January 26, 2023

Steve Mister
Megan Olsen
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1828 L Street, NW, Suite 810
Washington, D.C. 20036-5114

Re: Docket No. FDA-2020-P-1582

Dear Mr. Mister and Ms. Olsen:

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

1. "Exercise FDA's statutory authority and discretion 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") to "issue a regulation finding that hemp-derived [cannabidiol (CBD)] is a lawful dietary ingredient";
2. "Provide guidance clarifying when a substance is considered an "article" as that term is used in [section 201(ff)(3)(B) of the FD&C Act]"; and
3. "Enforce existing dietary supplement regulations already promulgated in the [FD&C Act] and Title 21 of the Code of Federal Regulations (CFR) with respect to hemp-derived CBD products being marketed as dietary supplements."

See Citizen Petition from Council for Responsible Nutrition (CRN), dated June 16, 2020, ("Petition") at pages 1 and 3.

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 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.[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]

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.[4] 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

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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.
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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).

[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] 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.

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").[5] 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,[6,7] 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.[8] 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.[9] 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,[10] statements on FDA's website,[11] and in communications with individual firms.

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[5] 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.

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

[7] 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.)

[8] 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.

[9] 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.

[10] 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.

[11] 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.

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.[12] 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.[13] 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").[14] 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.[15] 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.[16] 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.[17] The first priority of the high-level

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[12] 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.

[13] 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.

[14] 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.

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

[16] 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."

[17] 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-

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.[18] 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.[19]

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.[20] Numerous public statements from FDA similarly made this clear.[21] 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,[22] we also made

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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.

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

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

[20] 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.

[21] 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").

[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,

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.[23] 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.[24] At this time, having now gathered and reviewed a substantial amount of data and other information about the safety of CBD, we have developed serious concerns about the safety of CBD[25] 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.

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").

[23] 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").

[24] 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").

[25] In addition to the communications described in footnote 24, 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.

A. Request No. 1: FDA should issue a regulation finding that hemp-derived CBD is a lawful dietary ingredient

The Petition states that FDA has "explicit authority to promulgate a regulation finding that dietary supplements containing CBD may be lawfully marketed under the [FD&C Act], despite its use first as a drug" (Petition at page 2). The Petition claims that "FDA has stalled…in allowing CBD's use in dietary supplements," even though "Congress and industry have repeatedly requested that FDA use this authority to allow CBD to be a legal ingredient in dietary supplements" (Petition at page 2).[26] The Petition states that the exclusion clause "is a 'race-to-market' provision designed to help protect drug development, if a drug is approved (or substantially investigated) before a substance is marketed as a dietary ingredient" and states that "dietary supplement companies could not even enter the race until December 2018 when Congress removed hemp from the Federal Controlled Substances Act – well after CBD was being studied and approved as a drug ingredient" (Petition at page 2). The Petition asserts that "[b]y not acting to create a regulatory framework for CBD in dietary supplements, FDA is, in effect, creating a sweeping monopoly over CBD for drug use," that this "is not what Congress intended, in general, and particularly in this circumstance," and "that further delay on FDA's part continues to harm both consumers and the industry" (Petition at pages 4 through 5). The Petition argues that "[t]he action we request in this Petition will help ensure public safety and spur innovation and economic development for this already burgeoning industry" (Petition at page 3). Inaction, however, "currently, and in the future if [FDA] declines to promulgate a regulation, creates a public health concern in its own right," as "[o]ver 20 million Americans already take CBD dietary supplements" (Petition at page 8).

Furthermore, the Petition asserts that the exclusion clause "makes no mention of establishing a safe level for the 'article', which underscores the fact that the provision was inserted into [DSHEA] to balance the economic interests of pharmaceutical manufacturers with the dietary supplement market" (Petition at page 5). The Petition states that "Congress relied that FDA would be able to invoke the safety standards for dietary supplements otherwise in DSHEA [cite omitted] with respect to specific individual products *after* the initial balancing of economic interests had occurred under section 321(ff)(3)(B)" of the FD&C Act (Petition at page 5) (emphasis in original).

The Petition states:

> [A] safe level of CBD does not need to be predetermined before the rulemaking process can commence, as the regulatory framework already exists to ensure the safety of a dietary supplement through other statutory provisions and regulations <u>after</u> the rulemaking addressing the definitional objection is completed.

[26] The Petition states that it "does not address the legal status of other hemp constituents," although it states its concern that "FDA's continued inaction on CBD could put these ingredients in jeopardy as supplement companies grabble [sic] with how CBD's legal status affects the use of other constituents" (Petition at page 4, footnote 6). As this comment is outside the scope of CRN's request, FDA will not address it in this response except to note that we analyze whether a particular product fits within the definition of a dietary supplement on a case-by-case basis.

Petition at pages 5 through 6 (emphasis in original).

The Petition claims that "safety is intended to be addressed on a product-specific basis in the framework already carefully laid out by Congress and the FDA. This framework permits FDA to address safety in the context of each unique delivery form, ingredient matrix…, dosage, labeling and directions for use, and other unique considerations for each product," as "each unique manufacturer of…[a] CBD-containing ingredient would be required to file its own new dietary ingredient notification" (Petition at page 6).

Furthermore, the Petition argues that "it has become clear that safety data do exist that at least "**some level**" of CBD is safe" (Petition at page 6) (emphasis in original). It asserts that, in contrast to FDA, other regulatory bodies, such as the United Kingdom's Food Standards Agency (FSA) and the Australian Therapeutic Goods Administration (TGA), have "come to safety conclusions that allow consumers access to safe, beneficial health products up to specific daily levels" (Petition at page 6). The Petition states that CRN "commissioned its own assessment of the publicly available literature to add to the growing body of evidence demonstrating a safe level of CBD" (Petition at page 7).[27,28] Finally, the Petition points to "scientific experts who have recognized that data do exist to determine that hemp extracts containing CBD can be Generally Recognized as Safe (GRAS)" (Petition at page 7).

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 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.

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.[29] 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.[30] The FDA has not found adequate information showing how much CBD can be

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[27] The Petition states that CRN will be submitting this safety information to FDA (Petition at page 7, footnote 13), and we acknowledge that, in June 2020, CRN submitted data to the public docket that we established to obtain scientific data and information concerning CBD. Available at https://www.regulations.gov/document/FDA-2019-N-1482-4364.

[28] The Petition also points to other companies who have published scientific studies and analysis that purportedly contribute evidence that can be used to determine that a safe level of CBD exists (Petition at page 7).

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

[30] See, e.g., Ewing, L.E., et al., Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model, *Molecules*, 2019;24(9):1964; Kocis, P.T., Vrana, K.E., Delta-9-Tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions, *Medical Cannabis and Cannabinoids*, 2020;3:61-73. doi: 10.1159/000507998; Carvalho, R.K., et al., The effects of cannabidiol on male reproductive system: A literature review, *Journal of Applied Toxicology*, 2020; *40*:132-140; https://doi.org/10.1002/jat.3831; Carvalho, R.K., et al., Chronic exposure to cannabidiol induces

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.[31] 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 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.

The Petition asserts that a safe level of CBD does not need to be "predetermined" before FDA undertakes a rulemaking. But the Petition fails to explain why a rulemaking would be justified if safety problems exist. By statute, dietary supplements cannot be marketed unless they meet the relevant safety standard in the FD&C Act, and the Petition does not dispute that unsafe dietary supplements are unlawful. Instead, the Petition maintains that CBD *can* be safe in dietary supplements. Specifically, the Petition points to four sources of information to support the assertion that at least some level of CBD in dietary supplements is safe. However, for the reasons identified below, we find this evidence unavailing:

Source 1: A survey of publicly available literature commissioned by CRN concludes that 40 mg per day is a safe level.[32]

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reproductive toxicity in Swiss mice, *Journal of Applied Toxicology*, 2018;38:1215-1223 https://doi.org/10.1002/jat.3631; Huestis, M.A., et al., Cannabidiol Adverse Effects and Toxicity, *Current Neuropharmacology*, 2019;17:974-989.

[31] 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."

[32] As stated in the Petition, CRN submitted this assessment to the FDA's docket, Docket No. FDA 2019-N-1482, available at https://www.regulations.gov/comment/FDA-2019-N-1482-4364.

FDA's response: The petitioner, based on a CRN-commissioned assessment (CRN assessment) of the literature, proposes that 40 milligrams (mg) per day intake of CBD is a safe level. FDA has determined that the CRN assessment does not provide adequate information to demonstrate the safety of CBD at a proposed level of 40 mg/day. An acceptable daily intake level is typically based on an evaluation of toxicological studies to determine the highest appropriate experimental exposure dose level in animal studies that was shown to cause no adverse effect (i.e., no observed adverse effect level, or NOAEL), multiplied by appropriate uncertainty factors. Accordingly, the lower the NOAEL for a specific substance, the lower the resulting acceptable daily intake level for the substance. The higher the NOAEL, the higher the resulting acceptable daily intake level. To establish this proposed daily intake level, the CRN assessment cites to a NOAEL. Specifically, the CRN assessment relies on a NOAEL derived from a developmental toxicity study completed in rabbits. However, neither the Petition nor the CRN assessment explain why this is the appropriate NOAEL. Importantly, neither the Petition nor the CRN assessment address why other studies with lower[33] or no[34] NOAELs were not factored into the NOAEL determination. Generally, animal bioassays are evaluated to determine risk of harm from a chemical, with NOAELs selected based on the most sensitive critical endpoint in the most sensitive mammalian species which results in an effect relevant to humans.[35] By disregarding the additional studies that suggest more sensitive thresholds, the CRN assessment does not extrapolate from the most sensitive endpoint. Moreover, the CRN assessment does not adequately support why these additional studies were excluded from the NOAEL selection. Indeed, there is ample evidence that CBD has been shown to have more sensitive deleterious effects during development,[36] as well as in multiple organ systems including the liver[37,38] and reproductive system[33,34] in both humans and animals.

In addition to not supporting the selected NOAEL, the CRN assessment then fails to extrapolate from the selected NOAEL in a scientifically justified manner. While the CRN assessment applies a default value for intraspecies variation and an alternative factor for interspecies variation, it applies no other uncertainty factors. This is a shortcoming because the uncertainty factors applied fail to adequately account for other considerations, such as CBD interactions with biological targets, and differences in absorption, distribution, metabolism, and excretion between animals and humans. Furthermore, the CRN assessment failed to consider long-term (chronic)

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[33] Carvalho RK, et al., Chronic exposure to cannabidiol induces reproductive toxicity in male Swiss mice, *Journal of Applied Toxicology*, 2018;38:1215-1223.
[34] Rosenkrantz H, et al., Toxicity of short-term administration of cannabinoids to rhesus monkeys, *Toxicology and Applied Pharmacology*, 1998;58:118-131.
[35] National Research Council, Science and Decisions: Advancing Risk Assessment (2009). National Academies Press (US);193-205; available at http://nap.nationalacademies.org/12209.
[36] European Medicines Agency, Assessment report, Epidyolex. EMA/458106/2019. Available at https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf. Accessed November 14, 2022
[37] Ewing LE, et al., Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model, *Molecules*, 2019;24(9):1694.
[38] Watkins, et al. Cannabidiol and Abnormal Liver Chemistries in Healthy Adults: Results of a Phase I Clinical Trial, *Clinical Pharmacology & Therapeutics,* 2020;1224-1231.

toxicity testing results that would ordinarily require the application of an additional uncertainty factor.[39,40]

Separate and apart from the appropriateness of the selected NOAEL and uncertainty factors, the CRN assessment dismisses known CBD-drug interactions.[41,42] CBD inhibits multiple cytochrome P450s, the major family of enzymes involved in drug metabolism, particularly CYP3A4, which comprises up to 60% of total hepatic cytochrome P450 proteins. It is pivotal in the metabolism of an extensive range of both endogenous compounds and xenobiotics, and metabolizes over 50% of marketed drugs, including statins.[43,44,45] CBD's interaction with this enzyme raises serious concerns of adverse drug-drug interactions.[45,46]

Based on this information, we do not agree that the CRN assessment demonstrates that 40 mg/day of CBD is a safe level, nor has CRN shown that this level satisfies the relevant safety standard for dietary supplements under the FD&C Act.

Source 2: A review by the Australian Therapeutic Goods Administration (TGA)[47] concludes that CBD "presents a good safety and tolerability profile at the low dose range of under 60 mg/day" and that "there were potential conditions for low dose cannabidiol that would not require oversight by a medical practitioner." CBD oil has been legal in Australia since 2016; however, the only currently available CBD products are classified as Schedule 4 drugs. This means they can only be legally obtained via a doctor's prescription filled at a pharmacy. In December 2020, the TGA announced a down scheduling to Schedule 3 for low dose isolate-only CBD products. However, Schedule 3 CBD products would need to first be listed on the Australian Register of Therapeutic Goods. Because of the stringent requirements, there are still no CBD products available for purchase in this category.[48]

FDA's response: The Australian TGA is not charged with considering the dietary supplement safety standards under the FD&C Act, and therefore this review does not reflect a determination that CBD products may meet the dietary supplement safety standards in the FD&C Act. In addition, the review includes important caveats, such as the statement that "although it was

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[39] Dorne JL, Renwick AG, The refinement of uncertainty/safety factors in risk assessment by the incorporation of data on toxicokinetic variability in humans, *Toxicological Sciences*, 2005;86(1):20-26.
[40] Schilter B, et al., Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements, *Food and Chemical Toxicology*, 2003;41:1625-1649.
[41] Gatson et al., Interactions between cannabidiol and commonly used antiepileptic drugs, *Epilepsia*, 2017;58(9):1586–1592.
[42] Doohan et al., Cannabinoid interactions with cytochrome P450 drug metabolism: a full-spectrum characterization, *AAPS Journal*, 2021;23(4):91.
[43] Wang, et al., Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs, *The Pharmacogenomics Journal*, 2011;11:274-286.
[44] Kacevska M, et al., Inflammation and CYP3A4-mediated drug metabolism in advanced cancer: impact and implications for chemotherapeutic drug dosing, *Expert Opinion on Drug Metabolism and Toxicology*, 2008;4:137–149.
[45] Zanger UM, Schwab M., Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation, *Pharmacology and Therapeutics*, 2013;138:103–141.
[46] Brown JD, Winterstein AG., Potential adverse drug events and drug–drug interactions with medical and consumer cannabidiol (CBD) use, *Journal of Clinical Medicine*, 2019;8:989.
[47] See https://www.tga.gov.au/sites/default/files/review-safety-low-dose-cannabidiol.pdf#_blank.
[48] See https://www.auscannabisclinics.com.au/buy-cbd-oil-australia.

evident that there is a high potential for drug-drug interactions when used concomitantly with many other commonly prescribed drugs that are metabolized via CYP pathways. Currently there is insufficient evidence as to whether these would not occur with the use of low dose CBD." Furthermore, the review finds that it would be suitable to consider "down scheduling" CBD to a "schedule" that in the Australian system "requires interaction with a pharmacist that would further reduce any unintended drug-drug interactions." By contrast, the dietary supplement regulatory regime in the United States does not require interaction with pharmacists; thus, consumers in the United States would not have the same protection contemplated by this review. For these reasons, we conclude that the Australian TGA review does not demonstrate that CBD products would satisfy the relevant safety standard for dietary supplements under the FD&C Act.

Source 3: A notice issued by the United Kingdom's Food Standards Agency (FSA)[49] announces a deadline for CBD businesses to provide information about CBD products and their contents, recommends that "healthy adults" take no more than 70 mg/day of CBD, and advises "vulnerable groups" not to take CBD. The "vulnerable groups" who are advised not to take CBD are "those who are pregnant, breastfeeding or taking any medication."

FDA's response: The UK FSA is not charged with considering the dietary supplement safety standards under the FD&C Act, and therefore this notice does not reflect a determination that CBD products may meet the dietary supplement safety standards in the FD&C Act. With respect to the advisory regarding a 70 mg/day limit on CBD for "healthy adults," we note that the FSA has not determined 70 mg/day to be safe and states "this doesn't mean that these levels are definitely safe, but that the evidence we have suggests adverse health effects could potentially be seen above this."[50] As such, it recommends healthy adults not to exceed this amount while also advising such healthy adults to "think carefully before taking any CBD products."[51] With respect to the advisory that "vulnerable groups" avoid CBD altogether, we find it notable that these groups encompass not only those who are pregnant and breastfeeding, but also all adults who take *any* medication. For these reasons, we conclude that the UK FSA notice does not demonstrate that CBD dietary supplements would satisfy the relevant safety standard for dietary supplements under the FD&C Act.

Source 4: The Petition cites "recently published scientific studies and analysis" as evidence in support of the claim of an existing safe level of CBD.[52,53,54,55]

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[49] See https://www.food.gov.uk/news-alerts/news/food-standards-agency-sets-deadline-for-the-cbd-industry-and-provides-safety-advice-to-consumers#_blank.
[50] Food Standards Agency. Cannabidiol (CBD). May 9, 2022. Available at https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd (accessed November 3, 2022).
[51] See https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd (accessed July 14, 2022).
[52] Dziwenka, et al., Safety Assessment of a Hemp Extract Using Genotoxicity and Oral Repeat-Dose Toxicity Studies in Sprague-Dawley Rats, *Toxicology Reports* 2020;7:376-385.
[53] Lopez et al., Effects of Hemp Extract on Markers of Wellness, Stress Resilience, Recovery and Clinical Biomarkers of Safety in Overweight, but Otherwise Healthy Subjects, *Journal of Dietary Supplements*, 2020;17(5):561-586.
[54] Schmitz et al., Post Marketing Safety of Plus CBD Products, a Full Spectrum Hemp Extract: A 2-Year Experience, *Journal of Dietary Supplements*, 2020;17(5):587-598.
[55] Chesney et al., Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials, *Neuropsychopharmacology*, 2020;45:1799-1806.

FDA response: The Petition cites to these studies as "further contributing evidence that can be used to determine that a safe level of CBD exists." While we do not dispute these studies add to the universe of published information evaluating the safety of CBD, these studies have limitations[56,57,58,59] with respect to serving as a basis for establishing a safe CBD level. Three of the studies were conducted with different hemp extracts containing CBD and other compounds, not with CBD isolate. Therefore, it is unclear how the effects from these different materials can be compared to each other or be extrapolated more broadly to CBD. The complexity of CBD in a mixture may result in different adverse effects when compared with CBD isolate, and those uncertainties must be considered. In addition, the fourth study does not serve to identify a safe level of CBD. For these reasons, these studies do not demonstrate that CBD products would satisfy the relevant safety standard for dietary supplements under the FD&C Act.

Thus, the Petition does not change our assessment that the accumulating evidence about CBD suggests that there are considerable safety concerns with the potential use of CBD as a dietary supplement.

In addition to these assertions that CBD may be safe, the Petition also appears to assert that it is statutorily impermissible for FDA to weigh safety considerations in determining whether to undertake a rulemaking under section 201(ff)(3)(B) of the FD&C Act. Specifically, the Petition states that the provision "makes no reference to a scientific evaluation" (Petition at page 5) and that the purpose of this provision is to "protect commercial interests necessary to incentivize drug development" (Petition at page 4). Similarly, the Petition argues that "the statutory provision makes no mention of establishing a safe level for the 'article', which underscores the fact that the provision was inserted into the Dietary Supplement Health and Education Act (DSHEA) to balance the economic interests of pharmaceutical manufacturers with the dietary supplement market" (Petition at page 5). As support for the Petition's explanation of the purpose of the 201(ff)(3)(B) exclusion provision, the Petition cites to "S. Rep. 103-410, Part V, § 3 (1994); 140 Cong. Rec. S11,709 (daily ed. Aug. 13, 1994)," but does not identify a specific

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[56] Dziwenka et al., 2020 is a non-clinical study that evaluated the toxicity of hemp extract in Sprague-Dawley rats. The results demonstrate that the hemp extract test article induced clinical effects that included dose-dependent decreases in body weights, reduced food consumption and changes in activity of male rats. Additionally, hepatocellular hypertrophy was observed in both males and females but was accompanied by dose-dependent increases in absolute liver weight in females.

[57] Lopez et al., 2020 is a study on the effects of CBD-containing hemp oil in an overweight but healthy cohort in a 6-week randomized clinical trial. This trial had several limitations, such as a small sample size, a nonrepresentative cohort of overweight individuals, a single dose of CBD-containing hemp oil per day (i.e., not a dose-response study), and a 6-week duration which does not represent long-term exposure to CBD.

[58] Schmitz et al., 2020 is a post-market surveillance of full spectrum hemp extract under the brand PlusCBD™ manufactured by CV Sciences conducted over a two-year period. However, the surveillance data does not include CBD amount, frequency of exposure, or concomitant medication use per reported adverse event. Furthermore, data in a post-market surveillance is qualitative in nature, fails to represent chronic exposure, and cannot be used in lieu of a randomized controlled clinical trial to support a safe level of CBD.

[59] Chesney et al., 2020 is a systematic review and meta-analysis of the double-blind randomized clinical trials that investigated the safety profile of CBD. Of note, the analysis found that across all doses of CBD, there were more study withdrawals in the CBD groups compared with placebo groups and the likelihood of withdrawals was dose dependent. Additionally, the analysis found that CBD was associated with increased adverse events, which were strongly related to CBD doses. However, the authors exclude subjects taking concomitant medications which limits the applicability of the conclusion to a broader population using medicines (see note 11, 12). This study does not allow the determination of a safe level of CBD.

supporting passage in the Senate Report. A careful review of the legislative history of DSHEA indicates that Congress 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. Congress 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.[60] Thus, while it appears that Congress did consider drug development incentives in enacting the section 201(ff)(3)(B) exclusion provision, it also appears that Congress weighed regulatory oversight considerations.

With respect to the Petition's assertion that safety can be addressed post-rulemaking through the NDIN process, we disagree that the NDIN process would provide sufficient safeguards. The Petition's argument is that safety should be addressed on a case-by-case basis via NDINs. The Petition maintains that the information that would be included in NDINs would facilitate informed decision making. However, we do not agree that the NDIN process would sufficiently protect the public from CBD-containing products. 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

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[60] 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.
>
> 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).

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.

Because of the safety concerns expressed above, we would anticipate that NDINs that would be submitted for CBD-containing products 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.

Furthermore, the Petition suggests that refraining from rulemaking would contravene the purpose of the 2018 Farm Bill. We disagree. While the 2018 Farm Bill removed restrictions for "hemp" under the CSA, the Farm Bill did not remove the exclusion clause in section 201(ff)(3)(B) of the FD&C Act. Indeed, the 2018 Farm Bill explicitly preserved FDA's authorities. While individual members of Congress have subsequently expressed a range of views on this topic, the relevant statutory language has not been superseded.

The Petition also appears to assert that there is an injustice in FDA applying section 201(ff)(3)(B) of the FD&C Act to CBD, because according to the Petition, the pre-2018 status of "hemp" as a controlled substance restricted firms from marketing CBD as a food or dietary supplement and therefore companies were unable to avail themselves of the prior marketing exception to section 201(ff)(3)(B) of the FD&C Act. As discussed above, the 2018 Farm Bill explicitly preserved FDA's authorities and did not direct FDA to exercise its rulemaking authority under section 201(ff)(3)(B) of the FD&C Act. [61]

We also disagree with the Petition's suggestion that lack of rulemaking will create safety risks for consumers. The Petition asserts that by not undertaking rulemaking, we are "creating a market which many current, knowledgeable supplement companies are hesitant to enter, and in which FDA oversight is limited," with newer companies that "may not understand" dietary supplement regulations "producing questionable and even dangerous products" (Petition at page 8). But just because some companies may act in disregard of the law, that is not a basis for FDA to promulgate a rule under section 201(ff)(3)(B) of the FD&C Act. Furthermore, we have undertaken many activities to address unlawful CBD products and protect public health, for example, by sending warning letters to firms that sell violative CBD products and alerting the public to safety concerns, all while prioritizing our oversight to focus on products with the

[61] The Petition also argues that the application of section 201(ff)(3)(B) of the FD&C Act to CBD results in a "sweeping monopoly over CBD for drug use" (Petition at page 4). We disagree that the exclusion clause creates any impermissible "monopoly." The drug authorization pathway is open to all firms who choose to avail themselves of it. Thus, the FD&C Act does not prevent economic competition in the marketplace. To the extent that the Petition takes issue with the legal effect of section 201(ff)(3)(B) of the FD&C Act (i.e., the effect of excluding certain articles from the dietary supplement category), we note that this effect is not specific to CBD. Other articles that have been approved as a new drug and/or studied as new drugs are also subject to section 201(ff)(3)(B) of the FD&C Act.

greatest health risks.[62]

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

B. Request No. 2: Provide guidance clarifying when a substance is considered an "article" under section 201(ff)(3)(B) of the FD&C Act

The Petition asserts that "FDA has provided almost no clarity on when a substance would be considered the same 'article' as a drug" and argues that "[h]emp extract with CBD is a very different substance from [sic] CBD isolate found in Epidiolex" (Petition at pages 8 and 9). CRN goes on to state that the lack of guidance has left "companies with little understanding of whether CBD, in any form or amount, is permissible" and that the lack of clarity "includes whether broad spectrum hemp extracts that contain CBD among other constituents are also a precluded 'article' along with CBD isolate" (Petition at pages 8 through 9). According to the Petition, "[e]xtracts should be considered in their entirety, including the CBD component, because the behavior of the individual components depends on the extract's complexity and synergistic effects" and provides specific scenarios for FDA to consider (Petition at page 9). It thus appears that the Petition requests that FDA develop guidance addressing when products containing CBD may be subject to the exclusion in section 201(ff)(3)(B) of the FD&C Act and that the guidance interpret the exclusion provision to not encompass "broad spectrum hemp extracts" and other hemp products that include constituents in addition to CBD.

FDA does not at this time see a need to develop a guidance document of the type requested in the Petition. FDA has already provided information in multiple forums that address section 201(ff)(3)(B) of the FD&C Act,[63] and developing a hemp-specific guidance is not needed for FDA to provide regulatory clarity to firms. If there is any regulatory uncertainty, FDA encourages manufacturers to seek our feedback through the pre-notification and/or NDIN processes. For example, FDA already meets with potential notifiers who wish to ask questions and get preliminary, non-binding responses in connection with submitting an NDIN and issues

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[62] See https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products.

[63] See, e.g., Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues, at pages 42 through 44 (August 2016). This guidance document is currently in draft form. To date, FDA has received several NDINs related to hemp-derived products, and consistent with the process provided in the statute and FDA's regulations, we have made our responses publicly available. These responses may be of assistance to firms seeking to understand FDA's evaluation of other products. See https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/submitted-75-day-premarket-notifications-new-dietary-ingredients. Furthermore, FDA has addressed the exclusion clause in responses to citizen petitions. See e.g., 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, at pages 2 through 4 and 16 through 18, available at https://www.regulations.gov/document/FDA-2021-P-0938-0030 and Letter from Michael A. Chappell, Acting Associate Commissioner for Regulatory Affairs, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP responding to Citizen Petition FDA-2005-P-0259 submitted on behalf of Biostratum, Inc. (Jan. 12, 2009), at pages 3 through 6, available at https://www.regulations.gov/document/FDA-2005-P-0259-0004. Court opinions about the scope of the exclusion provision are also publicly available. See *Pharmanex v. Shalala*, 221 F.3d 1151, 1154-60 (10th Cir. 2000).

related to identity, among other topics, may be discussed at these meetings.[64] Such individualized feedback allows for consideration of preliminary information that is unique to each product, which we believe manufacturers have found helpful. Accordingly, we decline to develop guidance as requested in the Petition. However, FDA remains committed to reviewing and providing feedback about these products.

C. Request No. 3: FDA should enforce existing dietary supplement regulations with respect to hemp-derived CBD-containing products being marketed as dietary supplements

The Petition requests that "FDA enforce existing dietary supplement regulations against CBD products that are marketed as dietary supplements," adding that "[i]f a company holds its products out to consumers as dietary supplements…the company should be held to all dietary supplement regulatory standards" (Petition at page 10). Specifically, the Petition states that these products should be subject to NDIN requirements for dietary supplements, as well as requirements for good manufacturing practices that are applicable to dietary supplements (Petition at page 10). The Petition states that "FDA's lack of action and enforcement to ensure that CBD products are regulated as dietary supplements has led states to step into the role that should belong exclusively to FDA…creating an inconsistent patchwork of regulations" and "consumer confusion will result" (Petition at page 10). Further, the Petition states that "Congress has provided FDA with additional funds for enforcement actions and CRN urges FDA to use these funds to help ensure the existing marketplace is safe for consumers by ensuring products labeled as dietary supplements meet supplement regulatory standards" (Petition at page 10).

To the extent the Petition is asking FDA to take enforcement actions against firms, 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).

To the extent the Petition is asking us to apply statutory requirements for dietary supplements to products that do not meet the definition of "dietary supplement," we deny the request because the Petition has not identified applicable legal authority that would support such a request. The statutory requirements that the Petition identifies, such as dietary supplement current good manufacturing practice (CGMP) requirements under section 402(g) of the FD&C Act (21 U.S.C. 342(g))[65] and NDIN requirements under section 413 of the FD&C Act, apply only to "dietary supplements" (and dietary ingredients used in dietary supplements). The Petition does not identify a legal basis on which FDA could require compliance with these statutory provisions if a product does not meet the definition of "dietary supplement."[66]

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[64] For information about pre-notification meetings, see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues.

[65] The implementing regulation for this CGMP authority can be found in 21 CFR part 111 and, by its terms, only applies to dietary supplement products and components of dietary supplement products.

[66] We acknowledge that we have published guidance that explains our intent to exercise enforcement discretion with respect to the sale and distribution of certain products that contain an ingredient, N-acetyl-L-cysteine (NAC), that are labeled as dietary supplements. This enforcement discretion policy applies to products that would meet the

We agree with your suggestion that FDA should use appropriated funds as directed by Congress, but your Petition does not indicate that FDA has misused appropriated funds – and indeed we are not aware of the dietary supplement program misusing appropriated funds.

III. Conclusion

After reviewing the information submitted in your petition, we have decided to neither: (1) exercise our authority to issue a regulation finding that hemp-derived CBD is a lawful dietary ingredient; (2) provide guidance clarifying when a substance is considered an "article" as used in section 201(ff)(3)(B) of the FD&C Act; nor (3) enforce existing dietary supplement regulations with respect to hemp-derived CBD products being marketed as dietary supplements.

Accordingly, for the reasons discussed 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 07:43:39 -05'00'

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

definition of "dietary supplements" if NAC were not excluded from the definition of "dietary supplement." See FDA's guidance for industry entitled "Policy Regarding N-acetyl-L-cysteine," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-policy-regarding-n-acetyl-l-cysteine. However, this enforcement discretion policy does not do for NAC what the Petition appears to ask FDA to do for CBD. That is, the enforcement discretion policy does not impose statutory requirements that are applicable only to "dietary supplements" on products that do not meet the definition of "dietary supplement."