD’s use in products subject to its oversight and that food, dietary supplements or other non-drug products could include warnings against use by pregnant or lactating women.
- "Given that little is known about how and if many cannabis-derived products work, how and why women are using them, and their potential associated risks, there is a mounting need to consolidate and communicate what we know about these products and to identify knowledge gaps. Further, the use of these products during pregnancy and lactation raises additional questions and concerns," said Kaveeta Vasisht, FDA Office of Women's Health Director/Associate Commissioner for Women's Health.
- "There is a great deal that we simply do not yet know about CBD and beyond CBD, even more that we do not know about the other compounds found in hemp. We don't know very much about the cumulative effect and effects of cumulative and long-herm human exposure. We need to know a lot more about the effects of CBD and susceptible populations," said Douglas Throckmorton, Deputy Director for Regulatory Programs, CDER.

CBD and Gender Differences (cont'd)

- Key Take Aways
  - No major sex effects have been established for CBD and other cannabinoids in cannabis, including tetrahydrocannabinol (THC)
  - While THC appears to increase symptoms of severity, positive and negative symptoms of psychosis, CBD appears to have the opposite effect
  - CBD's potential benefits for relieving menopause symptoms is another area with research data lacking so far but is a potential study target
  - FDA continues to allow marketing food and dietary supplements with CBD that are not marketed with disease claims when otherwise FDA compliant
  - For about 2 years FDA has been looking at potential regulatory pathways for lawful use of CBD and hemp-derived ingredients in food and supplements but a lack of safety data has prevented any proposal while also keeping open indefinitely a docket for comment

CBD Regulatory Update

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Draft Guidance for Cannabidiol
Data needed to demonstrate bioequivalence (BE)
Sept 2020

- Guidance for future makers of generic CBD oral solution (100 mg/ml)] must:
  - have “the same active drug ingredient in the same concentration and dosage form as the reference listed drug” to qualify for exemption from conducting required *in vivo* bioequivalence study
  - Bioequivalence is used to assess biological equivalence of two proprietary preparations of drugs
    - If two drugs are bioequivalent, it means that they are expected to be same for all intents and purposes

Draft Guidance for Cannabidiol
Data needed to demonstrate bioequivalence (BE)
Sept 2020

- Guidance specifies that the generic cannot contain more than 0.10% THC by weight
- To assure identity of the botanical raw material (BRM), cannabis should be of the same species –as that used to manufacture the reference listed drug
  - Due to the many cultivars within this species, identification and authentication of plant species should be conducted at the cultivar(s) level
  - Plant parts used must be defined
  - Good agricultural and collection practices to optimize batch-to-batch consistency
  - Analytic methods specified
- References two existing FDA guidance documents for further direction:
  - Botanical drug development
  - Quality considerations for clinical research in cannabis and cannabis-derived compounds.
- The CBD-specific guidance regarding bioequivalence is one of a suite of product-specific bioequivalence guidance documents that FDA has issued
- Comment Period = Over

H.R. 8179 Hemp and Hemp-Derived CBD Consumer Protection and Market Stabilization Act of 2020

- Removes FDA's IND preclusion clause and makes hemp derived CBD lawful for use under FDCA

SECTION 1. SHORT TITLE.

This Act may be cited as the "Hemp and Hemp-Derived CBD Consumer Protection and Market Stabilization Act of 2020".

SEC. 2. USE OF HEMP AND CANNABIDIOL DERIVED FROM HEMP AS DIETARY INGREDIENT.

(a) IN GENERAL.—Beginning on the date that is 90 days after the date of enactment of this Act, notwithstanding section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(ff)(3)(B)), hemp, cannabidiol derived from hemp, and any other ingredient derived from hemp shall be lawful for use under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) as a dietary ingredient in a dietary supplement, provided that such dietary supplement complies with—

(1) the requirements for a dietary supplement which contains a new dietary ingredient in section 413 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350b); and

(2) all other applicable requirements for a dietary supplement in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) and the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.).

FDA Comments on H.R. 8179

(October 2020)

- FDA provides technical edits to HR 8179 that mitigate the public health and operational concerns
- In my opinion FDA has shown its cards
- What do FDA comments say?

FDA edits to H.R. 8179

- Hemp CBD only
  - exclude other cannabinoids (delta-8, THC, CBG, CBN, etc.)
  - exclude synthetic
- Safety
  - CBD limit
  - Required safety-related labeling
  - Require NDIN (pre-market evidence of safety)

FDA edits to H.R. 8179

- New enforcement tools to help FDA control the market
  - A New Prohibited Act
  - Change import and seizure provisions
  - Mandatory Product Listing
    - If products does not meet definition of a dietary supplement (e.g., synthetic or not listed) FDA can seize or refuse import