January 26, 2023

Daniel Fabricant, Ph.D.
Natural Products Association
440 1st Street, NW
Washington, DC 20001

Re: Docket No. FDA-2022-P-0600

Dear Dr. Fabricant:

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

1. Determine that cannabidiol (CBD) "is not excluded from the definition of a dietary supplement" 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"); or
2. Exercise "enforcement discretion in a specific and selective manner over CBD products following a safety review of a notification on an individual dietary supplement product submitted consistent with 21 C.F.R. Part [sic] 190.6."

Alternatively, your citizen petition asks that we recommend and support to the Secretary of the Department of Health and Human Services (HHS), that in his discretion he issue a regulation, after notice and comment, establishing that CBD is lawful under the FD&C Act. See the Citizen Petition from the Natural Products Association (NPA), dated February 21, 2022 ("Petition"), at page 2.

For the reasons stated below and in accordance with 21 CFR 10.30, FDA is denying the Petition in its entirety.

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)))[1] 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 HHS), in FDA's discretion, issues a regulation, after notice and comment, finding that the article would be lawful under the FD&C Act.[2]

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[1] 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.

[2] 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 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

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).[3]

Under section 413(d) of the FD&C Act,[4] the term "new dietary ingredient" is defined as "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994." Unlike section 413 of the FD&C Act, the exclusion clause does not distinguish between dietary ingredients marketed before October 15, 1994, and those first marketed after October 15, 1994. Nor does the exclusion clause distinguish between drugs approved before October 15, 1994, and those approved after October 15, 1994.

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

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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.
>
> 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).

[3] 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)).

[4] Current section 413(d) of the FD&C Act was added by DSHEA as section 413(c) of the FD&C Act. The FDA Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3885, amended section 413 of the FD&C Act by redesignating subsection (c) as subsection (d) and inserting a new subsection (c).

supplement containing the NDI will reasonably be expected to be safe.[5] Under section 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

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[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 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.

approved as a new drug under section 505 of the FD&C Act.[10] Thus, CBD is both an article 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.[15]

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").[16] 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.[17] 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

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[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.

[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] For a fuller discussion regarding the basis for FDA's conclusion that CBD is excluded from the dietary supplement definition, see Appendix A and Appendix B.

[16] 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.

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

containing cannabis or cannabis-derived compounds under the FD&C Act.[18] 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).

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.[19] 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.[20] 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.[21]

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.[22] Numerous public

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[18] 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."

[19] 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.

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

[21] See https://www.regulations.gov/docket?D=FDA-2019-N-1482.

[22] 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.

statements from FDA similarly made this clear.[23] While FDA stated that we were willing to 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,[24] 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.[25] 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.[26] 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.[27] At this time, having now gathered and

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[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 "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-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").

[24] 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").

[25] 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").

[26] Indeed, the Petition quotes a statement by former FDA Commissioner Stephen Hahn in which he emphasized the need to "develop high-quality data to close the knowledge gaps about the science, safety and quality" of CBD products. Petition at page 8 (quoting statement available at https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market).

[27] 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

reviewed a substantial amount of data and other information about the safety of CBD, we have developed serious concerns about the safety of CBD[28] for potential use in dietary supplements.

II. Petition Summary and FDA's Response

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

A. Request No. 1: FDA should conclude and state that CBD is not excluded from the definition of a dietary supplement

The Petition requests that FDA "conclude and state that CBD is a lawful dietary ingredient and is not excluded from the definition of a dietary supplement under [section 201(ff)(3)(B) of the FD&C Act]" (Petition at page 2). In asking that FDA conclude that CBD is a "lawful" dietary ingredient, the Petition seems to ask that FDA conclude that CBD is not subject to the exclusion in section 201(ff)(3)(B) of the FD&C Act. In support of this request, the Petition seems to make two arguments, one legal and one factual.

The Petition's *legal* argument relates to the distinction between dietary ingredients that are "new dietary ingredients" and those that are not. The Petition refers to this latter category as "old" dietary ingredients.[29] The Petition asserts that "Congress intended that articles that were marketed as both drugs and dietary ingredients prior to the effective date of DSHEA could continue to be marketed as such under section 201(ff)(3)" of the FD&C Act (Petition at page 6). The Petition cites to a section of a Senate Report referencing L-carnitine and caffeine, claiming it provides evidence for this proposition (Petition at pages 5 through 6).[30] The Petition notes that "[t]here is no authoritative list of old dietary ingredients that were marketed in dietary supplements prior to October 15, 1994," claiming that "[p]rior to DSHEA, there was no need for

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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").

[28] In addition to the communications described in footnote 27, 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.

[29] As indicated in the Petition (Petition at page 5), while the FD&C Act does not define the term "old dietary ingredient," it is understood to refer to a dietary ingredient that was marketed in the United States prior to October 15, 1994. In contrast, under section 413(d) of the FD&C Act (21 U.S.C. 350b(d)), the term "new dietary ingredient" is defined as "a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."

[30] The language quoted in the Petition is from S. Rep. No. 103-410 (1994), at V § 3.

a responsible distributor to be concerned with the approval date of a drug, biologic, or when a new drug was authorized for investigation" (Petition at page 5).

The Petition is wrong to suggest that section 201(ff)(3)(B) of the FD&C Act only applies to new dietary ingredients. The statutory language in section 201(ff)(3)(B) of the FD&C Act does not use the phrase "new dietary ingredient" (which Congress had defined in section 413 of the FD&C Act[31]), nor does it contain any other language that states or implies an exception for drugs that were approved prior to DSHEA, drugs that were authorized for investigation prior to DSHEA, dietary ingredients that were marketed in the United States prior to DSHEA, or substances that were marketed as both drugs and dietary ingredients prior to DSHEA. Thus, if Substance A was approved as a new drug in 1987 and was first marketed as a dietary supplement or as a food in 1992, the plain language of the exclusion clause precludes Substance A from being a dietary supplement any time after DSHEA's enactment (unless FDA issues a regulation providing otherwise).[32,33]

The Petition's *factual* argument is about evidence that supposedly shows that CBD was marketed as a dietary supplement or as a food prior to being approved or studied as a drug. Specifically, the Petition refers to an 1850 United States Pharmacopeia (USP) entry entitled *Extractum Cannabis, Extract of Hemp* and states that the "USP establishes the historical use of cannabis, its extracts, and its components – including CBD" and that "[t]he inclusion of *Extractum Cannabis. Extract of Hemp* in the 1850 edition of the USP definitively meets the bar established by the [FD&C] Act for a company to demonstrate that an ingredient was marketed in a product prior to the passage of DSHEA because it shows that CBD was marketed as a dietary ingredient nearly

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[31] As discussed above, current section 413(d) of the FD&C Act (which defines "new dietary ingredient") was added by DSHEA as section 413(c) of the FD&C Act. The FDA Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3885, amended section 413 of the FD&C Act by redesignating subsection (c) as subsection (d) and inserting a new subsection (c).

[32] FDA's interpretation of the exclusion clause does not give it retroactive effect. A statute has a retroactive effect if "it would impair rights a party possessed when he acted, increase a party's liability for past conduct, or impose new duties with respect to transactions already completed." *Landgraf v. USI Film Prods.*, 511 U.S. 244, 280 (1994). FDA's interpretation of the exclusion clause does none of these things. DSHEA was signed into law on October 25, 1994. The exclusion clause does not change the legality of acts committed before DSHEA's enactment. Rather, beginning on DSHEA's effective date, the exclusion clause impacted future conduct by providing that an article that is approved as a new drug cannot be a dietary supplement unless an exception applies (e.g., the article was marketed as a dietary supplement or as a food prior to its approval as a new drug).

[33] This plain language reading of the statute is in keeping with the Senate Report language that the Petition quotes (Petition at page 5). Contrary to the Petition's assertions, the Senate Report does not state that any substance that was marketed as both a drug and a dietary ingredient prior to the passage of DSHEA should be allowed to remain on the market as a dietary supplement after DSHEA's passage, regardless of whether the substance was marketed first as a drug or first as a dietary ingredient. Instead, the examples provided in the Senate Report (L-carnitine and caffeine) are both substances that were marketed as dietary ingredients before they were approved as drugs or the subject of substantial clinical investigations. See Letter from Douglas W. Stearn, Deputy Center Director for Regulatory Affairs, CFSAN, to Steve Mister and Megan Olsen, Council for Responsible Nutrition, and Daniel Fabricant, NPA, at pages 13 through 14, available at www.regulations.gov (Docket ID: FDA-2021-P-0938-0030). This is why they are used as two examples of "a substance that is properly included as a dietary ingredient in a dietary supplement (food) product [that] may also function as an active ingredient in a drug product." S. Rep. No. 103-410 (1994), at V § 3. The fact that both examples involve substances that were marketed as both drugs and dietary ingredients prior to the enactment of DSHEA is a natural consequence of the fact that the Senate Report was written prior to the enactment of DSHEA.

150 years before the passage of DSHEA" (Petition at pages 6 through 7). The Petition also asserts that "[t]he evidence demonstrating CBD's presence in the diet is widely available and irrefutable, so [FDA] should easily determine that CBD is not excluded from DSHEA's definition of dietary supplement/ingredient" (Petition at page 7). It further states

> [t]here are ample records available demonstrating that CBD was marketed as a dietary ingredient prior to CBD's approval as a drug or passage of DSHEA. However…it would be unworkable, inefficient, and unlikely to benefit consumers or public health to require companies to maintain records to demonstrate that such products were on the market prior to the passage of DSHEA.

Petition at page 7, footnote 8.

The Petition's assertions are not supported by the evidence. The Petition fails to demonstrate that CBD was marketed as a dietary supplement or as a food before it was authorized for investigation as a new drug for which substantial clinical investigations have been instituted and their existence made public. The 1850 reference provided in the Petition appears to be a reference to a medicinal monograph in the USP (the top of the page states "Materia Medica").[34,35] Reference to a medicinal monograph does *not* constitute evidence of marketing as a dietary supplement or as a food. Thus, for the plant that the Petition references – *Cannabis sativa* – variety *indica*—the Petition does not demonstrate that the plant was marketed for use as a dietary supplement (as defined in section 201(ff) of the FD&C Act) or as a food. Moreover, this "evidence" does not actually refer to CBD, so it cannot show that CBD was being marketed for anything – much less a food or dietary supplement use.[36]

Although the Petition asserts that there are "ample records available demonstrating that CBD was marketed as a dietary ingredient prior to CBD's approval as a drug or passage of DSHEA" (Petition at page 7, footnote 8), the Petition provides no such records, and we are not aware of any evidence that would support this claim.[37] We have thoroughly researched the question of when CBD was first marketed as a food or dietary supplement, and we have found that this was

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[34] According to Merriam-Webster, the term *materia medica* refers to substances used in the composition of medical remedies. See "materia medica." MerriamWebster.com Dictionary, Merriam-Webster, https://www.merriam-webster.com/dictionary/materia%20medica. Accessed June 28, 2022.

[35] In 1850, USP admitted cannabis as a recognized drug in the *United States Pharmacopeia* (USP) and published an Extractum Cannabis (or Extract of Hemp) monograph. See Gabriel I. Giancaspro, et al., *The Advisability and Feasibility of Developing USP Standards for Medical Cannabis*, U.S. Pharmacopeial Convention; available at: https://flboardofmedicine.gov/forms/usp-standards-cannabis.pdf.

[36] Furthermore, even if the Petition had identified evidence of CBD's use in a dietary supplement or food (which the Petition has not), such use alone would not be enough. Merely showing that a substance was present as a component in a marketed dietary supplement or food is not enough to show that the substance was "marketed" within the meaning of the exclusion clause. See *Pharmanex v. Shalala*, 2001 WL 741419, at *4 and n.5 (D. Utah, March 30, 2001).

[37] Footnote 8 goes on to state that "it would be unworkable . . . to require companies to maintain records to demonstrate that such products were on the market prior to the passage of DSHEA" and that there is "no basis in DSHEA" to require this. But this Petition concerns the application of section 201(ff)(3)(B) of the FD&C Act to CBD products, and as stated above, nothing in section 201(ff)(3)(B) of the FD&C Act differentiates between products marketed prior to DSHEA or after DSHEA. Accordingly, this argument has no bearing on the question of whether CBD is subject to the exclusion clause.

after CBD was authorized for investigation as a new drug for which substantial clinical investigations have been instituted and the existence of which have been made public.[38] The Petition does not refute these findings.

The Petition, therefore, fails to show that CBD was marketed as a dietary supplement or as a food before it had been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and their existence made public. We continue to conclude that CBD products are excluded from the dietary supplement definition under the exclusion clause.

For all these reasons, we deny this request.

B. Request No. 2: FDA should exercise enforcement discretion in a specific and selective manner over CBD products following a safety review of a notification on an individual dietary supplement product submitted consistent with 21 CFR 190.6

If we do not grant the Petition's first request, the Petition asks that we "exercise enforcement discretion in a specific and selective manner over CBD products following a safety review of a notification on an individual dietary supplement product submitted consistent with 21 CFR Part [sic] 190.6" (Petition at page 2). However, the Petition also asks that we "exercise enforcement discretion in a specific and selective manner to review the safety data of a CBD product consistent with 21 CFR Part [sic]190.6" and then states that "[s]hould FDA conclude that CBD is not lawful and is excluded from the definition of a dietary supplement under DSHEA's definitions, then [FDA] should state that it will scientifically review, [sic] safety data related to CBD, including any safety data submitted as part of any premarket regulatory submission" (Petition at page 2). These requests are made in the introductory portion of the Petition and in the "ACTION REQUESTED" portion of the Petition. However, in the "STATEMENT OF GROUNDS" portion of the Petition, the Petition does not seem to address these requests at all. Rather, the "STATEMENT OF GROUNDS" portion of the Petition presents facts and arguments related to only one company, cbdMD. In particular, the Petition requests that we "review cbdMD's safety data and respond substantively in an NDIN respond [sic] letter in earnest on its specific scientific merits" and that FDA "review the available safety data one notification at a time, the way they would for any other new dietary ingredient" (Petition at pages 13 and 14).[39]

To provide a comprehensive response to these different types of requests, we first address the requests related to "enforcement discretion" generally. We then turn to the requests and arguments related to cbdMD.

Requests regarding enforcement discretion

To the extent that the Petition is asking for FDA to exercise enforcement discretion, this request is denied because requests for enforcement discretion are not properly the subject of citizen petitions under 21 CFR 10.30. As stated in 21 CFR 10.30(k), § 10.30 does not apply to "referral

[38] See Appendix A and Appendix B.

[39] We also note that the Petition references certain discussions between FDA and the firm. If the firm wishes to continue those discussions, it may reach out to FDA through our standard communications channels.

of a matter to a United States attorney for the initiation of court enforcement action and related correspondence . . . ." Agency decisions to take, or refrain from taking, enforcement actions are related to referral of a matter to a United States attorney for the initiation of court enforcement action for violations of the FD&C Act.

To the extent that the Petition suggests that an exercise of enforcement discretion is required for FDA to scientifically review the safety data in an NDIN that refers to a CBD product, this request is denied for the reason that enforcement discretion is not needed in this circumstance. As discussed elsewhere and as the Petition concedes, FDA may review and respond to submitted NDINs concerning CBD products, including safety data included therein. Indeed, we have done so in multiple instances.[40] FDA's responses to safety information do not involve the exercise of enforcement discretion because, by choosing to evaluate the submitted safety data, FDA is not declining to enforce a regulatory requirement. While we are not required to review NDIN safety data when the subject of the NDIN is excluded from the dietary supplement definition, and we do not always do so, we have chosen to do so for certain NDIN submissions that raised significant regulatory issues that merited consideration of the submitted safety data.

For all these reasons, we deny the requests related to enforcement discretion.

Requests regarding cbdMD

The Petition asserts that "FDA has already received several NDINs for CBD" and that "[t]hese earlier notifications received letters indicating that, due to FDA's position on CBD being excluded from the definition of a dietary supplement, the notifications would not receive a substantive review of the submitted identity or safety data" (Petition at page 10). The Petition does acknowledge that with two recent NDINs, FDA provided response letters with comments as to the sufficiency of the safety evidence presented (Petition at page 10). However, it contends that "cbdMD will be forced to submit its NDIN without the full scope of safety data it has compiled unless [FDA] agrees to review the data and provide cbdMD, in the form of an NDIN response letter, with its determination of whether it agrees or objects to it on its scientific merits and not a broad policy statement on drug exclusion" (Petition at pages 8 through 9). Without this assurance from FDA, the Petition states that "submitting cbdMD's confidential data to [FDA] without the guarantee that it will be reviewed and appropriately replied to does nothing other than expose cbdMD to the risk of disclosure of the data along with potential misrepresentations of the data without any benefit to cbdMD" (Petition at page 9).

The Petition asserts that "cbdMD has compiled a dossier of identity and safety data…for submission in support of [an NDIN]" and "cbdMD has presented FDA with the information that they continue to say FDA lacks and are asking them to review it in earnest" (Petition at pages 8 and 14). The Petition claims that "nothing precludes [FDA] from reviewing cbdMD's submission on its merits and replying with a formal decision because [FDA] has NOT to date stated it could not review a single supplement product on its scientific merits" (Petition at pages 13 through 14) (emphasis in original). The Petition states that cbdMD has "sold millions of

[40] As the Petition acknowledges, we reviewed the safety data submitted in the notifications regarding NDI 1199 and NDI 1202. In each case, FDA's response letter stated that even if the NDI was not excluded from the definition of dietary supplement, FDA has significant concerns about the adequacy of safety evidence included in the NDIN.

products to consumers in the last few years and has never received an adverse event report from a consumer," has "conducted the robust testing that demonstrates that its products are reasonably expected to be safe," and that their safety data "was well-received by [FDA] representatives in attendance" during a pre-NDIN meeting (Petition at pages 11 and 12). In addition, the Petition suggests that reviewing cbdMD's data as requested would be in the interest of the public health (Petition at page 15). The Petition also asserts that refusing this request would "deny a regulatory path to market for safe CBD products made by reputable companies" and "incentivizes bad actors to avoid following the rules because they know that FDA currently has no intention of acknowledging CBD under an NDIN or taking action to remove otherwise unsafe products from the market" (Petition at page 11).

Thus, the Petition appears to ask FDA to review an NDIN to be submitted by cbdMD at some point in the future, including safety data that the company may submit. A citizen petition is not required for this. If cbdMD wishes to submit an NDIN, the company may do so.[41] FDA has never told the company otherwise. However, FDA cannot take any action on an NDIN until it is received.[42] Even after FDA receives an NDIN, the type of response that FDA would issue would depend on the information submitted. Examples of the types of response letters FDA commonly sends include: letter of acknowledgment without objection; letter listing deficiencies that make the notification incomplete under 21 CFR 190.6; objection letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under section 201(ff)(1) of the FD&C Act, or the product is excluded from the definition of "dietary supplement" under section 201(ff)(3)(B) of the FD&C Act).[43] Thus, even after we receive an NDIN, the type of response we issue would depend on the information included in the NDIN. Because it is already the case that cbdMD may submit an NDIN at any time and we cannot commit to responding in a particular way to a submission we have not received, we deny this request.[44]

With respect to other statements the Petition makes related to cbdMD, the Petition asks FDA to review the submission "on the merits" because the company has invested money in developing its product. But whether a company has invested money in developing a product cannot be a basis for FDA's approach to reviewing a company's submission. FDA reviews NDINs in accordance with the relevant legal standards, including FDA's procedural regulations for NDINs in 21 CFR 190.6. The Petition states that FDA should review an NDIN from cbdMD in order to ensure "a regulatory path to market for safe CBD products," but reviewing an NDIN cannot create a "regulatory path" for a product that cannot lawfully be marketed as a dietary supplement. Accordingly, to the extent the Petition acknowledges that cbdMD's product is subject to the exclusion in section 201(ff)(3)(B) of the FD&C Act, the Petition seems to ask FDA to review an NDIN from cbdMD, disregard the applicability of the exclusion in section 201(ff)(3)(B) of the FD&C Act, and not object to the product coming to market if the safety

[41] cbdMD also may choose to talk about its safety data with FDA in a pre-NDIN meeting, as has occurred.
[42] See generally 21 CFR 190.6.
[43] See generally FDA, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues," 81 FR 53486 (Aug. 12, 2016).
[44] We also note that the Petition states that FDA is not precluded from providing a "formal decision" on the cbdMD product. To the extent the Petition considers a "formal decision" on an NDIN to be equivalent to a final agency action, we disagree that FDA responses to NDINs constitute final agency action.

standard for dietary supplements is met (even if the product is excluded from the definition of a "dietary supplement"). This would seem to be a reiteration of the request that FDA exercise enforcement discretion, which as discussed above is not properly the subject of a citizen petition. Accordingly, we deny the request for the above-stated reasons.

With respect to the Petition's contention that "submitting cbdMD's confidential data to [FDA] without the guarantee that it will be reviewed and appropriately replied to does nothing other than expose cbdMD to the risk of disclosure of the data along with potential misrepresentations of the data without any benefit to cbdMD," the Petition seems to suggest that: (1) FDA will inappropriately disclose and misrepresent data we receive in an NDIN submission; and (2) FDA should reply to an NDIN submission in the manner that the notifier feels is appropriate so as to confer a "benefit" on the notifier. Beginning with the first point, FDA's obligations with respect to disclosure are the same for all NDIN submissions, regardless of whether our response addresses the safety data. Under section 413(a)(2) of the FD&C Act, FDA "shall keep confidential any information provided" in an NDIN "for 90 days following its receipt." The implementing regulation in 21 CFR 190.6(e) provides that FDA will "not disclose the existence of, or the information contained in, an NDI notification for 90 days after the filing date of the notification." Section 190.6(e) of the FD&C Act further provides that after the 90th day, the entire notification, except trade secrets and confidential commercial information, will be placed on public display, as prescribed in section 413(a) of the FD&C Act. Thus, FDA is required by law to protect any confidential commercial and trade secret information that is submitted in NDINs, and this requirement applies irrespective of whether a product is excluded from the dietary supplement definition and irrespective of whether FDA agrees with a particular company's safety conclusions. To the extent that the Petition suggests that FDA will disclose confidential data, that suggestion is without merit because FDA is required by law to protect confidential commercial and trade secret information. The Petition does not provide any evidence that FDA has not acted in accordance with this legal obligation. With respect to the Petition's suggestion that FDA will engage in "potential misrepresentations," the Petition also provides no substantiation for this assertion.

Regarding the second point, to the extent the Petition argues that the submission of CBD-related NDINs (or of cbdMD's NDIN in particular) is unlikely to confer any "benefit" on the notifier because FDA is likely to find that the CBD product is excluded from the dietary supplement definition (in which case FDA's response might not include an assessment of the submitted safety data), the NDIN process is not designed or required to confer "benefits." Furthermore, the Petition does not identify any legal obligation for FDA to analyze an NDIN's safety data when the relevant ingredient or product cannot legally be marketed as a dietary supplement. If cbdMD does not anticipate that they will benefit from the submission of an NDIN for a product that they think is likely to be excluded from the dietary supplement definition, then it is their prerogative not to bring such a product to market (and therefore not to submit such an NDIN).

The Petition argues that cbdMD's safety data "can only be reviewed and replied to if [FDA] changes course from its present practice of refusing to provide a substantive review and reply of safety data of NDINs concerning CBD – even after [FDA] has specifically requested such data" (Petition at page 11). However, the NDIN process is not the only way to submit data to FDA regarding the safety of CBD. As discussed above, we have established and left open a docket

specifically to receive such data and information, and this is an option cbdMD may choose to pursue. We also frequently grant requests for meetings to discuss CBD safety data.

Other Assertions

Also in the "STATEMENT OF GROUNDS" section of the Petition, the Petition asks that FDA review a cbdMD submission utilizing "the proper analysis applied to dietary supplements" (Petition at page 14). For the reasons stated above, we cannot agree to issue any particular kind of response to a submission that we have not yet received. Thus, to the extent that this argument about the standard FDA should apply to a cbdMD submission constitutes a separate requested action, we deny this request. However, we also take note of the misguided implication that FDA is applying the "wrong" safety standard to its review of CBD products. The Petition states that NPA's "review of the previously submitted NDINs demonstrates that the safety data requirements imposed by [FDA] relative to CBD differ from what has been required for other supplements and is akin the requirement [sic] for drug approval" (Petition at pages 11 through 12). The Petition argues that this is inappropriate, as "an NDIN need only present threshold evidence showing that the dietary ingredient is reasonably expected to be safe under the supplement's labeled conditions of use" (Petition at page 12). The Petition requests that FDA "review, consider, and issue a formal decision concerning cbdMD's safety and identity data utilizing the proper analysis applied to dietary supplements" (Petition at page 14). The Petition also requests that, even if FDA denies the request to review cbdMD's safety data and respond thereto, FDA "should acknowledge that FDA's overly rigorous safety data requirements for CBD have no basis in the [FD&C] Act" (Petition at page 13). But the Petition does not provide any evidence that FDA has applied the incorrect safety standard in evaluating CBD products. The sole citation the Petition provides to support this assertion is an excerpt from a scientific article written by scientists who are not FDA employees stating that "cannabis-containing consumer products have not undergone the type of drug safety and efficacy testing that was performed with Epidiolex or Marinol."[45] The article does not discuss what standard should be applied to these consumer products, nor does it reflect any FDA policies or procedures. To the extent the Petition appears to be referring to FDA's response to two NDINs submitted for full spectrum hemp extract (NDI 1199 and NDI 1202),[46] the Petition is incorrect that FDA's response looked to the "wrong" safety standard, as those response letters expressly cited to and considered the safety standard described in section 413(a)(2) of the FD&C Act. The Petition's assertions are therefore unsupported.

Should cbdMD or another company wish to submit an NDIN that refers to a CBD-containing product pursuant to 21 CFR 190.6, we would review and respond pursuant to our current procedures. Regarding what safety information cbdMD should include in a potential NDIN,

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[45] See Petition at page 12 (citing Bobst S., et al., ToxPoint: Toxicology Studies on Δ9-tetrahydrocannabinol and Cannabidiol-containing Products Available to Consumers Are Lacking, *Toxicological Studies,* Volume 178, Issue 1, November 2020. Available at https://doi.org/10.1093/toxsci/kfaa135).

[46] See Letter to Irwin Naturals from Cara Welch, Acting Director, Office of Dietary Supplement Programs (ODSP), CFSAN, dated July 23, 2021, available at www.regulations.gov (Docket ID: FDA-2021-S-0023-0050). See also Letter to Charlotte's Web Inc. from Cara Welch, Acting Director, ODSP, CFSAN, dated July 23, 2021, available at www.regulations.gov (Docket ID: FDA-2021-S-0023-0053). These response letters identified significant safety concerns with the products that were the subject of the notifications, such as how the information provided did not adequately address certain reported toxicity endpoints of CBD such as hepatotoxicity and reproductive toxicity.

there is information on this topic readily available on our website for its consideration.[47] If FDA concludes that the subject of a future NDIN is excluded from the dietary supplement definition, our response will state that. In such a situation, it is at FDA's discretion to decide whether to nonetheless address any of the safety data that is included in the NDIN.

We also disagree with the statement that our requirements for demonstrating the safety of hemp-derived products are a "moving target" (Petition at page 12). The Petition cites no evidence or examples to substantiate this assertion.

We disagree with the Petition's assertion that declining to review safety data of NDINs concerning CBD "incentivizes bad actors to avoid following the rules because they know that FDA currently has no intention of acknowledging CBD under an NDIN or taking action to remove otherwise unsafe products from the market" (Petition at page 11). As stated above, we have concluded that CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act and accordingly it is unlawful under the FD&C Act to market CBD products as, or in, dietary supplements. We have taken targeted actions to protect the public health in connection with CBD products, and we will continue to do so as we see fit and as resources allow.[48] We retain discretion as to whether to comment on safety data when we conclude that a product is excluded from the definition of a dietary supplement, and we will continue to evaluate each NDIN submission we receive regarding a CBD product on a case-by-case basis. Our approach to NDINs for CBD-containing products is in alignment with our authority, as provided in the FD&C Act and its implementing regulations.

C. Request No. 3: FDA should issue a regulation finding that CBD is a lawful dietary ingredient

The Petition asks that, in the alternative, we "recommend and support to the Secretary of HHS, that, in his discretion, he issues a regulation, after notice and comment, finding that CBD would be lawful under the [FD&C] Act" (Petition at page 15; see also Petition at page 2). The Petition does not offer any explanation for why such a rulemaking would have merit, but rather suggests that FDA has previously said that we "will possibly issue a regulation to create a pathway to market for CBD and possibly other cannabinoids in dietary supplements and conventional foods" (Petition at page 14).

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. One relevant

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

[48] See, e.g., Warning Letter to Shelle Rogers, CEO, Kingdom Harvest, from Donald Ashley, Director, Office of Compliance, Center for Drug Evaluation and Research, Neal Bataller, Director, Division of Drug Compliance, Office of Surveillance & Compliance, Center for Veterinary Medicine, and Ann M. Oxenham, Director, Office of Compliance, CFSAN, dated May 4, 2022, available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kingdom-harvest-625058-05042022. 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.

consideration for undertaking such a rulemaking to permit an article to be used in a dietary supplement is whether FDA has identified safety concerns with the article.

Here, the Petition has not offered any reasoned explanation for why FDA should undertake a rulemaking under section 201(ff)(3)(B) of the FD&C Act. The Petition has not proffered any evidence suggesting that CBD articles satisfy the relevant safety standards under the FD&C Act,[49] nor has it offered any other justification for the proposed rulemaking. The only suggestion as to why a rulemaking may be appropriate is the Petition's assertion that FDA has previously stated that we would "possibly" undertake such a rulemaking (Petition at page 14). This is not a sufficient basis to support your request, and we note that FDA has *not* committed to such a rulemaking.[50]

With respect to whether the safety profile of CBD would counsel in favor or against such a rulemaking, 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.[51] 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.[52] 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.[53] However, dietary supplements are not subject to the same

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[49] While the Petition does assert that cbdMD has invested in safety studies, the Petition does not provide the full results of such safety studies and, importantly, the Petition does not provide evidence about the safety profile of CBD generally.

[50] The "Regulatory History of CBD" section of this letter explains that FDA has not committed to undertake rulemaking under section 201(ff)(3)(B) of the FD&C Act.

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

[52] 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.

[53] 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

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 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.

For all these reasons, we deny your request that we initiate a rulemaking under section 201(ff)(3)(B) of the FD&C Act.

III. Conclusion

After reviewing the information submitted in your petition, we have decided to neither: (1) determine that CBD is not excluded from the definition of a dietary supplement under section 201(ff)(3) of the FD&C Act; (2) exercise enforcement discretion as requested; nor (3) initiate the process to promulgate a regulation, after notice and comment, finding that CBD is lawful under the FD&C Act.

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

Sincerely,

Douglas W. Stearn -S

Digitally signed by Douglas W. Stearn -S
Date: 2023.01.26 07:30:53 -05'00'

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

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."