Council for Responsible Nutrition
The Science Behind the Supplements

July 27, 2023

Members of the House Committee on Oversight and Accountability,
Subcommittee on Health Care and Financial Services:

These written comments are submitted on behalf of the Council for Responsible Nutrition (CRN)[1], the leading trade association representing the dietary supplement and functional food industry, to convey our concerns about FDA's inaction on the regulation of hemp-derived cannabidiol (CBD) over the past five years, and the agency's recent announcement that it will not regulate this botanical ingredient under the existing dietary supplement legal framework. CRN calls on Congress to demand that FDA complete the work Congress directed it to do in 2018 by permitting CBD and other hemp-derived cannabinoids to be lawfully marketed as dietary supplements using the appropriate safeguards found in the existing law.

Introduction

Five years ago, Congress enacted the 2018 Farm Bill that included provisions expressly removing hemp and its constituents from the Controlled Substance Schedules. Prior to that legislation, the Controlled Substances Act (CSA) did not distinguish between marijuana (that contains various levels of the compound delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana), and hemp, which contains other cannabinoids, but not appreciable amounts of THC. Congress explicitly delineated that difference by requiring that hemp shall not contain more than 0.3 percent THC.

In addition, the legislation expressly directed that,

> *"Nothing in this subtitle shall affect or modify … the Federal Food, Drug, and Cosmetic Act; … Section 351 of the Public Health Service Act; or … the authority of the Commissioner of Food and Drugs and the Secretary of Health and Human*

[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 and ingredient suppliers. CRN companies produce a large portion of the 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 200 companies that manufacture dietary ingredients and/or dietary supplements, 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 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.

> *Services … to promulgate Federal regulations and guidelines that relate to the production of hemp under the Act."*[2]

In other words, Congress fully anticipated that, with the removal of hemp and its non-THC constituents from scheduling, FDA would expeditiously provide pathways for the marketing of hemp-based products under its existing legal jurisdiction. FDA has ample authority to regulate these products as food, dietary supplements, cosmetics and over-the-counter and prescription drugs with the prescribed authorities in the current federal Food, Drug, and Cosmetic Act (FDCA) and related regulations.

Instead, FDA has spent the past five years metaphorically wringing its hands about this authority, ignoring Congress' directive, watching from the sidelines as a sizable, but unpredictable CBD marketplace evolved without meaningful enforcement of legal requirements, and ignoring (*even denying the existence of*) credible, well-conducted research that was presented to the agency to demonstrate the safety of well-made CBD products.

In January, FDA announced it would not do its Congressionally-mandated job of regulating the botanical constituent, declaring that the existing legal framework was not appropriate to regulate CBD products.[3] And in June, FDA hosted a stakeholder call entitled "A New Way Forward for Cannabidiol...," on which the agency called for an entirely new regulatory framework for all cannabis products, ignoring the distinction Congress made between hemp and marijuana. It was not a way forward. Rather, it was a series of excuses to step backwards from what Congress intended when it enacted the Farm Bill in 2018. Congress should flatly reject this proposal from the agency and direct FDA to do what it was instructed to do in 2018—use its existing authority to regulate the burgeoning marketplace for CBD and other non-THC cannabinoids.

<u>The Drug Preclusion Conundrum — And Three Different Solutions</u>

Shortly after the passage of the 2018 Farm Bill, FDA objected to the inclusion of hemp-derived CBD in dietary supplements, citing the "drug preclusion" provision that was added to the FDCA by the Dietary Supplement Health & Education Act of 1994 (DSHEA). This section prohibits the introduction of a dietary supplement containing the same "article" that has previously been approved as a drug, or studied in substantial clinical investigations which have been made public as a drug.

Specifically, the drug preclusion section of DSHEA (21 U.S.C. 321 (ff)(3)(B)) provides that a dietary supplement does –

> *(B) not include —*
>
> *(i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of title 42, or*
>
> *(ii) an article authorized for investigation as a new drug, antibiotic, or biologic for which substantial clinical investigations have been instituted and for which*

[2] 7 U.S.C. § 1639r - Regulations and guidelines; effect on other law.

[3] FDA Concludes that Existing Regulatory Frameworks for Foods and Supplements are Not Appropriate for Cannabidiol, Will Work with Congress on a New Way Forward-- https://www.fda.gov/news-events/press-announcements/fda-concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol

> *the existence of such investigations has been made public, 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] . . .* [4]

This provision essentially establishes a "race to market" between dietary supplements and pharmaceuticals that use the same ingredients. If the supplement is marketed first, the two categories (supplements and drugs) essentially "share" the ingredient; but if the drug is marketed first, or even if the article is first studied in substantive clinical trials that are made public, the drug industry can claim a monopoly over the article and prevent its eventual marketing in dietary supplements.[5]

That is essentially what happened to CBD when, in 2019, FDA announced that CBD was precluded from use in dietary supplements due to it being approved in 2018 in the drug Epidiolex, a prescription medication containing high dosages of purified CBD for indications related to seizures.

Even if FDA is correct in its assessment that Epidiolex predated any legal supplements containing CBD, the agency has several options that would have allowed the inclusion of CBD in dietary supplements.

1. First, FDA could determine that the pharmaceutical and dietary supplements are not using the same "article" and thus, these low dosage products are not precluded by the drug preclusion provision. CBD-containing dietary supplements that have been brought to FDA for review (*and objected to by the agency*) in a series of New Dietary Ingredient Notifications over the past five years, typically contain 20-65 mg of CBD per serving, whereas a standard maintenance dose of Epidiolex delivers more than 1,000 mg of purified CBD in adults. In addition, CBD in these supplements was provided as part of a "full spectrum hemp extract" that contained a variety of other cannabinoids and plant constituents not found in Epidiolex. FDA could determine that the two types of products are sufficiently different in dosage and composition or they could have proposed indications that they are not the same article.

2. Alternatively, FDA could invoke the rulemaking authority expressly granted to it by the statute and initiate a notice and comment rulemaking that would allow the legal marketing of CBD as a supplement. Even if the agency determined that CBD used in Epidiolex and in supplements are the same "article," Section 321 (ff)(3)(b) clearly grants the FDA discretion to issue a regulation as an exception to the general drug preclusion rule that the article "would be lawful" under the Act.[6] CRN has suggested to FDA that there is ample justification for this exception given the prior controlled substance status of hemp-derived CBD.[7] The typical "race to market" envisioned by the drug preclusion principle could not properly function since the article was a Schedule 1 substance and was prohibited from being sold as a dietary supplement prior to the passage of the Farm Bill in December 2018.

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[4] 21 U.S.C. § 321 (ff)(3)

[5] Various aspects of FDA's interpretations of the drug preclusion provision as it applies to a range of ingredients are currently the subject of a Citizen Petition before FDA filed by CRN earlier this year. See CRN Citizen Petition, submitted May 9, 2023, https://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/CRN-CitizenPetition-FDA-DrugPreclusion050923.pdf.

[6] See 21 U.S.C. § 321 (ff)(3)(B).

[7] See CRN Citizen Petition to FDA regarding CBD submitted June 16, 2020, https://www.regulations.gov/document/FDA-2020-P-1582-0001.

3. A third option available to FDA to bypass the drug preclusion issue is to ask Congress to amend the law to grant a special case for CBD. H.R. 1629, the Hemp and Hemp-Derived CBD Consumer Protection and Market Stabilization Act of 2023, in the current Congress would do just that.[8] It provides that "notwithstanding section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(ff)(3)(B)), hemp, cannabidiol derived from hemp, and any other ingredient derived from hemp shall be lawful for use under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) as a dietary ingredient in a dietary supplement…." FDA has opposed this option as well.

So when FDA feigns that its hands are tied by the drug preclusion language in the FDCA, Congress should inquire why none of these options have been pursued.

FDA's Concerns About Safety—And A Mountain of Ignored Evidence

FDA's second pretext for its inaction over the past five years is its claim that the agency lacks the safety data for CBD to appropriately provide safeguards for its supplement use. In January, FDA stated, "[g]iven the available evidence, it is not apparent how CBD products could meet the safety standards for dietary supplements or food additives."[9] First, FDA has blurred the lines of the requisite levels of safety evidence required for a dietary supplement. Unlike food additives, that require "a reasonable certainty of no harm" for FDA approval, dietary supplements are held to a different standard. New Dietary Ingredients must "reasonably be expected to be safe,"[10] but generally, FDA must demonstrate that a dietary supplement presents "a significant or unreasonable risk of illness or injury under…conditions of use recommended or suggested in labeling."[11] Additionally, FDA misrepresents that food regulation provides a risk elimination framework unsuitable for products that have inherent risks, yet all products, even sodium and sugar, have risks. When FDA postulates that the regulation of CBD presents unknown possibilities of risk that prevent it from being regulated like other botanical constituents, it ignores the long history of the successful regulation of a range of botanical ingredients under DSHEA.

But more concerning is FDA's suggestion that it does not have adequate data on the safety of CBD to properly regulate it as a supplement. In January, the agency stated, "[f]or example, we [FDA] have not found adequate evidence to determine how much CBD can be consumed, and for how long, before causing harm."[12] This statement is surprising given that other government bodies have established recommended maximum upper intake levels of CBD, as well as the vast amount of safety evidence presented to FDA over the past five years.

In 2020, the UK Food Standards Agency recommended an upper limit of 70 mg per day CBD for healthy adults, based on a review of evidence by the UK Committee on Toxicity.[13] Later that year, the Australian Therapeutic Goods Administration also released their safety assessment with the overall conclusion that "cannabidiol presents a good safety and tolerability profile at the low dose range of under 60 mg/day."[14]

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[8] Cite to H.R. 1629, https://www.congress.gov/bill/118th-congress/house-bill/1629/history?s=1&r=6.
[9] https://www.fda.gov/news-events/press-announcements/fda-concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol.
[10] 21 U.S.C. § 350b - New dietary ingredients, https://www.law.cornell.edu/uscode/text/21/350b.
[11] 21 U.S.C. § 342(f), https://www.law.cornell.edu/uscode/text/21/342.
[12] https://www.fda.gov/news-events/press-announcements/fda-concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol.
[13] https://www.food.gov.uk/news-alerts/news/food-standards-agency-sets-deadline-for-the-cbd-industry-and-provides-safety-advice-to-consumers
[14] https://www.tga.gov.au/sites/default/files/review-safety-low-dose-cannabidiol.pdf

In 2022, Health Canada's Science Advisory Committee on Health Products Containing Cannabis issued a review of CBD, stating that "CBD is safe and tolerable for short-term use (a maximum of 30 days) at doses from 20 milligrams per day (mg/day) to a maximum dose of 200 mg/day via oral administration for healthy adults provided they discuss the use of all other medications and substances used with their pharmacist."[15]

CRN has provided safety information related to CBD on several occasions. In 2019, CRN responded to FDA's Hearing and Request for Comment on Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds. In that heavily referenced submission, citing global data assessing the safety of CBD, CRN wrote:

> "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. [16]

In the following year, CRN provided the agency with a safety assessment conducted by a group of independent third-party scientific experts who proposed a tolerable upper intake level for CBD in dietary supplements of 40 mg/day.[17] This assessment, along with the safe levels/limits established by international government bodies, demonstrated that there is a safe level of CBD that can be consumed as a dietary supplement, even if the specific recommended values vary within an acceptable range. Additionally, in June 2020, CRN also filed a Citizen Petition with FDA providing additional evidence of safety.[18] In all these cases, FDA responded by raising a seemingly endless critique of the data that was presented, but never bothered to construct its own assessment of safety using the underlying data for products at the dosage levels being sought for use in dietary supplements.

CRN is hardly alone in providing scientific evidence to FDA on CBD. Two other organizations, the Consumer Healthcare Products Association (CHPA) and the Natural Products Association (NPA,) have also submitted citizen petitions to FDA with their own justifications of the safety of CBD. Further, CRN is directly aware of numerous companies that have met with FDA and shared unpublished data in their possession that support CBD's safety at levels relevant to the products they would market as dietary supplements. In addition, at least three companies have submitted their own dossiers of relevant safety evidence in connection with New Dietary Ingredient Notifications for CBD-containing ingredients:

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[15] https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/health-products-containing-cannabis/review-cannabidiol-health-products-containing-cannabis.html#a3.3.

[16] https://www.crnusa.org/sites/default/files/pdfs/comments-pdfs/CRN-Comments_FDA-Scientific-Data-Cannabis-Cannabis-Derived-Compounds-written-sub0719.pdf.

[17] Comment from CRN to FDA regarding CBD submitted June 25, 2020. https://www.regulations.gov/comment/FDA-2019-N-1482-4364

[18] See CRN Citizen Petition to FDA regarding CBD submitted June 16, 2020, https://www.regulations.gov/document/FDA-2020-P-1582-0001.

- Irwin Naturals, NDI 1199[19]
- Charlottes Web, NDI 1202[20]
- cbdMD safety dossier [21]

Despite the plethora of safety data available to FDA, the agency continues to claim that adequate safety evidence is lacking, while not appreciating that the safety profile of CBD-containing dietary supplements would be different than much higher-dosed approved drug products, as well as the body of evidence on the safety of CBD-containing hemp extracts. In a recently published review article on the oral toxicity of CBD, FDA scientists place undue weight on the Epidiolex dataset and trivialize evidence that examines lower dosages of CBD.[22] Further, they ignore the body of evidence of the safety of CBD-containing hemp extracts that have been developed for dietary supplement use. This research, conducted in accordance with regulatory test guidelines, provides evidence to support the use of various CBD-containing ingredients for their intended uses. By not considering the totality of relevant evidence, FDA's approach to assessing the safety of CBD is incomplete and therefore does not provide meaningful information to consumers and industry.

Existing Legal Authority Under DSHEA

The DSHEA defines a "dietary supplement" to include "an herb or other botanical" and a "concentrate, metabolite, constituent, extract or combination."[23] There is no question that CBD falls squarely within this definition. However, the agency now states that "FDA has concluded that a new regulatory pathway for CBD is needed that balances individuals' desire for access to CBD products with the regulatory oversight needed to manage risks." It raises the question why the existing dietary supplement framework would not suffice.

The regulatory framework for dietary supplements provides ample tools by which FDA can manage the risk associated with these products. Even as FDA calls for new authority, asserting that the current framework is "not appropriate to regulate CBD products," one wonders how the current tools are not sufficient. DSHEA gives FDA authority in these areas:

- ✓ Good Manufacturing Practices (GMPs) specific to dietary supplements allows FDA to prevent the introduction of contaminants like heavy metals, pathogens or solvents in the finished products
- ✓ mandatory recall authority (as dietary supplements are regulated as food, they are subject to the mandatory recall authority provided to FDA for food) would be available for unsafe CBD-containing supplements
- ✓ a safety standard for the removal of an unsafe ingredient already exists

[19] https://www.regulations.gov/document/FDA-2021-S-0023-0050.
[20] https://www.regulations.gov/document/FDA-2021-S-0023-0053.
[21] This dossier is not publicly available but is referenced in a citizen petition submitted by the Natural Products Association to FDA regarding CBD. https://www.regulations.gov/document/FDA-2022-P-0600-0001
[22] Gingrich, J., Choudhuri, S., Cournoyer, P., Downey, J., Muldoon Jacobs, K. Review of the oral toxicity of cannabidiol (CBD). April 2023:113799. doi: https://doi.org/10.1016/j.fct.2023.113799.
[23] 21 U.S.C. § 321(ff).

- ✓ New Dietary Ingredient notifications provide a process for bringing new ingredients, like CBD, to market under FDA oversight
- ✓ Dietary supplements are subject to serious adverse event reporting for health-related incidents, (all adverse event reports, whether serious or not, must be reviewed and maintained by the manufacturer for 6 years)
- ✓ Dietary supplement facilities must register with FDA every two years
- ✓ DSHEA provides oversight of labeling: (e.g., use of a mandatory Supplement Facts box, complete listing of ingredients, requirements that label claims must be truthful, supported by evidence, and cannot claim to cure, mitigate, prevent, or treat a disease, a required disclaimer for supplements making structure/function claims)
- ✓ Content limits per serving – dietary supplements may not present "a significant or unreasonable risk of illness or injury under…conditions of use recommended or suggested in labeling"[24] and FDA has precedent of imposing maximum serving levels on specific ingredients.

In sum, DSHEA provides a range of tools for FDA to mitigate risks and protect consumers while allowing access to safe botanicals, like CBD. Other possible safeguards that FDA imagines for a new category of cannabis products, could be achieved under the existing framework. While FDA currently lacks the authority to require that dietary supplements be listed with the agency (a concept referred to as "dietary supplement listing"), legislation to impose dietary supplement listing on all supplements could be enacted and implemented far more quickly than the creation of an entirely new category of regulated products. (CRN has supported legislation to establish dietary supplement listing for all dietary supplements.) If FDA effectively limited THC levels in the products and required cautionary label statements about the risk of ingestion by children, additional age purchase restrictions would be unnecessary. Further, FDA could work with the Consumer Product Safety Commission (CPSC) to develop required child-resistant packaging for these products, as it has with iron-containing dietary supplements.

These are the risk mitigation tools that FDA has called for in a new regulatory category for CBD-containing products. All these safeguards and tools for effectively minimizing risk either already exist or could be developed and implemented far more efficiently within the existing regulatory framework for dietary supplements. Instead, FDA downplays, underestimates and misrepresents its ability to enforce the law and to protect consumers as justification for creating a new Center within FDA and a new regulatory category that undermines the existing structure of the FDCA. Would this new Center be accompanied by exorbitant funding requests of Congress to set up and staff this new Center, or would FDA seek user fees on these products (something it does not possess for dietary supplements) and drive up the costs of these products for consumers?

Conclusion

In the five years since Congress enacted the 2018 Farm Bill, the dietary supplement market for products containing CBD has exploded. While FDA dithers on how to regulate this marketplace, consumers are exposed to a wide range of products—some well-made and accurately labeled, and others that are mislabeled, contain too much, too little, or even no CBD, ones containing contaminants, or intoxicants like THC or Delta 8, or that impermissibly claim to treat a range of diseases. It's too late to return the proverbial horse to the barn; consumers deserve to have a CBD marketplace that is regulated and

[24] 21 U.S.C. § 342(f), https://www.law.cornell.edu/uscode/text/21/342.

predictable Allowing CBD to be marketed in dietary supplements would address these needs. Congress should enact H.R. 1629 and demand that FDA implement it.