U.S. FOOD & DRUG ADMINISTRATION

OCT 25 2019

(b) (4)

Dear (b) (4) :

This letter is to inform you that the Food and Drug Administration (FDA) filed your notification that you submitted on behalf of BD Botanicals Ltd., 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)), on August 15, 2019. Your notification concerns a new dietary ingredient you call "*Mitragyna speciosa* strain XML007" that you intend to market as a bulk dietary supplement ingredient that you call "Kratura™".

According to your notification, the conditions of use are: "BD Botanicals recommends a maximum dosage of 600 mg Kratura per day. BD Botanicals does not intend for products containing Kratura to be used by pregnant or nursing women or children. BD Botanicals recommends a maximum dosage of 600 mg Kratura per day. Excluded population is nursing or pregnant women and children."

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 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 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 the Agency has significant concerns about the evidence on which you rely to support your conclusion that your new dietary ingredient, "*Mitragyna speciosa* strain XML007", will reasonably be expected to be safe under the conditions of use described in your notification.

FDA was unable to establish the safety of your new dietary ingredient, "*Mitragyna speciosa* strain XML007", based on the pre-clinical study provided in your notification. It is unclear how this 90-day repeated-dose oral toxicity study of "*Mitragyna speciosa* strain XML007" in rats contributes to a basis for a conclusion that a dietary supplement containing your new dietary ingredient has a reasonable expectation of safety under the proposed conditions of use described in your notification. For example, this 90-day study lacked the proper endpoints to evaluate the potential safety concerns related to the consumption of kratom

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(*Mitragyna speciosa*) and its pharmacoactive alkaloids (e.g., mitragynine and 7-hydroxymitragynine), which may include abuse potential, physical dependence, and withdrawal symptoms. Furthermore, the results of this study showed that oral administration of "*Mitragyna speciosa* strain XML007" at doses of 100, 1000 and 2000 mg/kg/day for 90 days followed by a 4-week recovery period for the high dose group only resulted in different degrees of toxicological effects. For example:

1) Oral administration of "*Mitragyna speciosa* strain XML007" at the doses of 100, 1000 and 2000 mg/kg/day to female and male Sprague-Dawley rats for 90 days resulted in a decrease in mean rearing counts at all dose levels and slightly lower arousal was observed in males treated at 2000 mg/kg/day.
2) Male rats treated with 2000 mg/kg/day exhibited ocular changes (i.e., lenticular opacities) that both persisted and progressed following the 4-week recovery period and was correlated with histopathological changes (minimal lenticular vacuolation observed at histological examination).
3) Organ weight increases in the thyroid/parathyroid of all animals treated with ≥ 100 mg/kg/day correlated with macroscopic findings of dark discoloration in this gland. In addition, these organ weight increases in male and female rats treated with ≥ 1000 mg/kg/day correlated with microscopic findings of pigmentation of the colloid and/or cytoplasm of follicular epithelial cells of the thyroid.

In the absence of another subchronic study that utilizes a different animal model that is relevant to human metabolism, or pharmacokinetics, or both; it cannot be determined whether the above changes are transient or persistent. Therefore, it is unclear whether the changes observed above 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 NOAEL for the study. In the absence of human historical consumption of safe use data, it is unclear how a single rodent sub-chronic toxicity study establishes the safety of the new dietary ingredient under the proposed conditions of use.

Furthermore, your 90-day study is inadequate to address the safety of your new dietary ingredient under the proposed conditions of use even at your determined NOAEL. Inasmuch as the new dietary ingredient is derived from kratom (*Mitragyna speciosa*) leaves, which are known to contain various pharmacoactive alkaloids including mitragynine and 7-hydroxymitragynine, the intrinsic alkaloids are known to cause untoward effects, such as abuse potential, physical dependence, and withdrawal symptoms. A more reliable safety assessment should include significantly higher safety factors to address the safety of a dietary supplement containing your new dietary ingredient under your proposed conditions of use (chronic use).

In addition, in the absence of human historical consumption of safe use data, a more reliable safety assessment should be included, such as genotoxicity testing. You stated in your notification that the new dietary ingredient is a combination of at least 7 different alkaloids including caffeic acid, which you stated was determined by the International Agency for Research on Cancer (IARC) to have a possible carcinogenic effect. Your notification did not include genetic toxicology testing (i.e., bacterial mutagenesis, *in vitro* cytogenetics, and *in vivo* mammalian test).

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, "*Mitragyna speciosa* strain XML007", when used under the conditions recommended or suggested in the labeling, would reasonably be expected to be safe.

FDA has also reviewed the relevant published scientific literature on kratom and its pharmacoactive alkaloids (e.g., mitragynine and 7-hydroxymitragynine) and its potential abuse. Based on this literature review, FDA has concluded that it is likely that consumption of these alkaloids (mitragynine and its analogues) can have significant adverse effects. The prolonged adverse effects of mitragynine may be due in part to its physical properties (i.e., mitragynine is a lipophilic alkaloid and is poorly soluble in water)[1]. It is a stimulant at low doses and has a long duration of action with a terminal half-life of 23-24 hours and has a very high volume of distribution.[2] Published human and animal studies suggest that mitragynine and 7-hydroxymitragynine are both acting as an opioid receptor agonist with high affinity to the mu-opioid receptor[3,4], which can lead to such adverse effects as analgesia and euphoria.[5] Furthermore, prolonged daily consumption of mitragynine can result in adverse effects, such as tolerance and physical dependence.[6] These findings suggest that mitragynine and its analogues are psychoactive compounds that may have an abuse or addiction potential,[7,8] which may include withdrawal symptoms,[9,10,11] as well as death.[12] Withdrawal symptoms have been reported to usually begin 18-24 hours after the last dose of kratom (i.e. kratom tea or extract) and continue for 1-14 days.[12] Your notification does not contain data or information that adequately addresses the above potential adverse effects in consumers who would use your "*Mitragyna speciosa* strain XML007." Therefore, FDA was unable to establish that your proposed new dietary ingredient, "*Mitragyna speciosa* strain XML007", 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 the new dietary ingredient, "*Mitragyna speciosa* strain XML007", 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

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[1] Ramanathan S, Parthasarathy S, Murugaiyah V, et al. Understanding the physicochemical properties of Mitragynine, a principal alkaloid of *Mitragyna speciosa*, for preclinical evaluation. Molecules 2015; 20: 4915–4927.

[2] Trakulsrichai S, Sathirakul K, Auparakkitanon S, et al. Pharmacokinetics of mitragynine in man. Drug Des Devel Ther 2015; 9: 2421–2429

[3] Yamamoto LT, et al. Opioid receptor agonistic characteristics of mitragynine pseudoindoxyl in comparison with mitragynine derived from Thai medicinal plant *Mitragyna speciosa*. *General Pharmacology*. 1999, 33 (1),73–81.

[4] Watanabe K, Yano S, Horie S, Yamamoto LT. Inhibitory effect of mitragynine, an alkaloid with analgesic effect from Thai medicinal plant *Mitragyna speciosa*, on electrically stimulated contraction of isolated guinea-pig ileum through the opioid receptor. *Life Sci*. 1997, 60(12):933-42.

[5] Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: Salvia divinorum and kratom. *Clin Toxicol (Phila)*. 2008, 46(2):146-152.

[6] Erowid E, Erowid F. "On Kratom... After 15 Years of International Availability." *Erowid Extracts*. May 2015, 27:12-1

[7] Suwanlert S. A study of kratom eaters in Thailand. *Bulletin on Narcotics*. 1975, 27(3), 21–27.

[8] 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.

[9] 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.

[10] 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.

[11] Ahmad K, Aziz Z. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. *J. Ethnopharm*. 2012, 141, 446–450

[12] Neerman MF, Frost RE, Deking J. A drug fatality involving Kratom. *J Forensic Sci*. 2013, 58 Suppl 1, S278-9.

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).

Your notification will be kept confidential for 90 days after the filing date of August 15, 2019. After the 90-day date, the notification will be placed on public display at www.regulations.gov as new dietary ingredient notification report number 1126. 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 Dr. Fred Hines, Consumer Safety Officer, Evaluation and Research Staff, at (240) 402-1756 and by email: Fred.Hines@fda.hhs.gov.

Sincerely,

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