DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
College Park, MD 20740

DEC 20 2016

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Industrial Chemical
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Dear (b) (4), (b) (6):

This letter is to inform you that the Food and Drug Administration filed your notification, which you electronically submitted on behalf of INI Botanicals, 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 September 8, 2016. Additional information was received on September 13, September 19, September 20, October 3, October 5, and October 11, 2016. You were informed that the information received on October 11,, 2016 was a substantive amendment and the filing date was changed to the date of receipt of the information that constitutes the substantive amendment as per the requirement of 21 CFR 190.6(d). According to your amendment of September 20, 2016, your dietary supplement containing your new dietary ingredient (NDI) is described as "a dietary supplement made from greater than 99% purity extract of Mitragynine from the dried leaves of *Mitragyna speciosa* Korth." You intend to market your dietary supplement under the trade name of "Mitrasafe".

According to your notification's electronic application and amendments, "Mitrasafe" contains (b) (4)" The conditions of use are as follows: "[T]ake up to 5 ml of Mitrasafe daily. Do not consume for more than 30 days. Do not consume … if you are a minor, if you are pregnant, or if you are lactating."

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 the dietary supplement product containing "99% Mitragynine extract" ("Mitrasafe") 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 "Mitrasafe" based on the evidence provided in your notification. For example, your notification did not provide adequate information on the manufacturing such as a flow chart, in-process quality and process controls, and controls for unwanted impurities that may be present in your new dietary ingredient as required by dietary supplement cGMPs (21 CFR 111). In addition, you did not provide a batch analysis from at least three lots to demonstrate that the manufacturing process consistently produces products that meet the product specifications; nor did you provide a certificate of analysis that lists the tests conducted, acceptance criteria, and results of the tests conducted. This information is required to demonstrate the purity and to verify the identity of your new dietary ingredient. Furthermore, your notification did not include product specifications (e.g. test parameters, acceptance criteria, and analytical methods) for your dietary supplement "Mitrasafe". The specifications are required by 21 CFR 111.70 to ensure your product meets established quality standards. In addition, your notification did not include any analytical methods and data to verify the "99% purity" claimed for your new dietary ingredient (e.g., HPLC data). The notification cited only scientific literature information about mitragynine. You have not provided a thorough description of mitragynine (99% extract) as it relates to your product of commerce "Mitrasafe". For example, no information was provided on the chemical structure, molecular formula, CAS number, and description of the extraction method. 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.

Because your notification did not provide adequate identity information, it is unclear how the history of use information or other evidence of safety that you provided can establish the safety of your NDI under the proposed conditions of use.

Nevertheless, FDA reviewed your safety information and has the following concerns. For example, FDA was unable to establish the safety of "Mitrasafe" based on the history of use provided in your notification. Your notification did not provide information that your ingredient or the product you intend to market has a history of use as conventional food. In addition, the notification stated that kratom leaves are traditionally ingested (e.g., chewing, smoking, brewing into a tea), but you did not compare the identity and the conditions of use of the ingested kratom leaves to the identity and the conditions of use of your ingredient, which you state is "99% pure mitragynine extracted from *Mitragyna speciosa*." Furthermore, the notification did not contain human historical exposure consumption data (including serving size, serving frequency, and duration of use) to estimate the amounts of dietary exposure of humans to mitragynine from *Mitragyna speciosa*. Therefore, 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, you were unable to establish the safety of "Mitrasafe" based on your referenced toxicology studies of mitragynine in rats, mice, and dogs. First, your notification did not include safety studies on the product that you intended to market under the proposed conditions of use. Second, you did not relate how the test article that is used in these studies is qualitatively and quantitatively similar to your ingredient. Third, the studies lacked data from doses at which there were no reported adverse effects. The acute and subacute toxicity studies showed significant safety concerns. For example, in the 28-day repeated dose oral

toxicity study of mitragynine (1, 10, or 100 mg/kg) in rats, mitragynine caused withdrawal signs and changed hematological parameters at all dose levels in both males and females, as well as liver, kidney, and brain toxicities at 100 mg/kg body weight. 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. Therefore, the toxicology studies you provided did not establish reasonable evidence of safety of your ingredient under the proposed conditions of use. In the absence of an adequate history of use and inadequate evidence of safety, FDA was unable to establish the safety of your new dietary ingredient under the proposed conditions of use.

For the reason discussed above, the information in your submission does not provide an adequate basis to conclude that "Mitrasafe" 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).

Your notification will be kept confidential for 90 days after the filing date of October 11, 2016. After the 90-day date, the notification will be placed on public display at FDA's Division of Dockets Management (see www.regulations.gov) as new dietary ingredient notification report number 944. 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.

Sincerely,

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