Council for Responsible Nutrition
1828 L Street, NW, Suite 810 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

May 4, 2023

Dr. Robert McKinnon Califf, FACC, MD
Commissioner
U.S. Food and Drug Administration
United States Department of Health and Human Services
10903 New Hampshire Avenue, White Oak Building One, Room 2217
Silver Spring, MD 20993
Via email: commissioner@fda.hhs.gov

Re: FDA review of the oral toxicity of cannabidiol (CBD)

Dear Commissioner Califf,

Since 2018, when Congress removed hemp from the Federal Controlled Substances Act (CSA), the Council for Responsible Nutrition (CRN)[1] has advocated for the Food and Drug Administration (FDA) to establish a regulatory pathway to legally market dietary supplements containing hemp-derived cannabidiol (CBD).[2,3] As you well know, the Agriculture Improvement Act of 2018 removed hemp from Schedule I of the CSA, but expressly left in place the authority of the Commissioner "to promulgate Federal regulations and guidelines that relate to the production of hemp…" under the Federal Food, Drug & Cosmetic Act (FD&CA).[4]

[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.

[2] CRN comments submitted to FDA's Docket 2109-N-1482. https://www.regulations.gov/document?D=FDA-2019-N-1482-4060. Published July 16, 2019. Accessed May 3, 2023.

[3] CRN CBD citizen petition. https://www.regulations.gov/document/FDA-2020-P-1582-0001. Published June 17, 2020. Accessed May 3, 2023.

[4] Sec 297D(c)(3), codified at 7 USC 1639r. https://www.congress.gov/115/plaws/publ334/PLAW-115publ334.pdf. Published December 20, 2018. Accessed May 3, 2023.

[5] 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. Published January 26, 2023. Accessed May 3, 2023.

So, CRN was deeply frustrated and dismayed by FDA's announcement earlier this year that, despite that authority, the Agency "has concluded a new regulatory pathway is needed that balances individuals' desire for access to CBD products with the regulatory oversight needed to manage risks."[5] In the announcement, FDA notes the need for "safeguards and oversight to manage and minimize risks" related to CBD-containing products and enumerates such needed tools as label oversight, prevention of contaminants, CBD content limits, and ways to mitigate the risk of ingestion by children.[5] What is particularly troubling is that FDA already has authority to implement these safeguards under the existing dietary supplement framework established by the Dietary Supplement Health & Education Act (DSHEA), itself an amendment to the FD&CA in 1994. Any additional legislative changes that would be necessary (such as creation of a product listing requirement) could be accomplished with minor revisions to DSHEA rather than the upheaval, considerable expense, and lengthy delays that would result from creation of an entirely new category of regulated products by FDA.

In that January announcement, FDA identified various potential safety concerns with the use of CBD-containing products but did not address the doses at which potential harm could occur. The Agency did not discuss the relevance of the data the Agency has received that raised safety concerns for CBD (mainly for the drug product, Epidiolex, which is a CBD isolate) to the breadth of hemp-derived CBD ingredients that have been developed for dietary supplement use. That the dose makes the poison, a realization credited to Paracelsus over 500 years ago, seems to have escaped notice by FDA.

We also noted with interest that FDA staff recently authored an article titled, "Review of the Oral Toxicity of Cannabidiol (CBD)" (the review article).[6] Perhaps, we thought, this survey of the scientific data upon which FDA presumably based its decision making would elucidate why the Agency believed the safety of CBD defies regulation under the framework of DSHEA. Upon reviewing the article, however, we were surprised to see that FDA continues to disregard the levels of exposure that may raise safety concerns relative to levels that would be consumed from dietary supplement use, as well as the body of evidence on the safety of CBD-containing hemp extracts. Using this limited dataset without considering the dose, and then to conclude, "the available data clearly establish CBD's potential for adverse health effects when consumed without medical supervision by the general population"[6] is disingenuous and is a disservice to both consumers and responsible industry. We further elaborate on our concerns about the review article below.

The review article disregards the relevance of the CBD doses used in the reviewed studies to the levels of exposure that would be consumed from dietary supplement use.

"The dose makes the poison"[7] is the fundamental principle of toxicology. In essence, it means that all substances can be toxic depending on the level of exposure. Without considering the level of exposure, conclusions that a substance "raises safety concerns" are not meaningful. The authors of the review article offer a disclaimer that the "review is not a risk assessment and does not seek to identify levels of exposure that may result in adverse effects or levels of exposure that are safe for test animals or for humans." Instead, the "review is intended to enable thorough toxicological hazard identification for

[6] 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. Accessed May 3, 2023.
[7] Common paraphrase of Paracelsus: "All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison."

orally consumed CBD and to aid in future risk assessments." However, considering that the vast majority of the data cited in the review article has been available for FDA's evaluation for years, it is unclear why the authors did not conduct a risk assessment. The Agency has had ample access to data and time to utilize the available data to determine a safe level of exposure. Other government bodies, including the United Kingdom's Food Safety Authority, Health Canada, and the Australian Therapeutic Goods Administration have established recommended maximum upper intake levels of CBD by healthy adults, except those planning to be or currently pregnant or breastfeeding.[8, 9, 10]

At the very least, the authors of the review article could have provided context to the data on CBD that raise safety concerns, in particular, the doses used in the identified studies. For example, the doses used in the clinical studies on Epidiolex (equivalent to 900 mg/day in adults) are far higher—*actually on a magnitude or 20 or more times higher*—than the range of levels that would be used in dietary supplements. Identifying potential hazards without consideration of exposure levels does not serve public health interests.

The review article ignores the body of evidence on the safety of CBD-containing hemp extracts that have been developed for dietary supplement use.

The review article authors acknowledge that "CBD is sometimes added to consumer products in the form of CBD-rich hemp extracts, which contain other plant-derived constituents" but focuses the review on "studies using relatively pure CBD." By limiting the review to data on CBD isolate, the authors ignore the body of evidence on the safety of CBD-containing hemp extracts that have been developed for dietary supplement use.

Industry stakeholders have responded to FDA's call for scientific evidence on the safety of CBD by investing in research on their ingredients, which encompass a range of CBD-containing hemp extracts, as well as CBD isolate. This research, conducted in accordance with regulatory test guidelines, provides evidence to support the safe use of various CBD-containing ingredients for their intended uses. The studies have been published in peer-reviewed literature, submitted to the public docket that FDA opened to facilitate submission of CBD data, or shared directly with the Agency. CRN is directly aware of numerous companies that have met with the Agency and shared unpublished data in their possession that support CBD's safety at levels relevant to the products they would market as dietary supplements. FDA has received some of these lengthy dossiers in connection with particular New Dietary Ingredient notifications, on which it has objected on drug preclusion grounds. The Agency has placed undue weight on the Epidiolex dataset and trivialized evidence that examines lower dosages, and that pattern continues with the recently published article. FDA has access to this range of safety data that is

[8] Cannabidiol (CBD) - Consumer advice on cannabidiol (CBD) extracts. Food Standards Agency. https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd. Updated March 31, 2022. Accessed May 3, 2023.
[9] Review of cannabidiol: Report of the Science Advisory Committee on Health Products Containing Cannabis. Health Canada. 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. Published July 28, 2022. Accessed May 3, 2023.
[10] Notice of final decisions to amend (or not amend) the current Poisons Standard - ACMS #36, joint ACMS-ACCS #29, ACCS #32. Therapeutic Goods Administration (TGA). https://www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-final-decisions-amend-or-not-amend-current-poisons-standard-acms-36-joint-acms-accs-29-accs-32. Published September 23, 2022. Accessed May 3, 2023.

absolutely relevant to the ingredients intended for use in dietary supplements at levels that would be commonly used in supplement products, but FDA has repeatedly disregarded this evidence, continuing to rely heavily on safety concerns related to high dosage Epidiolex.

CRN and responsible industry share FDA's priority of consumer safety. Consumers should be assured that the products they consume are safe under the intended conditions of use. Determination of safety must include consideration of the totality of relevant evidence, i.e., data on substances that reflect the ingredients intended for use and at the levels that will be consumed. FDA's approach, however, is incomplete and therefore does not provide meaningful information to consumers and industry.

Sincerely,

Steve Mister
President & CEO

Andrea Wong, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs

cc: Janet Woodcock, M.D., Principal Deputy Commissioner, Office of the Commissioner (janet.woodcock@fda.hhs.gov)
Julia Tierney, J.D., Chief of Staff, Office of the Commissioner (julia.tierney@fda.hhs.gov)
Douglas Stearn, J.D., Deputy Director, Office of Regulatory Affairs (douglas.stearn@fda.hhs.gov)
Donald Prater, D.V.M., Acting Director, Office of Food Policy and Response (donald.prater@fda.hhs.gov)
Cara Welch, Ph.D., Director, Office of Dietary Supplement Programs (cara.welch@fda.hhs.gov)
Jeremy Gingrich, Toxicologist, Office of Food Additive Safety (jeremy.gingrich@fda.hhs.gov)