U.S. FOOD & DRUG ADMINISTRATION

(b) (4)

November 5, 2021

Dear (b) (4)

This letter is to inform you that the notification 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 or we) on August 30, 2021. Your notification concerns the new dietary ingredient, (b) (4) extract of the dried ground leaf of *Mitragyna speciosa* (Korth.) Havil (Rubiaceae)", also called "kratom extract", that you intend to market in a dietary supplement and as a bulk dietary ingredient.

According to your notification, the conditions of use are: "Dietary supplements containing the dietary ingredient kratom extract are intended to be used by adults over the age of 18. The finished dietary supplement will be (b) (4) . The recommended serving will be (b) (4) The label will also contain numerous other warnings and directions for use." (b) (4) "

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

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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.

FDA has carefully considered the information in your submission and we have significant concerns about the evidence on which you rely to support your conclusion that your dietary supplement containing "kratom extract" 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, "kratom extract", based on the evidence provided in your notification. For example, your notification did not provide specific information on the origin of the botanical raw material and the strict procedures for the selection of the raw leaf material used in the production of your new dietary ingredient to ensure quality of the final dietary ingredient. Your description of the manufacturing process did not include a flow chart and in-process quality controls to establish the purity and quality of the finished dietary supplement. Your manufacturing information did not describe how the dietary supplement was standardized to contain a specific level of the new dietary ingredient (i.e., kratom extract that delivers 20 mg of mitragynine per serving). Moreover, your notification did not include the amount (percent composition) of each ingredient in the dietary supplement. Furthermore, your specification information did not include the acceptance criteria and analytical methods for Mitragynine Analogs A, B, C, D, E, & F in the botanical raw material, the new dietary ingredient, and the product. Your notification did not provide the analytical data, calculations, and results used to verify that specifications are met for the botanical raw material, the new dietary ingredient, and the dietary supplement. Without such information, it is unclear how the product that 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.

FDA was unable to establish the safety of your new dietary ingredient, "kratom extract", based on the history of use provided in your notification. For example, your notification did not establish how the identity and composition of traditional kratom leaf preparations are quantitatively and qualitatively related to the identity and the composition of your proposed new dietary ingredient. Your notification cited several references describing the serving size and daily consumption rates of kratom from various user preparations (e.g., chewing leaves and tea preparation methods) for different purposes (e.g., increasing stamina, managing opioid abuse, and attenuating chronic pain) that resulted in ingestion of various concentrations and amounts of the active alkaloid mitragynine. Moreover, your notification stated on page 28 that ingestion of the proposed new dietary ingredient is (b) (4) This comparison is inconsistent with the published literature[1,2] that shows kratom leaves have been found to contain

[1] Tanguay, P., 2011. Kratom in Thailand: decriminalisation and community control? Legislative Reform Drug Policies 13, 1–16.

[2] Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N. H., Suhaimi, F. W., Vadivelu, R., . . . Müller, C. P. (2013). From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev*, *37*(2), 138-151.

(b) (4)

Therefore, it is unclear how the kratom leaf preparations with various concentrations of mitragynine and consumption practices are quantitatively and qualitatively related to the product that you intend to market or how they address the safety of your new dietary ingredient under your proposed conditions of use. Furthermore, it is unclear how the conditions of use (i.e., serving sizes, frequencies of use, durations, target populations and adverse events) that were reported in published studies[3,4,5,6] of traditional kratom preparations, that result in multiple ranges of daily mitragynine intakes (b) (4) are adequate to address the safety for your new dietary ingredient under your proposed conditions of use.

Therefore, FDA was unable to establish, based on the history of use provided in your notification, that your proposed new dietary ingredient, "kratom extract", when used under the conditions recommended or suggested in the labeling, would reasonably be expected to be safe.

In addition, FDA was unable to establish the safety of your new dietary ingredient, "kratom extract", based on "other evidence of safety" provided in your notification. Your current notification contains the same toxicology studies that were relied upon in your previous submissions. FDA objected to your previous new dietary ingredient notifications #992 and #1063 in part because you did not include adequate "other evidence of safety." For example, the results of the (b) (4) In the absence of other subchronic data that utilizes a different animal model that is relevant to human sensitivity, metabolism, or pharmacokinetics; it cannot be determined whether the changes at a (b) (4) . Therefore, it is unclear whether the changes observed following the repeated oral dose toxicity study can be considered biologically significant or toxicologically relevant. For this reason, FDA was not able to determine a no-observed-adverse-effect-level (NOAEL) for the study and disagrees with your determined (b) (4) Furthermore, your 90-day study was inadequate to address the safety of your new dietary ingredient under the proposed conditions of use even at your determined NOAEL. Your new dietary ingredient was derived from kratom (*Mitragyna speciosa*) leaves, known to contain various pharmacoactive alkaloids including mitragynine and 7-hydroxymitragynine[7], can cause untoward effects. For the reasons stated above, FDA was unable to establish, based on the pre-clinical studies provided in your notification, that your proposed new dietary ingredient, "kratom

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[3] Singh, D., Yeou Chear, N. J., Narayanan, S., Leon, F., Sharma, A., McCurdy, C. R., . . . Balasingam, V. (2020). Patterns and reasons for kratom (Mitragyna speciosa) use among current and former opioid poly-drug users. *J Ethnopharmacol*, *249*, 112462.

[4] 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, 283-8.

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

[6] European Monitoring Centre for Drugs and Drug Addiction. (2015). *Kratom Drug Profile*. Retrieved June 22 from https://www.emcdda.europa.eu/publications/drug-profiles/kratom_en

[7] Maxwell, E. A., King, T. I., Kamble, S. H., Raju, K. S. R., Berthold, E. C., León, F., . . . Sharma, A. (2020). Pharmacokinetics and Safety of Mitragynine in Beagle Dogs. *Planta Med*, *86*(17), 1278-1285.

extract", when used under the conditions recommended or suggested in the labeling, would reasonably be expected to be safe.

In addition, FDA has reviewed the relevant published scientific literature on *Mitragyna speciosa* and concluded that it is likely that constituents of this plant, such as mitragynine and its analogues, are psychoactive compounds that may have an abuse or addiction potential,[8,9] which may include withdrawal symptoms,[10,11,12] as well as death.[13] Withdrawal symptoms have been reported to usually begin 18-24 hours after the last dose of kratom (i.e., kratom tea or extract) and continued for 1-14 days.[12] However, your notification did not contain history of use or other evidence of safety information that adequately addressed the above potential adverse effects in consumers who would use your new dietary ingredient, "kratom extract." Therefore, FDA was unable to establish that your proposed new dietary ingredient, "kratom extract", when used under the conditions recommended or suggested in the labeling, would reasonably be expected to be safe.

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

Your notification will be kept confidential for 90 days after the filing date of August 30, 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 1220. 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.

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[8] Suwanlert S. A study of kratom eaters in Thailand. *Bulletin on Narcotics*. 1975, 27(3), 21–27.
[9] Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH. Self-treatment of opioid withdrawal using kratom (*Mitragyna speciosa* Korth.). *Addiction*. 2008, 103, 1048–1050.
[10] Saingam D, Assanangkornchai S, Geater AF, Balthip Q. Pattern and consequences of krathom (*Mitragyna speciosa* korth.) use among male villagers in southern Thailand: a qualitative study. *Int. J. Drug Policy*. 2013, 24, 351–358.
[11] Singh D, Muller CP, and Vicknasingam,BK. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug and Alcohol Dependence*. 2014, 139, 132-137.
[12] Ahmad K, Aziz Z. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. *J. Ethnopharm*. 2012, 141, 446–450
[13] Neerman MF, Frost RE, Deking J. A drug fatality involving Kratom. *J Forensic Sci*. 2013, 58 Suppl 1, S278-9.

If you have any questions concerning this matter please contact Jeanne Skanchy, R.Ph., Division of Research and Evaluation, at (240) 402-8790 and by email: NDITEAM@fda.hhs.gov.

Sincerely,

Ali A. Abdel-rahman -S

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