January 26, 2023

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Anne Marie Murphy
Deputy General Counsel
Consumer Healthcare Products Association
1625 Eye Street, NW, Suite 600
Washington, DC 20006

Re: Docket No. FDA-2019-P-5394

Dear Mr. Spangler and Ms. Murphy:

This letter responds to your citizen petition requesting that the Food and Drug Administration (FDA or we) take the following actions:

1. "Establish a regulatory pathway to legally market dietary supplements containing [cannabidiol (CBD)] derived from hemp" as defined in 7 U.S.C. 1639o(1),[1] by promulgating regulations under section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(ff)(3)(B)) (the "exclusion clause"), stating that the article, hemp-derived CBD, is lawful under the FD&C Act;
2. "Maintain the status quo for medicines containing CBD, meaning continue to enforce the statutory requirements and protections under the [new drug application (NDA)] process, including with regard to approved indications and established safe dosages";
3. "Continue and increase enforcement action against unscrupulous manufacturers making illegal drug claims or otherwise failing to comply with the [FD&C Act] with regard to CBD-containing products"; and
4. "Continue to monitor emerging safety issues, if any, concerning CBD-containing products."

See Citizen Petition from Consumer Healthcare Products Association (CHPA), dated November 14, 2019 ("Petition"), at page 2.

For the reasons stated below and in accordance with 21 CFR 10.30, FDA is denying the Petition in part and granting it in part.

[1] This provision states, "[t]he term 'hemp' means the plant 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."

I. Legal Background and Regulatory History of CBD

A. Legal Background

The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325, amended the FD&C Act to, among other things, define the terms "dietary supplement" and "new dietary ingredient" (NDI) and change the way dietary supplements are regulated. Under section 201(ff) of the FD&C Act, "dietary supplement" is defined using a multipart definition. Part of the definition lists specific categories of "dietary ingredients" (section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)))[2] and requires the product to bear or contain one or more of those ingredients.

Under the exclusion clause, the term "dietary supplement" excludes:

> (i) an article that is approved as a new drug under section 505 [of the FD&C Act], certified as an antibiotic under section 507 [of the FD&C Act], or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or
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> (ii) 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,
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> 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 Act.

Thus, under the exclusion clause, if an article has been approved as a new drug under section 505 of the FD&C Act or 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, the article is outside the definition of a dietary supplement unless either of two exceptions applies. First, there is an exception if the article was marketed as a dietary supplement or as a food before such approval or authorization. In such a case, the article was on the market first as a food or dietary supplement and does not lose its ability to be marketed as a dietary supplement if a drug manufacturer later chooses to study or seek approval for the article as a new drug. Second, there is an exception if FDA (under authority delegated by the Secretary of Health and Human Services), in FDA's discretion, issues a regulation, after notice and comment, finding that the article would be lawful under the FD&C Act.[3]

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[2] As defined in section 201(ff)(1) of the FD&C Act, a "dietary ingredient" is any one of the following: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above.

[3] The chief sponsors of DSHEA expressly disclaimed as a source of legislative intent everything but a short Statement of Agreement. See Statement of Agreement, 140 Cong. Rec. H28668 (Oct. 6, 1994). Courts, nonetheless, have looked to the disclaimed legislative history, including a Senate Report (S. Rep. No. 103-410 (1994)). See *Pharmanex v. Shalala*, 221 F.3d 1151, 1158 (10th Cir. 2000). A careful review of the history of

As part of this new framework for dietary supplement regulation, DSHEA also amended the FD&C Act by adding section 413 (21 U.S.C. 350b), which defines the term "new dietary ingredient" (NDI). Section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)) requires the manufacturer or distributor of an NDI, or of the dietary supplement that contains the NDI, to submit a premarket notification to FDA (an NDI notification, or NDIN) that contains information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing the NDI will reasonably be expected to be safe, unless the exception set forth under section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) applies. The manufacturer or distributor of an NDI, or of the dietary supplement that contains the NDI, must submit the NDIN pursuant to 21 CFR 190.6 (§ 190.6).[4]

FDA reviews an NDIN to determine whether it complies with the applicable statutory and regulatory requirements. Under section 413(a)(2) of the FD&C Act, the NDIN must contain the information, including any citation to published articles, which provides the basis on which the manufacturer or distributor of the NDI or dietary supplement has concluded that a dietary supplement containing the NDI will reasonably be expected to be safe.[5] Under section

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DSHEA indicates that Congress not only expressed concern that allowing an article to be marketed as a dietary supplement after it had been first approved or studied as a drug would be unfair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would therefore serve as a disincentive to the significant investment needed to gain FDA approval of new drugs; but also expressed concern that allowing such marketing would enable manufacturers to escape appropriate safety and efficacy review and FDA oversight by being classified as dietary supplements. See, e.g., 140 Cong. Rec. S12104 (Aug. 18, 1994), Statement of Sen. Harkin ("[T]he [Hatch-Harkin] compromise assures that prescription drugs cannot escape appropriate review and oversight by being classified as dietary supplements. This concern was raised by a number of Senators and the legislation before us addresses it in a sensible manner."); S. Rep. No. 103-410 (1994), at V § 3 ("During consideration of S. 784, concerns were expressed that manufacturers or importers of drugs could avoid the drug approval process by marketing drug products as dietary supplements. Although current authorities should be adequate to deal with such potential problems, the committee is sensitive to those concerns.

Accordingly, Senators Harkin and Hatch agreed to formulate additional language prior to consideration of S. 784 in the Senate."). Senator Hatch explained the impetus for the Hatch-Harkin compromise language (the exclusion clause) as follows:

> Drafters of the legislation . . . were criticized for a definition of dietary supplement which some felt was overly broad. We have tried to tighten that up.
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> Some then believed that the language would allow drugs such as taxol to be marketed in the United States as dietary supplements. Senator Harkin and I worked for some time after the markup to resolve that issue, and the language we present today addresses that concern.

140 Cong. Rec. S22413 (Aug. 13, 1994), Statement of Sen. Hatch. Taxol, the drug that Senator Hatch mentioned as a reason for the exclusion clause, was approved in December 1992, prior to DSHEA's enactment, with an injection route of administration (i.e., a route of administration other than ingestion).

[4] To help industry comply with DSHEA, FDA issued a regulation (21 CFR 190.6) to implement the FD&C Act's premarket notification requirement for dietary supplements that contain an NDI (62 FR 49886; Sept. 23, 1997). The regulation specifies the information that the manufacturer or distributor must include in its NDIN (21 CFR 190.6(b)).

[5] Our NDI notification regulation (21 CFR 190.6), which implements section 413(a)(2) of the FD&C Act, specifies the procedure for submitting an NDI notification and the information the manufacturer or distributor must include in

402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)), a dietary supplement containing an NDI is adulterated unless there is adequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

Pursuant to § 190.6(c), FDA must send an acknowledgement of the receipt of the premarket notification noting the filing date. Following our review of the safety and identity information provided in an NDIN, FDA's practice is to send a response letter to the notifier that provides this acknowledgement as well as information about our review. For example, in this letter, FDA may state that we have no objection to the NDIN or, alternatively, list deficiencies that make the submission incomplete under § 190.6, or raise safety concerns or other regulatory issues (e.g., the product is excluded from the definition of "dietary supplement").[6] In accordance with §190.6(e), FDA will not disclose the existence of, or the information contained in, the NDIN for 90 days following the filing date of the notification. After the 90th day, FDA will place all information, aside from trade secret or otherwise confidential commercial information, on public display.

B. Regulatory History of CBD

Based on available evidence, FDA's longstanding position has been that CBD is excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act. FDA first took this position publicly as early as 2015, based on the fact that CBD had been authorized for investigation as a new drug for which substantial clinical investigations had been instituted and for which the existence of such investigations had been made public,[7,8] and noting that, based on available evidence, FDA had concluded that CBD had not been "marketed as" a dietary supplement or a conventional food before the new drug investigations were authorized.[9] In June 2018, the prescription drug Epidiolex, which contains CBD as the active ingredient, was approved as a new drug under section 505 of the FD&C Act.[10] Thus, CBD is both an article

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the notification to support the conclusion that a dietary supplement containing the NDI will reasonably be expected to be safe.

[6] Redacted copies of FDA's response letters are publicly available. Information on how to access them is available at https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/submitted-75-day-premarket-notifications-new-dietary-ingredients.

[7] See https://web.archive.org/web/20150520223457/http://www.fda.gov:80/newsevents/publichealthfocus/ucm421168.htm.

[8] For example, two such substantial clinical investigations include GW Pharmaceuticals' investigations regarding Sativex and Epidiolex. (See "Phase II/III Sativex US cancer pain trials begin" available at https://www.pmlive.com/pharma_news/phase_iiiii_sativex_us_cancer_pain_trials_begin_9271?SQ_ACTION=clear_design_name&full=true, and "GW Pharmaceuticals Receives Investigational New Drug (IND) From FDA for Phase 2/3 Clinical Trial of Epidiolex® in the Treatment of Dravet Syndrome" available at https://www.globenewswire.com/news-release/2014/05/07/633784/10080331/en/GW-Pharmaceuticals-Receives-Investigational-New-Drug-IND-From-FDA-for-Phase-2-3-Clinical-Trial-of-Epidiolex-R-in-the-Treatment-of-Dravet-Syndrome.html.)

[9] See, e.g., Warning Letter from William A. Correll, Director, Office of Compliance, Center for Food Safety and Applied Nutrition (CFSAN), to Sana Te Oils, dated February 4, 2016. This and other Warning Letters relating to CBD products are available at https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products.

[10] For more information about the approval of Epidiolex, see https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms.

approved as a drug and the subject of substantial clinical investigations the existence of which has been made public. FDA has consistently communicated its position that CBD is excluded from the dietary supplement definition over the course of multiple years and in many different ways, including numerous Warning Letters,[11] statements on FDA's website,[12] and in communications with individual firms.

FDA is not aware of any evidence that would call into question our conclusion that CBD is excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act. For years, FDA has invited interested parties to present us with any evidence that they think has a bearing on this issue. For example, FDA's website dedicated to the regulation of cannabis and cannabis-derived products contains a statement specifically inviting interested parties to present us with such data.[13] FDA's Warning Letters have also stated that the recipient of the letter may present FDA with any evidence that has bearing on this issue.[14] To date, FDA has not received or found evidence that changes our position on this issue. CBD is an article that has been the subject of substantial clinical investigations the existence of which have been made public (as well as being an article that is approved as a new drug), and CBD was not first marketed as a food or dietary supplement.

The Agriculture Improvement Act of 2018 (Pub. L. No. 115-334, the "2018 Farm Bill") changed how cannabis is treated under the Controlled Substances Act (CSA) by removing "hemp" from the definition of "marihuana" (commonly referred to as "marijuana").[15] This means hemp is no longer a controlled substance under Federal law. Because many CBD products may meet this new definition of "hemp," the 2018 Farm Bill served to spark substantial commercial interest in the marketing of CBD products.[16] However, while the 2018 Farm Bill changed how "hemp" is regulated under the CSA, it did *not* change how "hemp" is regulated under the FD&C Act. To the contrary, the 2018 Farm Bill explicitly preserved FDA's authority to regulate products containing cannabis or cannabis-derived compounds under the FD&C Act.[17] Accordingly, the FD&C Act continues to apply to products that meet the definition of "hemp," including the FD&C Act's exclusion clause in section 201(ff)(3)(B).

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[11] FDA's Warning Letters relating to CBD products are available at https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products.

[12] See, e.g., https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#dietarysupplements and https://www.fda.gov/news-events/press-announcements/fda-warns-companies-illegally-selling-cbd-products.

[13] See https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. This website states: "Interested parties may present the agency with any evidence that they think has bearing on this issue [of the exclusion under section 201(ff)(3)(B) of the FD&C Act]." This invitation to submit data to FDA has been on our website since May 2015.

[14] See, e.g., Warning Letter from William A. Correll, Director, Office of Compliance, CFSAN, to Sana Te Oils, dated February 4, 2016. This and other Warning Letters relating to CBD products are available at https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products.

[15] The 2018 Farm Bill created a new definition of *hemp*, which includes cannabis and derivatives or extracts of cannabis (such as CBD) with no more than 0.3 percent by dry weight of delta-9 tetrahydrocannabinol. *See supra* footnote 1.

[16] See Brightfield Group's US CBD Market Data reports for additional information.

[17] See 7 U.S.C. § 1639r(c) (stating that "[n]othing in this subchapter shall affect or modify, (1) the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); (2) section 262 of Title 42; or (3) the authority of the Commissioner of Food and Drugs and the Secretary of Health and Human Services – (A) under (i) the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) or (ii) section 262 of Title 42."

Following the interest in CBD that the 2018 Farm Bill generated, FDA increased its focus on CBD. FDA formed a high-level workgroup dedicated to coordinating our approach to CBD policy-making, including considering the appropriateness of potential pathways for dietary supplements containing CBD to be lawfully marketed.[18] The first priority of the high-level workgroup was to obtain and assess safety data for CBD, given FDA's public health mission. Although FDA has approved one drug, Epidiolex, that contains CBD, Epidiolex is approved for use in a limited population at a specific dose; was studied for safety and efficacy in rigorous randomized clinical trials; and is available only by a prescription from a licensed medical professional. The approval of Epidiolex therefore does not answer the question of whether CBD is safe enough to be marketed in other contexts, such as in dietary supplements. As part of the workgroup's efforts to obtain safety and other information about CBD, FDA convened a public hearing to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds.[19] The hearing was attended in person by more than 600 people, with over 2,000 more viewing it online, and included presentations from more than 100 speakers, representing a broad and diverse array of stakeholders, including patients, consumers, and their advocacy groups; health care providers; academia; manufacturers, retailers, and distributors; agricultural coalitions; and state, tribal, and local government representatives. Subsequently, FDA reopened the public hearing docket, which has remained open as one mechanism for stakeholders to share data.[20]

At the same time, we have consistently made clear that the 2018 Farm Bill did not alter the exclusion in 201(ff)(3)(B) of the FD&C Act. For example, we made this clear on our landing page dedicated to the regulation of cannabis and cannabis-derived products.[21] Numerous public statements from FDA similarly made this clear.[22] While FDA stated that we were willing to

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[18] The workgroup was described in various public-facing documents, including testimony provided to Congress. See https://www.agriculture.senate.gov/imo/media/doc/Testimony_Abernethy%2007.25.19.pdf. The workgroup was subsequently expanded to cover additional cannabis regulatory matters; Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance FDA's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products (April 2, 2019), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation. In addition, the workgroup created the opportunity for stakeholders to meet with workgroup members and offer input.

[19] See https://www.federalregister.gov/documents/2019/04/03/2019-06436/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds.

[20] See https://www.regulations.gov/docket/FDA-2019-N-1482.

[21] See FDA webpage entitled "FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)," available at https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd.

[22] See "Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds" (December 20, 2018), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys (stating that "it's unlawful under the FD&C Act to . . . market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived"); "Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products" (April 2, 2019), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-

consider the possibility of rulemaking under section 201(ff)(3)(B) of the FD&C Act to create a regulatory pathway for CBD dietary supplements by removing the exclusion,[23] we also made clear that we would only do so if we could determine that CBD products would satisfy the relevant safety standards in the FD&C Act.[24] We never stated that we were actively engaged in rulemaking or that we had in fact decided to pursue rulemaking under section 201(ff)(3)(B) of the FD&C Act. To the contrary, we made clear that we were actively engaged in a very different task: gathering data to better understand CBD's safety profile. As FDA made progress on that task, we became aware of data that heightened our concerns about the safety of CBD, and we took steps to alert the public to those safety concerns.[25] At this time, having now gathered and

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new-steps-advance-agencys-continued-evaluation (stating that "it is unlawful to introduce food containing added CBD, or the psychoactive compound THC, into interstate commerce, or to market CBD or THC products as dietary supplements. This is because CBD and THC are active ingredients in FDA-approved drug products and were the subject of substantial clinical investigations before they were marketed as food"); and "FDA is Committed to Sound, Science-based Policy on CBD" (July 17, 2019), available at https://www.fda.gov/news-events/fda-voices/fda-committed-sound-science-based-policy-cbd (stating that "it is currently illegal to put into interstate commerce a food to which CBD has been added, or to market CBD as, or in, a dietary supplement").

[23] See "Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds" (December 20, 2018), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys (stating that "the FDA would only consider doing so if the agency were able to determine that all other requirements in the FD&C Act are met, including those required for food additives or new dietary ingredients"); and "Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products" (April 2, 2019), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation (stating that "the agency considers whether it could be appropriate to exercise its authority to allow the use of CBD in dietary supplements and other foods").

[24] See "Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products" (April 2, 2019), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation (stating that "the FDA would only consider this path if the agency were able to determine that all other requirements in the FD&C Act are met, including those required for food additives or new dietary ingredients"); "FDA is Committed to Sound, Science-based Policy on CBD" (July 17, 2019), available at https://www.fda.gov/news-events/fda-voices/fda-committed-sound-science-based-policy-cbd (stating that "An important component of this work is obtaining and evaluating information to address outstanding questions related to the safety of CBD products that will inform the Agency's consideration of potential regulatory frameworks for CBD while maintaining the FDA's rigorous public health standards").

[25] One example of our communication with the public about our safety concerns with CBD is through the use of Consumer Updates on our website. See "What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD" (March 5, 2020), available at https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis (stating that "CBD has the potential to harm you"). Additional FDA communications materials identified similar concerns. See, e.g., "FDA warns 15 companies for illegally selling various products containing cannabidiol as agency details safety concerns," available at https://www.fda.gov/news-events/press-announcements/fda-warns-15-companies-illegally-selling-various-products-containing-cannabidiol-agency-details (stating that "we want to be clear that a number of questions remain regarding CBD's safety – including reports of products containing contaminants, such as pesticides and heavy metals – and there are real risks that need to be considered").

reviewed a substantial amount of data and other information about the safety of CBD, we have developed serious concerns about the safety of CBD[26] for potential use in dietary supplements.

II. Petition Summary and FDA's Response

The Petition makes four requests of FDA. We discuss these requests and our responses to each in the sections that follow.

A. Request No. 1: FDA should issue a regulation stating that dietary supplements containing CBD may be lawfully marketed under the FD&C Act

The Petition requests that "FDA…exercise its authority under [section 201(ff)(3)(B) of the FD&C Act] and promulgate regulations stating that dietary supplements containing CBD derived from hemp (as defined in 7 U.S.C. § 1639o(1)) may be lawfully marketed under the [FD&C Act]" (Petition at page 2). The Petition argues that "FDA's authority and discretion to take this path is explicit in the statute and needed to ensure that products are appropriately regulated" (Petition at page 2). The Petition also proposes that "the resulting regulation require that manufacturers of CBD-containing dietary supplements submit new dietary ingredient (NDI) notifications to FDA" (Petition at page 1).

The Petition asserts that "FDA would not need to predetermine the precise safe dietary supplement dose for CBD prior to proposing a rule" because "the burden of providing safety evidence falls to the party notifying FDA" in an NDIN (Petition at page 3). The Petition suggests that "manufacturers would need to file [NDINs] for CBD" and that the requested rule "should be explicit in this regard" (Petition at page 3). The Petition also encourages FDA to issue specific guidance on the "appropriate content and format" of NDINs for CBD-containing dietary supplements, as such a guidance "will increase efficiency of FDA's review of these notifications" (Petition at page 4).

The Petition argues that the NDIN process "will provide FDA with much-needed data on CBD" and "will provide FDA with assurance that it is aware of [CBD-containing] products produced and distributed by reputable manufacturers" (Petition at page 4). While the Petition urges FDA to act swiftly and issue an interim final rule (IFR)[27] in response to its rulemaking request, it also requests that "if FDA engages in notice and comment rulemaking, we urge that it be accompanied by guidance on enforcement discretion for reputable companies that comply with the terms of any proposed rule as well as all other applicable law" (Petition at page 3). The Petition suggests that such enforcement discretion be "conditioned on manufacturers and

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[26] In addition to the communications described in footnote 25, FDA provided in-depth information about CBD's toxicological profile during a June 2022 Science Board to the FDA Advisory Committee meeting. See "Slides – Challenges in regulatory oversight…(afternoon session)," slides 67 through 87, available at https://www.fda.gov/advisory-committees/science-board-food-and-drug-administration/background-materials-june-14-2022-meeting-science-board-fda. For additional information on this meeting, see https://www.fda.gov/advisory-committees/committees-and-meeting-materials/2022-meeting-announcement-science-board-fda-06142022.

[27] The Administrative Procedure Act requires public notice and comment unless an agency "for good cause finds…that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest" (5 U.S.C. 553(b)(B)). An IFR is one tool that an agency can use to bypass notice and comment procedures. It is a rule effective immediately upon publication and adopted without prior public input.

suppliers of CBD-containing dietary supplements taking certain steps to assure product quality" and proposes what those steps could be (Petition at page 4).

When a substance is excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act, the exclusion applies unless FDA, in its discretion, issues a regulation, after notice and comment, finding that the article would be lawful under the FD&C Act. We agree that FDA has explicit authority to engage in rulemaking under the exclusion clause. However, we disagree that FDA should exercise this authority in the context of CBD. The accumulating evidence about CBD suggests that there are considerable safety concerns with its potential use as a dietary supplement, and it is not apparent from your Petition or the available evidence how a CBD product would be able to meet the applicable safety standard that the law provides for dietary supplements.[28] The use of CBD raises safety concerns, especially with long-term use. Scientific studies show possible harm to the male reproductive system, including testicular atrophy; harm to the liver; and interactions with certain medications.[29] The FDA has not found adequate information showing how much CBD can be consumed, and for how long, before causing harm. This is particularly true for vulnerable populations like children and those who are pregnant. For this reason, we have concerns as to whether CBD products could meet the safety standard for dietary supplements. The potential risks to consumers from using a prescription drug product containing CBD, such as Epidiolex, can be managed at different stages – for example, during the FDA drug approval process to evaluate dosage and potential adverse effects, among other things, as well as when the product is taken under medical supervision.[30] However, dietary supplements are not subject to the same approval process as drugs and are generally not prescribed by, nor is their use generally overseen by, a physician. When considering the use of CBD in non-drug products such as dietary supplements, FDA must evaluate different factors than for a prescription drug product. Dietary supplements are directly available to a wide range of consumers, which can include vulnerable populations such as pregnant or nursing individuals, children, the elderly, those with chronic illnesses, and those taking medications that might interact with CBD. Dietary supplements are also available without

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[28] Turck, E., et al., Statement on Safety of Cannabidiol as a Novel Food: Data Gaps and Uncertainties. *EFSA Journal*. 2022 26 Apr.

[29] See, e.g., Ewing, L.E., et al., Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model, *Molecules*, 2019 May; 24(9): 1964; Kocis, P.T., Vrana, K.E., Delta-9-Tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions, *Med Cannabis Cannabinoids*, 2020;3:61-73. doi: 10.1159/000507998; Caravalho, R.K., et al., The effects of cannabidiol on male reproductive system: A literature review, *Journal of Applied Toxicology*, 2020 Jan, *40*, 132-140, https://doi.org/10.1002/jat.3831; Caravalho, R.K., et al., Chronic exposure to cannabidiol induces reproductive toxicity in Swiss mice, *Journal of Applied Toxicology*, 2018 May, https://doi.org/10.1002/jat.3631; Huestis, M.A., et al., Cannabidiol Adverse Effects and Toxicity, *Current Neuropharmacology*, 2019, *17*, 974-989.

[30] For further discussion of why the Epidiolex approval does not necessarily indicate that CBD is safe in other contexts, see Statement of Amy Abernethy, MD, PhD, Principal Deputy Commissioner, Before the Committee on Agriculture, Nutrition, and Forestry, United States Senate, "Hemp Production and the 2018 Farm Bill," July 25, 2019, available at https://www.agriculture.senate.gov/imo/media/doc/Testimony_Abernethy%2007.25.19.pdf. For example, Dr. Abernethy stated: "Through the approval of the CBD-containing drug Epidiolex, which was based on adequate and well-controlled clinical studies, FDA has learned that CBD is not a risk-free substance. During our review of the marketing application for Epidiolex, we identified certain safety risks, including the potential for liver injury. In that context, the risks are outweighed by the benefits of the approved drug to the particular population for which it was intended . . . [A]pproved drugs have uniform strength and consistent delivery that support appropriate dosing needed to treat patients, particularly patients with complex and serious conditions such as the epilepsy syndromes that Epidiolex was approved to treat. Moreover, patients using an approved prescription drug are under medical supervision to monitor any potential adverse effects of the drug."

discussions with a doctor or other medical professional. For these reasons, we have safety concerns with allowing CBD in dietary supplements. Accordingly, at this time, we do not believe it is appropriate to undertake a rulemaking under section 201(ff)(3)(B) of the FD&C Act to permit the lawful use of CBD in dietary supplements.

Further, we do not agree that requiring manufacturers to file NDINs for CBD-containing products, as the Petition proposes, would sufficiently protect the public. While the NDIN requirement set forth in section 413(a) of the FD&C Act provides a tool for FDA to be able to evaluate the safety of certain NDIs contained in dietary supplements, this tool is not sufficiently robust to protect the public health from potentially unsafe dietary supplements. Under current law, FDA has no systematic way to know when new dietary supplements are introduced to the marketplace and whether they have complied with the NDIN requirement. Further, even when an NDIN has been submitted and evaluated by FDA, the NDIN authorities do not always prevent unsafe products from being marketed. For example, if an FDA response letter raises identity or safety concerns with a particular NDI, but the notifier nonetheless proceeds to market, FDA's only recourse (once it becomes aware of such marketing) is to attempt to remove the product from the market by undertaking a resource-intensive enforcement action in which we would bear the burden of proof to demonstrate that the product is adulterated. In the meantime, the unsafe dietary supplement could remain on the market. The new regulation proposed by the Petition would not change this outcome.

Because of the safety concerns expressed above, we would anticipate that NDINs that would be submitted for CBD-containing products under a new regulation as proposed in the Petition would describe products that would not meet the safety standard for dietary supplements and would therefore be adulterated. However, as a practical matter, FDA does not have the resources to take enforcement action against every violative product in this exploding market. The Petition's suggested approach would potentially strain our limited enforcement and NDIN review resources because they would be skewed toward CBD products at the expense of the rest of the dietary supplement marketplace, which would be to the detriment of the public health.

Regarding the argument that the NDIN process will provide FDA with much-needed data on CBD, we note that we have already gathered and reviewed a substantial amount of data and other information that raises serious concerns about the safety of CBD in consumer products and already have mechanisms in place to continue to obtain data about CBD. As discussed above, we have established and left open a docket specifically to receive such data and information. We also frequently grant requests for meetings to discuss CBD safety data.

Regarding the argument that the NDIN process will provide FDA with assurance that it is aware of CBD-containing products produced and distributed by reputable manufacturers, we do not find this to be sufficient justification for the requested action, due to the shortcomings of the NDIN process and our safety concerns about CBD, as described above.

For all these reasons, we decline to propose a rule stating that dietary supplements containing CBD may be lawfully marketed under the FD&C Act. As we are denying this rulemaking request, we will not reach the question of whether issuance of an IFR is the appropriate mechanism for such a rulemaking. Similarly, because we are denying the rulemaking request, it

is not necessary for us to reach the Petition's request that, if FDA were to engage in such rulemaking, we should at the same time establish, through a guidance document or other appropriate regulatory mechanism, the conditions under which we would exercise enforcement discretion for "responsible manufacturers" of CBD-containing products that would be in effect while such a rulemaking is pending (Petition at page 4). We also decline to provide specific guidance as to the "appropriate content and format" of NDINs for CBD-containing products, because NDINs would only be required if FDA issued a rule to bring CBD products under the dietary supplement definition. In that event, regarding what safety information should be included in a potential NDIN, we note that there is information on this topic that is readily available on our website.[31]

B. Request No. 2: FDA should continue enforcement of the statutory requirements and protections established through the NDA process

The Petition states its support of "FDA's continued enforcement of the statutory protections established through the NDA process for medicines that contain CBD" (Petition at page 4). It states that "drug indications are off limits…and dosages for which safety has been established under an NDA…should remain subject to the drug approval process and not be considered appropriate for CBD-containing dietary supplements" (Petition at page 4). Further it argues that "[t]he NDA premarket approval process should also be available to manufacturers of nonprescription medicines containing CBD, provided that the sponsor submits sufficient data and other information needed to support the proposed nonprescription use" (Petition at page 5).

Regarding the NDA premarket approval process for nonprescription drugs, the Petition does not appear to request that FDA take any administrative action with respect to this process, and we also note that the Petition does not identify any factual or legal grounds for FDA taking administrative action on this topic.[32] However, we note that an applicant may submit an NDA for a proposed nonprescription CBD drug product that includes data that shows the drug product is safe and effective for nonprescription use.

To the extent you are requesting that an FDA rulemaking to allow CBD products to be marketed as dietary supplements should be limited so as not to include certain dosages, we need not reach this issue because we are denying your request to undertake rulemaking, as discussed above. To the extent that you are requesting that FDA take enforcement actions, we deny the request because requests for FDA to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures. See 21 CFR 10.30(k).[33] Therefore, to the extent the Petition is requesting enforcement action, your requests are denied.

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[31] See https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/new-dietary-ingredients-dietary-supplements-background-industry.

[32] See 21 CFR 10.30(b)(3) (requiring citizen petitions to include the factual and legal grounds on which the Petition relies).

[33] See 21 CFR §10.30(k) (Section 10.30 "does not apply to the referral of a matter to a United States attorney for the initiation of court enforcement action…."); see also 21 CFR §10.3 (excluding from the definition of "Administrative action" "the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral").

C. Request No. 3: FDA should continue and increase enforcement action against manufacturers making illegal drug claims or otherwise failing to comply with the FD&C Act with regard to CBD-containing products

The Petition expresses concern regarding "products [containing CBD] that bear egregious and unsupported drug or other claims or otherwise violate the [FD&C Act]" (Petition at page 5). While it acknowledges that Warning Letters[34] have been sent with regard to particularly egregious claims, it asserts that additional actions should be taken, including "[c]onducting more facility inspections and issuing Warning Letters accordingly," "[i]ssuing consumer alerts and playing a greater role in raising public awareness about unsupported claims," and "increasing scrutiny and other enforcement activities related to imported products" (Petition at page 5). The Petition notes that "FDA can step up these important enforcement activities under existing authority, without further legislation or rulemaking" (Petition at page 5).

As discussed in subsection II.B., to the extent that you are requesting that FDA take enforcement action,[35] such matters are not appropriate for a citizen petition, and therefore, your requests are denied.[36]

D. Request No. 4: FDA should continue to monitor emerging safety issues

The Petition states that its "requested action for dietary supplements containing CBD would not interfere with FDA's ability to monitor any safety signals that may emerge" (Petition at page 5). It states that FDA's "Center for Food Safety and Applied Nutrition Adverse Event Reporting System captures both spontaneous reports and serious adverse events that manufacturers of CBD-containing dietary supplements would be required to report," and that "[t]hese reports, if any, may be useful as FDA continues to establish a broader regulatory framework for CBD products" (Petition at pages 5 through 6).

As discussed above, we are denying your request to promulgate regulations that would allow for the lawful marketing of CBD products as dietary supplements. However, we note that health professionals, consumers, and patients can voluntarily report observed or suspected adverse events that they believe are associated with the use of CBD products to FDA.[37] FDA reviews these reports and exercises our independent scientific judgment in determining how best to track potential safety signals. As FDA does with all products we regulate, we will continue to exercise our independent judgment in monitoring adverse event reports for any safety signals. And as we do for all products we regulate, we will continue to prioritize potentially severe adverse effects. Because you ask that we "[c]ontinue to monitor emerging safety issues, if any, concerning CBD-

[34] When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning letters are issued to achieve voluntary compliance and to establish prior notice. See FDA's Regulatory Procedures Manual (June 2022) § 4-1-1, available at https://www.fda.gov/media/71878/download.

[35] We appreciate that the Petition expresses support for FDA issuing consumer alerts, and we will continue to issue consumer alerts as appropriate.

[36] *Supra n*ote 33.

[37] See https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program and https://www.safetyreporting.hhs.gov.

containing products" (Petition at page 2), we interpret the Petition to ask that FDA continue to use its independent judgment in determining how best to monitor potential safety signals for CBD products. To the extent that this is what the Petition is asking, we grant the request.

III. Conclusion

After reviewing the information submitted in your petition, we: (1) decline the request to promulgate regulations stating that dietary supplements containing CBD may be lawfully marketed under the FD&C Act; (2) decline the request to take enforcement action regarding the NDA process; (3) decline the request to take enforcement action against manufacturers making illegal drug claims or otherwise failing to comply with the FD&C Act with regard to CBD-containing products; and (4) agree to continue to exercise our independent judgment in determining how best to monitor emerging safety issues, if any, regarding CBD-containing products.

Accordingly, for the reasons stated above and in accordance with 21 CFR 10.30(e)(3), we are denying your petition in part and granting it in part.

Sincerely,

Douglas W. Stearn -S Digitally signed by Douglas W. Stearn -S
Date: 2023.01.26 07:50:17 -05'00'

Douglas W. Stearn
Deputy Center Director for Regulatory Affairs
Center for Food Safety
and Applied Nutrition