U.S. FOOD & DRUG ADMINISTRATION

January 4, 2023

(b) (4)

Dear (b) (4) :

This letter is to inform you that the notification that you submitted, on behalf of Johnson Foods LLC, 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 October 21, 2022. Your notification concerns the new dietary ingredient you call "NPI-001, a dried kratom leaf powder", that you intend to market as a dietary supplement under the Trade Name "Mitra-Leaf".

According to your notification, the conditions of use are, "To be consumed intermittently with a labelled serving size of 50 mg/day, not to be consumed more than 15 days in a row or for more than 15 days per 30-day period." The maximum serving of NDI in the dietary supplement is "50 mg/day". The target population is "Intended for use in adults (18 years or older), excluding any adult who is, or may become, pregnant or is breastfeeding."

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.

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 "NPI-001, a dried kratom leaf powder" will reasonably be expected to be safe under the conditions of use described in your notification.

U.S. Food and Drug Administration
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FDA was unable to establish the identity of your new dietary ingredient, "NPI-001, a dried kratom leaf powder", based on the information provided in your notification. For example, your notification provided (b) (4) Without such information, it is unclear how the identity and composition of 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, "NPI-001, a dried kratom leaf powder." For example, (b) (4) . As another example, (b) (4) FDA evaluated your submitted studies and the current literature on *Mitragyna speciosa*. FDA has concluded that prolonged daily consumption of kratom products containing mitragynine and its analogs can result in adverse effects such as tolerance and physical dependence[1], abuse or addiction potential[2,3], which may include withdrawal symptoms,[4,5,6] neurotoxicity and memory deficits,[7,8] drug-drug interaction,[7,9,10] and even death.[7,11]

Your notification does not contain adequate data to address the safety concerns and potential adverse effects in consumers who would use your "NPI-001, a dried kratom leaf powder." Therefore, FDA was unable to establish that your proposed new dietary ingredient, "NPI-001, a dried kratom leaf powder", when used under the conditions recommended or suggested in the labeling, would reasonably be expected to be safe.

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[1] Erowid E, Erowid F. "On Kratom... After 15 Years of International Availability." *Erowid Extracts*. May 2015, 27:12-16.
[2] Suwanlert S. A study of kratom eaters in Thailand. *Bulletin on Narcotics*. 1975, 27(3), 21–27.
[3] 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.
[4] 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.
[5] 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.
[6] Ahmad K, Aziz Z. Mitragyna speciosa use in the northern states of Malaysia: a cross-sectional study. *J. Ethnopharm*. 2012, 141, 446–450
[7] Suhaimi FW, Hassan Z, Mansor SM, and Meuller CP, 2021. The effects of chronic mitragynine (Kratom) exposure on the EEG in rats. Neurosci Lett. 745(6).
[8] Rusydan AM, Lukitaningsih E, and Fakhrudin N. 2022. Mitragyna speciosa: Opioid Addiction Treatment and Risk of Use. Journal of Pharmaceutical Science and Clinical Research. 2: 238-256.
[9] Hanapi NA, Chear NJ, Azizi J, and Yusof SR. 2021. Kratom Alkaloids: Interactions with Enzymes, Receptors, and Cellular Barriers. Front Pharmacol. 12:751656.
[10] Tanna RS, Tian DD, Cech NB, Oberlies NH, Rettie AE, Thummel KE, and Paine MF. 2021. Refined Prediction of Pharmacokinetic Kratom-Drug Interactions: Time-Dependent Inhibition Considerations. J Pharmacol Exp Ther. 376:64–73.
[11] Jittasopa W, and Srisont S. 2021. The Causes of Death and Pathological Findings of Kratom Users. Am J Forensic Med Pathol. 42(4):335-40.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that your new dietary ingredient, "NPI-001, a dried kratom leaf powder", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, a product containing your new dietary ingredient 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).

Your notification will be kept confidential for 90 days after the filing date of October 21, 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 1264. 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 Markeesa Scales, MPH, Division of Research and Evaluation by email: NDITEAM@fda.hhs.gov.

Sincerely,

Philip Yeager -S

Digitally signed by Philip Yeager -S
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R. Philip Yeager, PhD, JD, DABT
Director
Division of Research and Evaluation
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and Applied Nutrition