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July 16, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: FDA's Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments. 84 Fed. Reg. 12969 - 12975 (April 3, 2019). Docket No. FDA-2019-N-1482.

The Council for Responsible Nutrition (CRN)[1], the leading trade association that represents dietary supplement and functional food manufacturers and ingredient suppliers, appreciates the opportunity to provide comments in response to the U.S. Food and Drug Administration's (FDA or agency) request for scientific data and information about products containing cannabis or cannabis-derived compounds. CRN is providing comments on FDA's regulation of the cannabis constituent – cannabidiol (CBD) – and its use in food and dietary supplements when it is derived from hemp (as that term is defined by the Agriculture Improvement Act of 2018 (2018 Farm Bill)).[2] CRN appreciates FDA's willingness to accept public comments from the dietary supplement and food industries on the regulation of CBD in these products.

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[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

[2] CRN recognizes that other ingredients derived from the hemp plant may be of interest to companies for use in food and supplements, as well as that other forms of cannabis (*i.e.*, forms with

As CRN noted at FDA's public meeting about cannabis and cannabis-derived compounds held on May 31, 2019 (hereinafter referred to as "May 31 Public Meeting"), FDA needs to act quickly and decisively to address the substantial market that has already developed for hemp-derived CBD products and ensure consumers, who have expressed strong interest in these products, have access to safe products.

The market for hemp-derived CBD products is expected to exceed over $500 million by the end of 2021.[3] Further, as attendees at FDA's May 31 Public Meeting learned, based on a recent survey by Consumer Reports, an estimated 64 million Americans (more than 25% of the U.S. population) have tried CBD within the past two years.[4]

CRN has heard FDA's concerns both about CBD's preclusion from food and supplements because of its use first in clinical drug investigations and whether it is safe for use in food and supplements. FDA has been given the tools to adequately and expeditiously address both. CRN strongly believes that these tools provide FDA the means to advance its public health mission by providing consumers access to safe products, while preserving the distinction between food, supplements, and drugs. As we will discuss in this comment, (1) FDA already has the authority to allow CBD use in food and supplements; (2) exercising this authority will provide FDA the flexibility to appropriately address safety in the fact-specific manner that the Food, Drug, and Cosmetic Act (FDCA) and FDA regulations intended; (3) authoritative reviews have found that CBD is likely safe when used by healthy adults and, as such, can be regulated by FDA like any other botanical ingredient; and (4) allowing CBD to be used in food and dietary supplements is unlikely to disincentivize drug research and development and, in fact, could stimulate research, which in turn would continue to improve public health.

CRN urges FDA to act quickly to put in place a regulatory framework to market CBD. This framework would squarely place CBD dietary supplement and food products under the same

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more than 0.3% tetrahydrocannabinol (THC)) may be studied for drug uses. CRN's comments, for the purposes of this letter, however, are limited in scope to the use of hemp-derived CBD in food and dietary supplements. Hemp is defined by the 2018 Farm Bill as all parts of the *Cannabis sativa L.* plant with 0.3% THC or less by dry weight. Agriculture Improvement Act of 2018, Pub. Law 115-334 (enacted Dec. 20, 2018).

[3] Presentation from Natural Products Expo West, Natural Products Hemp and CBD Summit, March 5, 2019, Clare Morton, New Hope Network, The CBD Business Opportunity, *available at*, https://www.newhope.com/sites/cet.com/files/expo-west-2019-hemp-cbd-summit-slides.pdf.

[4] Consumer Reports, *CBD Goes Mainstream CR surveyed more than one thousand CBD users nationwide to find out whether it's changing their lives – and how*, (April 11, 2019), *available at*, https://www.consumerreports.org/cbd/cbd-goes-mainstream/.

regulatory framework that thousands of other products are already safely sold and appropriately regulated by FDA, eliminating market confusion and ensuring that consumers have access to safe and quality CBD supplement and food products.

FDA Regulatory Framework Already Accounts for Safety – FDA Must Develop the Pathway to Access this Framework

FDA takes the position that CBD cannot be used in dietary supplements and food because of provisions in the FDCA that preclude a substance from being used in these products, if that substance was an "article" that (1) was "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;" and (2) "which was not before such . . . authorization marketed as a dietary supplement."[5] A similar provision of the FDCA precludes a substance from being used in food if it meets the criteria described above.[6] These provisions were enacted to protect commercial interests necessary to incentivize drug development,[7] not because of any safety concerns about the use of an ingredient in both dietary supplements/food, and drugs. FDA takes this position because the agency determined that CBD was the subject of substantial clinical investigations that were made public for and approved as a drug product (Epidiolex) prior to its use in supplements or food.[8]

Congress also gave FDA the discretion to issue regulations allowing an article to be used in a dietary supplement or food despite a determination that the substance was first used as a drug. Thus, the final clause of both the supplement and food drug preclusion sections of the FDCA recognize that circumstances would arise that would justify exceptions to the general presumption and allow "the Secretary, in the Secretary's discretion [to issue] a regulation, after notice and comment, finding that the article would be lawful . . . ."[9]

Nowhere in the statutory language or the legislative history of these provisions did Congress require or intend FDA to address the safety of dietary supplements or food when determining whether it should invoke its notice and comment rulemaking authority. The regulatory

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5 FDCA § 201(ff)(3)(B).

6 FDCA § 301(ll).

7 *See e.g.*, S. Rep. 103-410, Part V, § 3 (1994); 140 Cong. Rec. S11,709 (daily ed. Aug. 13, 1994).

8 FDA Guidance, FDA Regulation of Cannabis and Cannabis-Derived Products: Questions and Answer, last updated April 2, 2019, *available at*, https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers.

9 FDCA §§ 201(ff)(3)(B) and 301(ll).

framework already exists to ensure the safety of a dietary supplement or food through other statutory provisions and regulations.

Safety is intended to be addressed on a product-specific basis in the framework already carefully laid out by Congress and FDA. This framework permits FDA to address safety in the context of each regulatory channel (*e.g.*, dietary supplements versus food), unique delivery form, ingredient matrix (*e.g.*, CBD isolate versus hemp extract), dosage, and other unique considerations for each product. Trying to adopt an across-the-board safety determination for all dietary supplement and food products would likely be unworkable, is ill-fitted to the vast range of hemp-derived CBD products already on the market, would stifle innovation as new research about CBD emerges, and would not take into account the wide array of tools that FDA and dietary supplement and food companies have to ensure safety (such as delivery systems, dosage levels, cautionary labeling, etc.).

Under FDA's current position, unless the agency works to resolve the first issue (*i.e.,* creating a regulatory pathway outside of the drug preclusion provisions), FDA cannot even reach the question of safety. If a company submits safety data today, such as in the form of a New Dietary Ingredient (NDI) notification or Generally Recognized as Safe (GRAS) notice, for a hemp-derived CBD product, that submission will be turned away because the ingredient is not recognized by FDA as a legitimate dietary or food ingredient.

In fact, this has already occurred. For example, in an NDI hemp product submission filed in 2017, FDA objected to the submission, not for safety reasons, but because the product contained CBD, which FDA concluded was excluded from the dietary supplement definition under Section 201(ff)(3)(B) of the FDCA. The FDA letter specifically notes that the agency was "providing no response with respect to whether there is an adequate basis of safety for your product under 21 U.S.C. § 350b(a)(2) (section 413(a)(2) of the Act) . . . ."[10]

By not acting to create a regulatory framework for CBD in dietary supplements and food, FDA would be, in effect, creating a sweeping monopoly over CBD for drug use. This is not what Congress intended, in general, and particularly in this circumstance. Members of Congress have noted to FDA, on multiple occasions, that its "intent was clear with the passage of the Farm Bill

[10] Letter to M. Mottaghian (Honey Colony) from R. Durkin, Deputy Director, Office of Dietary Supplement Programs, FDA, April 5, 2017, regarding NDI 984, *available at*, file://hs.local/shared/COURES/Redirection/Documents/molsen/My%20Documents/Letter_from_FDA_CFSAN_to_HoneyColony_regarding_NDI_984_-_Superior_Hemp_Oil.pdf.

that [CBD products] should be legal, and our farmers, producers, and manufacturers need clarity as well as a workable pathway forward regarding the agency's enforcement and potential regulatory plans for certain CBD products."[11] FDA can fulfill Congress's intent and provide this clarity through its notice and comment rulemaking authority already granted to the agency in the FDCA.

FDA's Inaction Creates a Public Health Concern of its Own

FDA's inaction, currently and if the agency declines to promulgate a regulation in the future, creates a public health concern in its own right. For example, entities that have significant experience with dietary supplement and food products, including many CRN members, are reluctant to enter the market until the legal status of CBD in supplements is clarified. Companies that may not understand dietary supplement or food regulations – or may not care to follow these regulations – can use this opportunity to fill a marketplace void and may be producing questionable and even dangerous products.

Marketplace studies by both FDA and other parties suggest this is already happening. These studies, which have tested levels of CBD in various products already on the market, indicate that there are a number of products available to consumers where CBD levels do not match those listed on product labels.[12]

FDA also has indicated that it does not have a policy of formal enforcement discretion for dietary supplement and food products containing CBD, but the agency has not taken any enforcement action against companies distributing CBD dietary supplement and food products, unless those companies are also making claims that the product can prevent, cure, treat, or mitigate a disease. Such claims are already prohibited for dietary supplements and food. In the absence of

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[11] Press Release from Senator Mitch McConnell, *Leader McConnell Discusses Hemp, CBD with Acting FDA Commissioner*, June 27, 2019, *available at* https://www.mcconnell.senate.gov/public/index.cfm/pressreleases?ID=0B71B14E-5F77-4283-9084-561F67EFBC70; *see also* Letter from Senator Ron Wyden to the Honorable Alex Azar, Secretary, Department of Health & Human Services and the Honorable Ned Sharpless, Commissioner, U.S. Food and Drug Administration (June 25, 2019) (noting that "[t]he passage of the 2018 Farm Bill is Congress's clear intent to further advance and support the domestic production and sale of hemp and hemp derivatives like CBD").

[12] FDA, Warning Letters and Test Results for Cannabidiol-Related Products (last updated April 2, 2019), *available at*, https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products. *See also* Comments at May 31 Public Meeting by Bill Gurley, University of Arkansas for Medical Sciences, College of Pharmacy.

enforcement action, but no formal enforcement discretion policy, FDA is creating further confusion and potentially signaling to consumers that CBD products on the market are safe and acceptable at their current levels and forms.

To ensure that consumers are receiving safe products and to give experienced dietary supplement companies clarity to provide consumers with safe and quality products, CRN strongly urges FDA to formalize the enforcement discretion policy under which it currently appears to be acting. Such a step should be coupled with strong guidance and agency action that products being marketed as dietary supplements will be treated as dietary supplements (with similar actions taken for foods) for the purposes of FDA's other regulatory requirements. These products should, for example, be manufactured in FDA registered facilities, following good manufacturing practice requirements; the products should bear compliant labels; and manufacturers should properly record and report adverse events, among following the other FDA regulations necessary to ensure safety.

While FDA Engages in Notice and Comment Rulemaking Companies Need Clearer Guidance on the Scope of Drug Preclusion Provisions

FDA's statements about what specifically is the "article" that is subject to the drug preclusion provisions of FDCA sections 201(ff)((3)(B) and 301(ll) have been very broad and general, leaving companies with little understanding of whether CBD, in any form or amount, is permissible. For example, in FDA's current guidance document on the regulation of cannabis and cannabis-derived products, FDA simply notes that "CBD products are excluded from the dietary supplement definition . . . ."[13] Statements in FDA Warning Letters and other documents have been similarly broad and sweeping.

CBD can, however, be found in many forms and amounts in dietary supplement and food products, such as where it is a constituent in hemp-derived ingredients and one of hundreds of cannabinoids in hemp extracts to highly purified and isolated CBD being used as the sole dietary ingredient in a supplement. Thus, these broad statements are misplaced and cause significant confusion among consumers, retailers, and manufacturers about how hemp can be used in dietary supplements and food. CRN believes that, at a minimum, hemp extracts cannot be

[13] FDA Guidance, *FDA Regulation of Cannabis and Cannabis-Derived Products: Questions and Answers* (last updated April 2, 2019), *available at*, https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers#dietarysupplements.

classified as the same "article" that is subject to the drug preclusion provisions of the FDCA, simply because those extracts contain CBD. FDA has addressed this issue in other situations, such as where the agency has noted that naturally occurring amounts of lovastatin found in red yeast rice are not the same "article" as when that substance is used in a drug product approved for lowering cholesterol levels.[14] Under the precedent created by FDA's review of lovastatin levels in red yeast rice products, simply distributing a product that contains CBD, as would be the case for hemp extracts, would not violate Section 201(ff)(3)(B) of the FDCA.[15]

FDA should recognize this distinction and provide more specific guidance as to what the agency considers precluded by the FDCA drug preclusion sections. This would not only provide consumers, retailers, and manufacturers clarity over what products FDA believes are permissible as dietary supplements, but would help shape the scope of issues that FDA must address in rulemaking on CBD use in dietary supplements and food. It would also incentivize the NDI process, as companies would have confidence that NDI notifications would be reviewed on their merits and FDA would have greater access and oversight of safety.

Finally, CRN would like to use this opportunity to point out a concern with FDA's interpretation of the drug preclusion provisions, in general, as it has important implications for (1) companies trying to understand what evidence would be necessary to overcome the FDA's determination that CBD is precluded in food and dietary supplements because of Sections 201(ff)(3)(B) and 301(ll); and (2) generally how FDA interprets these provisions to preclude food and dietary supplements that are first used in drug investigations.

Specifically, Section 201(ff)(3)(B) excludes a substance from being used as a dietary ingredient if it was "an article 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 . . . which was not before such . . . authorization marketed as a dietary supplement or as a food." This provision indicates that there are three requirements that must be met to preclude a substance's use in dietary supplements – (1) the substance must be authorized for investigation as a new drug (IND); (2) substantial clinical investigations must be instituted; and (3) the substantial clinical investigations must be made public.

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[14] FDA Letter to S. Pape, May 20, 1998 (summarizing FDA's decision that Cholestin (a product containing lovastatin) was not a dietary supplement because of the FDCA drug preclusion provisions).

[15] 2001 U.S. Dist. LEXIS 4598, at *5.

In FDA draft dietary supplement guidance, however, the agency suggests that the date before which a substance needed to have been used in food or supplements is the date that the IND went into effect – not the date that all three of the elements cited above were met.[16] Under this interpretation, a company could receive IND authorization, but wait a number of years before conducting substantial clinical investigations and making these investigations public. In the meantime, another company could invest significant resources into developing and distributing an ingredient as a dietary supplement, including developing safety data and formulating products, only to lose that investment if the first company subsequently completes substantial, public, clinical investigations.[17] In other words, simply receiving IND authorization would be enough for a drug company to stifle dietary supplement and food innovation.

Authoritative Reviews Have Found CBD Likely to be Safe for Healthy Adults

While CRN is not providing data on specific safe levels of CBD identified by ongoing research in this comment, FDA should find comfort that well-respected authoritative reviews have found CBD to be relatively safe for healthy adults. These data, in addition to demanding adherence to the safety requirements already in the FDA's regulatory framework for food and supplements, provide FDA ample opportunity to analyze and evaluate the safety data specific to each product formulation.

The safety of orally ingested CBD has been comprehensively reviewed in a series of reports from recognized authoritative scientific bodies (RASB) and published systematic reviews. While some reviews have focused on potential toxicity from CBD exposure, others have examined CBD safety in the context of adverse events (AEs) and its addictive potential. Generally, CBD, when orally ingested appears to have a wide margin of safety. It may interact with certain medications via inhibition of certain liver cytochrome P450 enzymes, but these risks likely could be managed by cautionary consumer communications.

In 2016, the Food Standards Australia New Zealand (FSANZ) conducted a hazard profile on CBD and concluded that ". . . CBD has been shown to be well tolerated at doses greater than 1000 mg

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[16] *See* FDA Draft Guidance, Dietary Supplements: New Dietary Ingredient Notification and Related Issues, Question 10 (Aug. 2016) (noting that "whether the date the IND went into effect was before or after the date the ingredient was first marketed as a food or a dietary ingredient" is the date FDA will use to determine if a substance is precluded from dietary supplement use).

[17] FDA includes this interpretation in dietary supplement guidance, but CRN believes it should be addressed for both food and dietary supplements, as the similarities in language between the food and dietary supplement drug preclusion clauses could cause FDA to interpret them the same way.

per day. No reports of adverse effects attributable to oral CBD were located in the published literature . . . ."[18] The World Health Organization, in 2018, released a critical review report in which it concluded, ". . . CBD is generally well tolerated with a good safety profile . . ." and there was no evidence identified of ". . . any public health-related problems associated with the use of pure CBD . . . ."[19] The latter statement was in reference to the addictive potential of CBD. As part of its approval of the prescription drug Epidiolex, FDA concluded that, ". . . [i]n general, the risks associated with CBD treatment appear acceptable . . . ."[20] The agency noted that adverse events (AEs) with mild to moderate severity included somnolence and sedation, decreased appetite and diarrhea, transaminase elevations, and infections (*e.g*., pneumonia), while serious and/or severe AEs were generally related to transaminase elevations, somnolence and lethargy, and infections. FDA concluded that 5 mg/kg bw/day (approximately 350 mg/day in a 70 kg adult) dose showed a safety profile comparable to placebo, and that potential risks of liver injury could be appropriately managed with labeling, education, etc.

A 2011 review of 132 original studies,[21] excluding studies of mixed cannabinoids or CBD extracts, but including 23 studies of oral administration of CBD in healthy volunteers and/or patients ranging from 15 to 600 mg/day for up to 4.5 months concluded there were no significant side effects. No significant effects were observed on physical examination, cardiovascular parameters, neurological parameters, psychological measurements, task and motor performance, psychotic symptoms, behavior, intoxication, or sedation.

In 2017, Iffland and Grotenhermen concluded that the ". . . favorable safety profile of CBD was confirmed . . . "[22], but that there was the potential for CBD to impact the metabolism of certain drugs (*e.g*. via inhibition of CYP1A2, 2C19 and 3A4) at clinically relevant doses. A systematic

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[18] Cannabidiol hazard profile – Proposal P1042. Low THC Hemp Seeds as Food. Food Standards Australia New Zealand, 2016 http://www.foodstandards.gov.au/code/proposals/Documents/P1042%20Low%20THC%20hemp%20CFS%20SD2%20Cannabidiol%20hazard.pdf

[19] Cannabidiol (CBD) Critical Review Report. Expert Committee on Drug Dependence Fortieth Meeting Geneva, 4-7 June 2018. World Health Organization https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf

[20] Center for Drug Evaluation and Research. Application Number 210365Orig1s000. Summary Review, June 22, 2018. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000SumR.pdf

[21] Bergamaschi MM, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf*. 2011 Sep 1;6(4):237-49.

[22] Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis Cannabinoid Res*. 2017 Jun 1;2(1):139-154.

review by Lattanzi et al. examined four trials involving 550 epilepsy patients treated with CBD doses ranging from 700 – 1400 mg/day.[23] The authors noted that the incidence of AEs was significantly higher with CBD treatment vs. placebo and included somnolence, decreased appetite, diarrhea, and increased serum aminotransferases. In another recent systematic review examining pediatric epilepsy patients in a combination of randomized, controlled trials (RCT) and observational studies involving CBD adult equivalent doses of 175 – 1400 mg/day for between 10 days and 10 years, results also demonstrated a higher rate of AEs in the treatment vs. placebo groups.[24] The authors noted that the CBD-associated AEs are likely related to an interaction with concomitant epilepsy medications.

Concern has been raised regarding the potential exposure to delta-9-tetrahydrocannabinol (THC), the constituent in marijuana responsible for its psychoactive effects, from dietary supplements or foods containing hemp extracts. Hemp is non-intoxicating, with significantly lower levels of THC compared to marijuana, and must be 0.3% THC or less by dry weigh to be used as a food or supplement ingredient.[25] Manufacturers of hemp extracts for use in foods and supplements have the capability of establishing specifications to limit the amount of THC in their products to avoid introducing unsafe levels to consumers. Indeed, there is ample precedent of manufacturers establishing limits for naturally occurring, but undesirable constituents present in raw botanical materials. Pyrrolizidine alkaloids (PAs) are highly toxic compounds that occur naturally in many plant species. The combination of guidance from authorities, availability of fit-for-purpose analytical methods and advances in processing have allowed industry to establish and deliver safe botanical products with low PA levels.[26]

Similar efforts are under way for quantification of cannabinoids in hemp extracts, including THC.[27] This work will complement that already completed on the characterization of the

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[23] Lattanzi S, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. *Drugs*. 2018 Nov;78(17):1791-1804.

[24] Stockings E, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry*. 2018 Jul;89(7):741-753.

[25] Agriculture Improvement Act of 2018, Pub. Law 115-334 (enacted Dec. 20, 2018).

[26] European Medicines Agency, May 2016 Committee on Herbal Medicinal Products (HMPC) Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids. Transitional recommendations https://www.naturesway.com/Product-Catalog/Petadolex-Pro-Active-60-softgels; https://www.amazon.com/Herb-Pharm-Comfrey-Liquid-Extract/dp/B077X22X19

[27] https://www.aoac.org/AOAC_Prod_Imis/AOAC_Docs/StandardsDevelopment/CASP/CASP_03122018-Final.pdf

constituents naturally present in the raw hemp plant. Therefore, there is both ample precedent and the availability of standards to allow manufacturers to establish low THC limits in hemp-based products.

In summary, the safety of orally ingested CBD in humans has been examined in a combination of RCTs, systematic reviews and RASB reports. Higher doses (above 100 mg/day) in combination with certain medications (particularly those used to treat epilepsy) has been associated with AEs, including elevated liver enzyme levels. Collectively, these data suggest oral CBD is likely to be safe at lower doses in normal healthy adults. Risks associated with CBD-drug interactions could likely be managed through cautionary consumer communications. Concerns regarding THC exposure from hemp extracts can be mitigated by establishing low THC limits (e.g. < 10 ppm) for ingredients and finished products.

Allowing CBD to be used in Supplements and Food is Unlikely to Affect Drug Research and Development

Finally, FDA has sought comments on the impact of CBD in foods and dietary supplements on drug research and development. This is an important factor for FDA to consider, as the drug preclusion provisions of the FDCA were designed to protect investments and incentives in drug development. CRN believes any impact on drug research and investment would be minimal for a number of reasons.

(i) **As a function of safety, CBD doses in dietary supplements and food are likely to be much lower than those used in drugs.**

Once a clear legal pathway is made available for CBD-containing foods and dietary supplements, existing provisions in the FDCA will need to be adhered to by manufacturers and marketers of these products. These include market entry requirements, such as determining if CBD ingredients are GRAS and filing NDI Notifications for inclusion of CBD ingredients in dietary supplements. These safety provisions must be addressed in order for CBD-containing products to be lawfully marketed. In a food or supplement context, achieving the safety standards (reasonable certainty of no harm for GRAS; reasonable expectation of safety for a NDI) will likely require CBD doses in these products to be well below that currently approved for use as a prescription drug for epilepsy (Epidiolex, 1400 mg/day) and future therapies. This dose discrepancy between foods, dietary supplements and drugs would help to preserve the research space aimed at exploring CBD's therapeutic effects.

(ii) **Foods and dietary supplements cannot prevent, cure, diagnose, treat or mitigate disease.**

The clear legal distinction between the intended use of a food and a dietary supplement and a drug also helps to preserve the incentive to invest in medical research for comparable substances. This includes, but is not limited to CBD-containing products. For example, fish oils, containing long-chain omega-3 fatty acids had long been marketed in/as foods and dietary supplements prior to being investigated as, and subsequently approved as a new drug to lower serum triglycerides. In this case fish oils, one of the most popular and rapidly growing dietary supplement product categories, did not discourage investment in medical research. On the contrary, it is likely that the success in the dietary supplement space was a factor in stimulating the investment in drug development, and the clear distinction in intended use provided the clarity and protection for that process to occur successfully. Today the two categories coexist well.

(iii) **CBD in foods and dietary supplements will stimulate research, not stifle it.**

Allowing CBD-containing foods and dietary supplements to be lawfully marketed will stimulate research in the areas of nutrition and well-being. As a naturally occurring constituent derived from a plant consumed in the food supply, CBD is considered a "bioactive compound" or phytonutrient.[28] There is strong interest in studying the effects of these compounds; there are over 21,000 citations in PubMed for "bioactive compounds" and over 27,000 citations or "phytochemical" or "phytonutrient". As with other phytochemicals that have been added to foods or dietary supplements, a legal pathway for CBD in these products will also stimulate research by the nutrition and wellness communities, with resources coming from both industry, as part of the product innovation process, and from government and academia as scientists investigate the public health benefits of these products. This is a common positive feedback loop where policy and industry innovation combine to drive research, which in turn, informs policy and innovation, and so forth.

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[28] Frank J, et al. "Terms and nomenclature used for plant-derived components in nutrition and related research: Efforts toward harmonization". *In process.*

CRN thanks FDA in advance for its careful consideration of these views and continues to stress the need of the agency to act quickly and decisively. As CRN has noted on multiple occasions, FDA already has the tools to address the issues raised by hemp-derived CBD use in dietary supplements and food. By using these tools – first, to conduct notice and comment rulemaking to allow hemp-derived CBD to be used in food and dietary supplements; and second, to use the existing, extensive regulatory framework to address safety – FDA can swiftly bring clarity to the hemp-derived CBD supplement and food market, while upholding the agency's public health mission to ensure that consumers have access to safe products they can trust.

CRN, and its members, continue to be ready to assist FDA in any way possible as it develops its CBD regulatory framework moving forward.

Sincerely,

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