July 23, 2021

(b) (4)

Dear (b) (4)

This letter is to inform you that the notification that you submitted, on behalf of Irwin Naturals, pursuant to 21 United States Code (U.S.C.) § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)), was received and filed by the Food and Drug Administration (FDA or we) on March 3, 2021. Additional information was received on March 22 and May 3, 2021. The amendment received on May 3, 2021, was deemed a substantive amendment, which reset the filing date to May 3, 2021, as per 21 CFR 190.6(d). Your notification concerns the new dietary ingredient (NDI) Full-Spectrum Hemp Extract (FSHE) (hereinafter "NDI 1199") that you intend to market in a dietary supplement.

According to your notification, the conditions of use are: "Dietary supplements containing the NDI will only be intended for use by adults over 18 years of age." Further, the conditions of use "specify that the NDI can be taken various times per day, depending on the ingestible form (i.e., tablet, capsule, soft gel, gelcap, or liquid), and the total amount recommended will not exceed 765 mg of FSHE/MCT-oil per day, which includes approximately 65 mg/day of naturally occurring CBD." Further, "The product label will advise that the dietary supplement is not intended to be used by pregnant and lactating women; or by individuals taking medications, or individuals having pre-existing medical conditions without speaking to their physician first."

Under 21 U.S.C. § 350b(a), the manufacturer or distributor of a dietary supplement containing a NDI that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. § 350b(a)(2), there must be a history of use or other evidence of safety establishing that the NDI, when used under the condition recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. § 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your notification and other available information and determined that your NDI 1199 cannot be used in dietary supplements pursuant to the dietary supplement exclusion provision in 21 U.S.C. § 321(ff)(3)(B) (section 201(ff)(3)(B) of the Act).

U.S. Food and Drug Administration
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The definition of a dietary supplement is set forth in 21 U.S.C. § 321(ff) (section 201(ff) of the Act), which states in relevant part:

> (ff) The term 'dietary supplement' . . . (3) does . . . (B) not include – (i) an article that is approved as a new drug under section 355 of this title . . . or (ii) 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 approval . . . 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 chapter.

FDA has concluded that CBD products are excluded from the dietary supplement definition under 21 U.S.C. § 321(ff)(3)(B) (section 201(ff)(3)(B) of the Act). CBD is the active ingredient in the approved drug product, Epidiolex. Furthermore, the existence of substantial clinical investigations involving CBD has been made public. FDA has also determined that CBD was not marketed as a dietary supplement or conventional food before it was authorized for investigation as a new drug.[1] FDA has concluded that NDI 1199 is a CBD product and is therefore subject to the exclusion that is described above. Based on the record, FDA has concluded that NDI 1199 is designed to ensure consistent levels of CBD; that it is produced from hemp plants that contain robust amounts of CBD; that the manufacturing process results in a product that delivers a relatively high amount of CBD per day, comparable to a drug product; and that currently marketed products indicate that you market "full-spectrum hemp extract"-containing products as CBD products. Looking at the totality of the record, FDA has concluded that your NDI 1199 is a CBD product and thus is subject to the exclusion from the definition of dietary supplement under 21 U.S.C. § 321(ff)(3)(B). Accordingly, your product may not be marketed as or in a dietary supplement.

We also conclude that, even if NDI 1199 was not excluded from the definition of dietary supplement, the agency has significant concerns about the adequacy of safety evidence included in your notification as a basis for concluding that a dietary supplement containing your NDI 1199 will reasonably be expected to be safe when used under the conditions of use described in your notification. For example, your notification asserted a general history of use of various cannabis preparations (including extracts) and preclinical and clinical studies of certain cannabis preparations. These categories of evidence had deficiencies on their own and, even when all of the evidence was considered as a whole, the notification failed to show that the NDI will reasonably be expected to be safe. For example, your evidence for history of use was vague and did not provide an adequate description of the cannabis preparations (e.g., composition), serving levels, or frequency and durations of use which makes it difficult to compare this history of use to the proposed conditions of use for your ingredient and establish the safety of your product. Furthermore, you provided preclinical and clinical studies on different phytocannabinoid mixtures that, in some cases, were not completely characterized and could not be compared to your ingredient; therefore, you did not adequately establish how these study results inform the

[1] *See* "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#dietarysupplements

expectation of safety of your ingredient. Moreover, your notification did not adequately address certain reported toxicity endpoints of CBD such as hepatotoxicity and reproductive toxicity. For these reasons, the information in your submission indicates that, even if NDI 1199 were not excluded from the definition of a dietary supplement, your notification does not provide an adequate basis to conclude that a dietary supplement containing the ingredient, when used under the conditions recommended or suggested in the labeling of your product, would reasonably be expected to be safe. Therefore, if it were a dietary supplement, a product containing your NDI 1199 may be adulterated under 21 U.S.C. § 342(f)(1)(B) (section 402(f)(1)(B) of the Act).

If you have additional or new information that has a bearing on the issues discussed in this letter, you may present it to FDA for our consideration.

Your notification will be kept confidential for 90 days after the filing date of May 3, 2021. After the 90-day date, the notification will be placed on public display at www.regulations.gov as new dietary ingredient notification report number 1199. Prior to that date, you may wish to identify in writing specifically what information you believe is trade secret or confidential commercial information and include an explanation of the basis for this belief.

If you have any questions concerning this matter please contact Jeanne Skanchy, R. Ph, by email at NDITEAM@fda.hhs.gov.

Sincerely,

Cara Welch -S Digitally signed by Cara Welch -S
Date: 2021.07.23 16:20:11 -04'00'

Cara Welch, Ph D.
Acting Director
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition