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MEMORANDUM

From: Martin J. Hahn
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Re: **Cannabis Regulation Update: FDA Announces Public Meeting on Cannabis; FDA and FTC Issue Warning Letters to Manufacturers of CBD Products; Proposal to Add Cannabis Extracts and THC to Proposition 65**

This memorandum summarizes several regulatory developments related to cannabis and cannabis-derivatives, including cannabidiol (CBD). The Food and Drug Administration (FDA) recently announced it will hold a public meeting on May 31, 2019 and open a docket for public comments to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds.[1] FDA, in coordination with the Federal Trade Commission (FTC), also issued three Warning Letters to companies marketing CBD products positioned as foods and dietary supplements.[2] The Warning Letters explain that FDA determined these products are unapproved new drugs, while the FTC indicated that efficacy claims appearing in these products' advertising may not be substantiated by competent and reliable evidence. Finally, California's Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) has proposed to include THC and "cannabis extracts" on the Proposition 65 list of developmental toxicants.[3] We discuss each of these developments in further detail below.

As brief background, the 2018 Farm Bill clarified that Cannabis sativa containing less than 0.3% delta-9 tetrahydrocannabinol (THC) on a dry weight basis is "hemp," exempt from the Controlled

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[1] Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments, 84 Fed. Reg. 12969 (April 3, 2019).

[2] *See* FDA Warning Letter to PotNetwork Holdings, Inc., March 28, 2019, *available at* https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm634738.htm; FDA Warning Letter to Advanced Spine and Pain, LLC (d/b/a Relievus), March 28, 2019, *available at* https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm634781.htm; FDA Warning Letter to Nutra Pure LLC, March 28, 2019, *available at* https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm634776.htm.

[3] Request for Relevant Information on the Reproductive Toxicity (Developmental Toxicity Endpoint) of Cannabis and Cannabis-Related Chemicals, *available at* https://oehha.ca.gov/proposition-65/crnr/request-relevant-information-reproductive-toxicity-developmental-toxicity

Substances Act (CSA) definition of marijuana, and therefore not a controlled substance.[4] However, the Farm Bill preserved FDA's authority under the Federal Food, Drug, and Cosmetic Act (FFDCA) to regulate the use of cannabis-derived ingredients, including hemp-derived ingredients, in FDA-regulated products. FDA has taken the position that CBD is prohibited from use in foods or dietary supplements because CBD has been, and is currently, the subject of substantial clinical investigations as a drug, which have been made public. Therefore, under the so-called "exclusionary clauses" of the FFDCA, FDA views CBD derived from hemp as precluded from use in food or dietary supplements.

In recent testimony before the House Appropriations Committee, Commissioner Gottlieb acknowledged that the agency "heard Congress loud and clear" with respect to the 2018 Farm Bill and understands that Congress wants FDA to remove obstacles to CBD-containing products in the marketplace, while underscoring that the 2018 Farm Bill preserved FDA's legal authority entirely. Commissioner Gottlieb explained that the agency can go through notice and comment rulemaking to authorize the use of CBD in food and dietary supplements, and that the agency is exploring whether to undertake such rulemaking. In a series of tweets, Commissioner Gottlieb reiterated that the agency is committed to exploring an appropriate, efficient, and predictable framework for cannabis-derived products, but that the agency will take action against companies illegally selling these types of products when they are putting consumers at risk. Commissioner Gottlieb also shared concerns about "several national pharmacy chains and other major retailers" who have begun to sell or will soon begin to sell CBD products in several states, and that FDA will be contacting them to "remind them of FDA obligations and our commitment to protect consumers against products that can put them at risk."

FDA Public Meeting on Cannabis and Cannabis-Derived Compounds

FDA announced a public meeting and opened a docket for public comments on a number of issues related to the use of cannabis and cannabis-derived ingredients in FDA-regulated products. The public meeting and comment period is the first step for the agency to gather information about cannabis derivatives to inform the agency's actions in developing a lawful pathway for such products. The issues raised in FDA's notice are broader than the use of CBD in foods and dietary supplements, and the questions are geared towards cannabis and cannabis-derivatives more generally, as well as uses of cannabis derivatives across all FDA-regulated product categories.

FDA acknowledges that "some companies are marketing products containing cannabis and cannabis-derived compounds in ways that violate the FD&C Act," and highlights the Warning Letters the agency has issued against CBD products that were intended to prevent, diagnose, mitigate, treat, or cure serious diseases. FDA explains that selling unapproved drug products is not merely a technical violation of the FFDCA, but also raises public health concerns for patients who may be influenced to use such products over approved therapies to treat serious diseases. FDA states that questions remain about the safety considerations raised by widespread use of cannabis-derived products. Regarding CBD, FDA notes that safety concerns were identified during the agency's review of Epidiolex, the FDA-approved drug containing CBD as an active ingredient, with respect to potential for liver injury at certain doses. FDA explains that these risks can be managed when the

[4] For our previous summary of the implications of the 2018 Farm Bill for regulatory oversight of hemp-derived products including CBD, *see* our previous update, *available at* https://f.datasrvr.com/fr1/218/55985/2018_12_21_Pharma_alert_President_Signs_2018_Farm_Bill_with_Hemp_Reforms.pdf.

product is taken under medical supervision in accordance with the FDA-approved labeling of the product, but that it is less clear how this risk might be managed if the substance is used far more widely, without medical supervision, and not in accordance with FDA-approved labeling. FDA also has concerns about potentially undermining the drug approval process if the agency allows the use of a drug ingredient in a food.

FDA's goal with the public meeting and comment is to obtain additional scientific data and other information related to cannabis and cannabis-derived compounds, both from botanical and synthetic sources, to inform the agency's regulatory oversight of these products. To that end, FDA's notice contains several questions related to the health and safety risks, manufacturing and product quality, and marketing, labeling, and sale of cannabis and cannabis-derived products:

Health and Safety Risks

1. Based on what is known about the safety of products containing cannabis and cannabis-derived compounds, are there particular safety concerns that FDA should consider regarding its regulatory oversight and monitoring of these products? For example:

    - What levels of cannabis and cannabis-derived compounds cause safety concerns?
    - How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?
    - How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

2. Are there special human populations (e.g., children, adolescents, pregnant and lactating women) or animal populations (e.g. species, breed, or class) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

3. What are the characteristics of a successful system to collect representative safety information at the national or State level about products containing cannabis and cannabis-derived compounds?

    - Are there systems that currently exist for the collection of this information (other than FDA's systems)?
    - Are there particular safety concerns related to the overlap of therapeutic dose levels from approved drug products, with potential exposure from other uses (e.g., from food, dietary supplements, cosmetics)? Please identify any safety concerns and include relevant data or studies.

4. What endpoints or outcomes would define a maximal acceptable daily intake from all products?

    - What margin of exposure would represent an appropriate and safe level from anticipated cumulative exposure? Does that margin of exposure vary based on the form of consumption (e.g., from ingestion, absorption, inhalation)? Please explain your reasoning and include relevant data or studies.

- What mechanisms would be available to help ensure that this margin of exposure was maintained at a level sufficiently protective of public health?

5. Are there any data known that would support the safe use of cannabis and cannabis-related compounds in general food use (including dietary supplements), including data regarding exposure levels to cannabis and cannabis-related compounds in foods (including dietary supplements) that would be acceptable from a food safety perspective?

    - What data are available about residues of cannabis-derived compounds in human foods (e.g., meat, milk, or eggs) that come from animals that consume cannabis or cannabis-derived compounds? Are there residue levels that should be tolerated in these foods? Please provide data or other information to support your reasoning.

6. How does the existing commercial availability of food products containing cannabis-derived compounds such as CBD (which may in some cases be lawful at the State level but not the Federal level) affect the incentives for, and the feasibility of, drug development programs involving such compounds?

    - How would the incentives for, and the feasibility of, drug development be affected if food products containing cannabis-derived compounds, such as CBD, were to become widely commercially available? How would this change if FDA established thresholds on acceptable levels of cannabinoids, including CBD, in the non-drug products it regulates?
    - What else could FDA do to support drug development from cannabinoids?

Manufacturing and Product Quality

1. Are there particular standards needed to address any safety issues related to the manufacturing, processing, and holding of products containing cannabis and cannabis-derived compounds (e.g., genotoxic impurities, degradation of active compounds)? Please identify or describe those standards.

2. Are there particular standards or processes needed to ensure manufacturing quality and consistency of products containing cannabis or cannabis-derived compounds, including standards applied to evaluate product quality? Please identify or describe those standards.

3. What validated analytical testing is needed to support the manufacturing of safe and consistent products?

4. Are there any currently used standardized definitions for the ingredients in cannabis products (e.g., “hemp oil”)? If standardized definitions would be helpful, what terms should be defined and what should the definition(s) be?

5. What are the functional purposes of adding cannabis-derived compounds, such as CBD, to foods (e.g., nutritive value, technical effect), both in terms of manufacturer intent and consumer perceptions and/or expectations? To the extent a compound is added to food to achieve a particular functional purpose, what evidentiary support is available to demonstrate that the addition of such compound has the intended or perceived effect?

Marketing/Labeling/Sales

1. How should consumers be informed about the risks associated with such products (e.g., directions for use, warnings)? What specific risks should consumers be informed about? Are there any subpopulations for which additional warnings or restrictions are appropriate? Please explain your reasoning.

2. What conditions, restrictions, or other limitations on the manufacturing and distribution of these products have been put in place under State or local law, particularly with respect to food products containing cannabis-derived compounds such as CBD (which may, in some cases, be lawful at the State level but not the Federal level)? What other conditions, restrictions, or other limitations might be appropriate to ensure adequate consumer information and to protect the public health?

3. What statutory or regulatory restrictions are in place under State or local law to warn about the use of these products by certain vulnerable human populations (e.g., children, adolescents, pregnant and lactating women) or animal populations (e.g. species, breed, or class)? Are there other steps that should be taken to warn about use by vulnerable populations? Please identify such steps and how they would apply to a particular subpopulation.

4. What other information should FDA consider in the labeling of specific product categories of cannabis and cannabis-derived products?

FDA is accepting public comments on these issues until July 2, 2019.

FDA and FTC Warning Letters for CBD Products

FDA and the FTC jointly issued three Warning Letters to companies marketing products containing CBD. The products implicated in these Warning Letters included "hemp oil," "CBD softgels," CBD gummies, CBD crystals, "CBD Salve," "CBD Oil,"[5] and "CBD for Dogs," which were positioned as foods or dietary supplements for humans or animals. FDA explains that each of these products are unapproved new and misbranded drug products, both because of the prohibition on the use of CBD in foods and supplements under the exclusionary clause, and because the products are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or because they are intended to affect the structure or any function of the body. Specifically, each of these products had labeling or advertising claims related to the cure or treatment of serious diseases, including Alzheimer's, anxiety, depression, fibromyalgia, inflammation, cancer, and chronic pain, among others.

These three Warning Letters are the first time that the FTC has co-signed a FDA Warning Letter regarding CBD-containing products. In the Warning Letters, the FTC raised concerns that the efficacy claims on these products may not be substantiated with competent and reliable scientific

[5] FDA also noted that the CBD Oil product is intended to be taken sublingually, and that dietary supplements are defined as products "intended for ingestion." Because sublingual products are intended to enter the body directly through the skin or mucosal tissues, FDA concluded sublingual products are not "intended for ingestion" and do not meet the definition of a dietary supplement.

evidence. The FTC reiterated that it is unlawful under the FTC Act to advertise a product can prevent, cure, or treat disease unless substantiated by competent and reliable scientific evidence, including, where appropriate, well-controlled human clinical studies.

Proposal to Add THC and Cannabis Extracts to California's Proposition 65

As background, California's Safe Drinking Water and Toxic Enforcement Act (also known as Proposition 65) requires the Governor to publish, at least annually, a list of chemicals known to the State to cause cancer or reproductive toxicity. Businesses are required to provide a "clear and reasonable" warning before knowingly and intentionally exposing anyone in California to a listed chemical.[6] Before a chemical can be included on the Proposition 65 list as a reproductive toxicant, the Developmental and Reproductive Toxicant Identification Committee (DARTIC) of OEHHA's Science Advisory Board issues an opinion about whether a chemical has been clearly shown to cause reproductive toxicity. OEHHA has directed DARTIC to review the following chemicals related to cannabis for possible listing under Proposition 65 as reproductive toxicants (based on a developmental toxicity endpoint):

- Cannabis (marijuana)
- Marijuana (cannabis) smoke[7]
- Cannabis extracts
- Delta-9 tetrahydrocannabinol (THC)

The proposal does not further define cannabis, cannabis smoke, or cannabis extracts. OEHHA is accepting public comments on the proposal until April 29, 2019.

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These developments underscore the importance of continuing to monitor closely federal developments and enforcement actions if you are developing or marketing CBD-containing products. We will continue to monitor developments at FDA, the FTC, USDA and in the states regarding cannabis-derived products. Please contact us if you are interested in submitting comments to FDA's docket, or if you have any questions on this or any other matter in the meantime.

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6 Cal. Health & Safety Code § 25249.6.

7 Marijuana smoke is currently listed as a carcinogen under Proposition 65.