U.S. FOOD & DRUG ADMINISTRATION

(b) (6), (b) (4)

APR 2 8 2017

Dear (b) (6), (b) (4)

This letter is to inform you that the notification, dated February 16, 2017, that you submitted on behalf of American Botanicals Corporation 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) on February 17, 2017. Your notification concerns a dietary supplement containing a new dietary ingredient that you call "(b) (4) and describe as an (b) (4) of the dried leaf of *Mitragyna speciosa* (Korth.) Havil (Rubiaceae) standardized to contain (b) (4) You intend to market the new dietary ingredient in your liquid dietary supplement.

According to your notification, you intend to market a liquid dietary supplement containing the new dietary ingredient with the following conditions of use: "The recommended serving size is 40 mL/day of (b) (4) , equivalent to 20 mg/day of mitragynine / day. The dietary supplement will contain the following additional statements and warnings regarding its intended use: [f]irst time users try half and wait 20 minutes. Do not exceed 1 bottle per day. Do not consume for more than 4 consecutive weeks. Never mix with alcohol or medication; excessive use may cause nausea. Not intended for those under 18. Do not consume on an empty stomach. Do not consume if pregnant or breastfeeding, or if operating a motor vehicle, machinery, or if you have liver disorder, heart disease, high blood pressure, CNS disorder, or other medical condition, or are taking medication. Use responsibly."

Under 21 U.S.C. § 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient 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 new dietary ingredient, when used under the conditions 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 new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

U.S. Food and Drug Administration
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College Park, MD 20740
www.fda.gov

FDA has carefully considered the information in your submission and the Agency has significant concerns about the evidence on which you rely to support your conclusion that "(b) (4)" will reasonably be expected to be safe under the conditions of use described in your notification.

FDA was unable to establish the identity of your new dietary ingredient "(b) (4)" based on the evidence provided in your notification. For example, although your notification provided a list of your formulation ingredients, you did not provide the percent composition of your ingredients in your dietary supplement and a certificate of analysis was not provided for the (b) (4) (b) (4) used in the manufacturing of the dietary supplement. Moreover, your notification did not provide adequate information on the manufacturing of your dietary ingredient and supplement, such as in-process controls for unwanted impurities that may be present in your new dietary ingredient as required by the current good manufacturing practices (CGMPs) for dietary supplements (21 CFR 111). Your notification did not include a batch analysis from at least three lots to demonstrate the manufacturing process consistently produces products that meet the product specifications. Furthermore, you did not provide adequate specifications (e.g., a list of analytical test procedures that include tests for undesirable impurities and contaminants, appropriate acceptance criteria that have numerical limits, ranges, or other criteria for the tests described) for the identity, purity, strength, and composition of the finished batches of your dietary supplement. The specifications are required by 21 CFR 111.70 to ensure your product meets established quality standards. Without such information, it is unclear how the product you intend to market is qualitatively and quantitatively similar to the substances described in the information that you rely on as evidence of safety or how that information forms the basis for a reasonable expectation of safety under the intended conditions of use.

In addition, FDA was unable to establish the safety of your new dietary ingredient, "(b) (4)" based on the history of use provided in your notification. For example, your notification did not provide evidence that your new dietary ingredient or the product that you intend to market has a history of use as a conventional food. Furthermore, your notification did contain quantitative data comparing the serving level and identity of your new dietary ingredient to traditional kratom consumption (e.g. herbal drinking tea); however, you did not provide documentation to support your statement of its consumption, such as the frequency and duration, target population, and how the adverse events were monitored. Moreover, your notification cites several references describing the serving size and daily consumption rates of kratom from various user preparations (e.g. chewing leaves and tea preparation methods) which result in various concentrations of the active alkaloid, mitragynine. Therefore, it is unclear how the concentrations of kratom consumption derived from various preparations are quantitatively and qualitatively related to the product that you intend to market. Furthermore, your notification did not adequately address the adverse events that were reported in these studies[1,2,3] or how consumers who would use your product under the proposed conditions of use would result in a reasonable expectation of safety.

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[1] Vicknasingam, B., et al., The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. Int J Drug Policy, 2010. 21(4): p. 283-8.

[2] Assanangkornchai, S., et al., The Use of Mitragynine speciosa ("Krathom"), an addictive plant, in Thailand. Subst Use Misuse, 2007. 42(14): p. 2145-57.

[3] Singh, D., C.P. Muller, and B.K. Vicknasingam, Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend, 2014. 139: p. 132-7.

Without such information, it is unclear how the history of use information will establish the basis for the safety of your ingredient under the proposed conditions of use.

In addition, FDA was unable to establish the safety of your new dietary ingredient, " (b) (4) based on the pre-clinical studies provided in your notification. For example, the duration of your sub-acute study (7 days) was short, which is inconsistent with your proposed conditions of use. Furthermore, the results of the sub-acute study (although limited to a single oral daily dose) showed significant safety concerns including clinical, biochemical, hematological and histopathological changes, and mortality in 60% (3/5) of female rats. Furthermore, your referenced 28-day rat study is inadequate to address the safety of your product under the proposed conditions of use. For example: 1) you did not relate how the test article that is used in this study is qualitatively and quantitatively related to your product that you intend to market and 2) the results of the study suggested that there were withdrawal signs and changes in hematological parameters that occurred at all dose levels in both males and females, as well as liver, kidney, and brain toxicities at 100 mg/kg body weight[4]. As a result, FDA was unable to determine the no-observed-adverse-effect-level (NOAEL) based on the information you provided since adverse effects were observed at all dose levels. In the absence of an adequate history of use and other evidence of safety, FDA was unable to establish the safety of your new dietary ingredient under the proposed conditions of use.

In addition, FDA was unable to establish the safety of your new dietary ingredient, " (b) (4) based on the cited clinical studies provided in your notification. For example, your notification cited a study in healthy users administered a daily oral dose of kratom tea containing 6.35-23.0 mg of mitragynine for 7 days, and subjects reported increased blood pressure and heart rate with onset delay to 8 hours after drinking kratom tea[5]. This dosage is comparable to your dietary ingredient, " (b) (4) which contains 20 mg of mitragynine per day. Therefore, it is unclear how your clinical studies in your notification form a basis for a reasonable expectation of safety for daily chronic consumption of your dietary ingredient at the proposed serving level.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that your liquid dietary supplement product containing " (b) (4) when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. § 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. § 331(a) and (v).

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[4] Sabetghadam, A., et al., Subchronic exposure to mitragynine, the principal alkaloid of Mitragyna speciosa, in rats. J Ethnopharmacol, 2013. 146(3): p. 815-23.

[5] Trakulsrichai, S., et al., Pharmacokinetics of mitragynine in man. Drug Des Devel Ther, 2015. 9: p. 2421-9.

Your notification will be kept confidential for 90 days after the filing date of February 17, 2017. After the 90-day date, the notification will be placed on public display at www.regulations.gov as new dietary ingredient notification report number 992. Prior to that date, you may wish to identify in writing specifically what information you believe is trade secret or confidential commercial information and an explanation of the basis for this belief.

If you have any questions concerning this matter please contact Dr. Fred Hines, Consumer Safety Officer (CSO), Evaluation and Research Staff, at (240) 402-1756 or by email: Fred.Hines@fda.hhs.gov.

Sincerely,

Robert J. Durkin, Esq., M.S., R.Ph.
Deputy Director
Office of Dietary Supplement Programs
Center for Food Safety
and Applied Nutrition