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July 16, 2019

Lowell J. Schiller, J.D.  
Principal Associate Commissioner for Policy  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Comments on scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds.  
Docket No. FDA-2019-N-1482

Dear Commissioner Schiller;

We previously presented comments at the public meeting in May of 2019 on this subject, we appreciate this opportunity to provide added commentary. By way of introduction, the Natural Products Association (NPA) is the leading and largest trade association representing the entire natural products industry. We advocate for our members who supply, manufacture and sell natural ingredients or finished products for consumers. The Natural Products Association promotes good manufacturing practices as part of the growth and success of the industry. Founded in 1936, NPA represents approximately 1,000 members accounting for more than 10,000 locations of retailers, manufacturers, wholesalers and distributors of natural products, including foods, dietary supplements and health/beauty aids. Prior to my current role at NPA, I served as the Director of the U.S. Food and Drug Administration's Division (now Office) of Dietary Supplements, and on the FDA marijuana task force.

Per the federal register notice there were specific issues for consideration and request for data and information we'll address those points in the requested order:

- A. Health and Safety Risks – Specific to Cannabidiol (CBD), which was the thrust of the meeting on May 31<sup>st</sup>, FDA has resources and personnel to establish a daily exposure level for a healthy population using CBD. This strategy was proposed by former FDA commissioner Dr. Scott Gottlieb during the March 2019 House of Representatives Agriculture Appropriations Hearing. Dr. Gottlieb indicated that the most

straightforward path was based on intended use “*one concentration where the product is a drug and another concentration where the product is a food and/or dietary supplement*”. Additionally, FDA has previously used this exact policy of enforcement discretion to reconcile natural products that appear in the marketplace that have some level of an active pharmaceutical ingredient (API) present in the dietary supplement or food. Red yeast rice, *Monascus purpurea*, which contains monacolin K (lovastatin), is the most prevalent example however there are others. Generally, the agency does this by establishing a level of the ingredient or daily amount via establishing a health hazard evaluation (HHE). While it does not appear that the agency has established a level in foods or dietary supplements regarding CBD that would be considered a hazard at this time, the World Health Organization (WHO) has established such a level<sup>1</sup>. Regarding abuse potential WHO established a limit of 600 mg per day in healthy subjects. The document states “*An orally administered dose of 600mg of CBD did not differ from placebo on the scales of the Addiction Research Centre Inventory, a 16 item Visual Analogue Mood Scale, subjective level of intoxication or psychotic symptoms. In contrast, THC (10mg oral) administration was associated with subjective intoxication and euphoria as well as changes in ARCI scales reflecting sedation and hallucinogenic activity. THC also increased psychotic symptoms and anxiety. While THC increased heart rate, CBD had no physiological effects.*” Regarding general toxicity WHO states amongst other things that “*It has no effect on a wide range of physiological and biochemical parameters or significant effects on animal behaviour unless extremely high doses are administered (e.g., in excess of 150 mg/kg iv as an acute dose or in excess of 30 mg/kg orally daily for 90 days in monkeys)*”. A 30 mg/kg oral dose would far exceed the 600 mg a day exposure in a 70 kg human. Some recent studies have proposed liver toxicity<sup>2</sup>, however those studies used an animal model that which are known to have a high frequency of spontaneous liver tumors<sup>3</sup>. While based on the pillars of

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<sup>1</sup> [https://www.who.int/medicines/access/controlled-substances/5.2\\_CBD.pdf](https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf)

<sup>2</sup> Ewing L.E. et al. (2019). Hepatotoxicity of a cannabidiol-rich cannabis extract in the mouse model. *Molecules* 24: 24091694.

<sup>3</sup> Bell P. et al. (2006). Analysis of Tumors Arising in Male B6C3F1 Mice with and without AAV Vector Delivery to Liver. *Molecular Therapy* 14: Issue 1, P34-44; Moser G.J. et al. (2008). Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced liver tumorigenicity). *Experimental and Toxicologic Pathology* 61 (2009): 101 - 111

- food and drug law firms would have to have safety studies (i.e. 90-day toxicology studies) specific to their product and the levels of CBD contained therein, these data points should serve as the basis for the FDA to establish an initial level that would allow FDA to take quick enforcement action on products exceeding a daily exposure level that renders the products as unapproved drugs on their face. This would afford the agency to strike a balance between consumer availability via enforcement discretion by understanding the dose at which a natural product becomes a drug and then as such has drug like side effects, which we don't experience in foods or dietary supplements both by our legal frame work which has given us the safest food and drug supply in the world, and by the tenants of science<sup>4</sup>;
- B. Manufacturing and product quality – Specific to CBD manufacturers as of June 6, 2019. Per our FOIA request, FOIA #2019-3350, we asked for records involving manufacturers of CBD and 483's of companies making CBD. The FOIA indicated that only four (4) firms have been inspected, and of those firms three (3) received a 483. Four inspections when there are an estimated 1,500 CBD products on the market is in no way adequate. More troubling is in that FOIA we also asked for information on samples taken and how many were tested for Tetrahydrocannabinol (THC). There were only 29 testing entries three of which mentioned THC, however they appeared partially redacted, so the disposition of such sampling is unknown to us. These numbers do not send a message of a willingness to engage on enforcement regarding CBD products and especially those that could possible contain levels of THC, which is still a schedule I substance. More testing and inspections of firms making CBD should be a top priority for the agency with a proliferation of products on the market; and
- C. Legal authorities – Lastly, the agency can and must act on what has been described in section A & B now. While FDA has not made any written statements on it exercising enforcement discretion, the fact that approximately 1,500 products have come to market and FDA has not acted on them based on the definitional aspects of the ingredient means that they are allowing the product to stay on the market via enforcement discretion. The definitional aspects can be addressed by notice and

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<sup>4</sup> [https://en.wikipedia.org/wiki/The\\_dose\\_makes\\_the\\_poison](https://en.wikipedia.org/wiki/The_dose_makes_the_poison)



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comment rulemaking, in the interim rulemaking does NOT prohibit the agency from stabilizing the marketplace now while adding real regulatory oversight and effort.

Thank you for your consideration of this matter,

Daniel Fabricant, Ph.D.  
President and CEO