February 26, 2018

Via electronic and regular mail

Sung Park
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Dear Mr. Park:

This letter responds to recent correspondence regarding the new dietary ingredient ("NDI") notification for the ingredient "Mitrasafe," submitted by Industrial Chemicals, LLC, on behalf of INI Botanicals on September 8, 2016, to which FDA responded on December 20, 2016 (the "Response Letter"). The notification described Mitrasafe as a greater than 99% purity extract of mitragynine from the dried leaves of *Mitragyna speciosa* Korth, commonly known as kratom. Mitragynine is one of the principal bioactive alkaloids in kratom.

You and your client, Industrial Chemicals, LLC, have asked FDA to respond to additional information that your client submitted following FDA's December 20, 2016 response. As we have previously explained to you, FDA does not intend to respond to this additional information because FDA has already completed its review of that notification. Your client originally submitted the notification under 21 U.S.C. § 350b(a)(2) on September 8, 2016, and then submitted additional information on September 13, September 19, September 20, October 3, October 5, and October 11, 2016. The information submitted on October 11, 2016 was considered a substantive amendment, thereby resetting the filing date of the notification under 21 C.F.R. § 190.6(d).

As you know, FDA responded to your client's notification on December 20, 2016. Pursuant to 21 U.S.C. § 350b(a), and as explained in the Response Letter, FDA kept the notification confidential for 90 days after the October 11, 2016 filing date. FDA subsequently placed the notification (along with the Response Letter) on public display, as required by 21 U.S.C. § 350b(a). This concluded FDA's review of your client's pre-market notification. We do not respond to information submitted regarding an NDI notification after we have completed our review and responded to the notifier. If you would like for us to consider and respond to additional information related to Mitrasafe, your client should submit a new NDI notification.

Moreover, we have become aware that your client's website, www.mitrasafe.us, includes inaccurate and misleading statements about the legal status of Mitrasafe. Although your client may have complied with the procedural requirement to submit a pre-market NDI notification for Mitrasafe, meeting this threshold requirement does not relieve your client of the obligation to comply with other legal requirements that apply to Mitrasafe and dietary supplements containing Mitrasafe, such as the prohibition on marketing adulterated dietary ingredients and dietary supplements. *See, e.g.*, 62 Fed. Reg. 49,890 (Sept. 23, 1997) ("[A]cknowledgement of the receipt of the premarket notification does not constitute a finding by FDA that the new dietary ingredient . . . is safe, or that it is not adulterated"). In fact, the Response Letter expressly advised your client that FDA had "significant concerns about the evidence on which you rely to support your conclusion that the dietary supplement product . . . will reasonably be expected to be safe" and that our review found that this evidence "does not provide an adequate basis to conclude that 'Mitrasafe' will reasonably be expected to be safe." Response Letter at 1, 3.

Our view that an adequate basis for a reasonable expectation of safety was lacking was based on two factors. First, because the notification did not adequately describe what Mitrasafe is (its "identity," which includes structure, composition, and physical and chemical properties), the notification could not establish that the safety information provided applied to Mitrasafe. *Id.* at 2. Second, even if the notification had adequately established the ingredient's identity, we still had significant safety concerns. In particular, we found that the history of use information in the notification did not establish a basis for the safety of Mitrasafe, and that the toxicology studies your client relied on, even if relevant to the ingredient, did not provide evidence supporting a reasonable expectation of safety. *Id.* at 2-3. In fact, one of the rodent toxicology studies on which the notification relied showed adverse effects at all dose levels. *Id.* at 3. As a result, the Response Letter warned your client that "your product may be adulterated" and that introducing an adulterated product into interstate commerce would violate 21 U.S.C. §§ 331(a) and (v). *Id.*

Nevertheless, your client issued a December 27, 2017 press release that incorrectly states, "Mitrasafe™ is a New Dietary Ingredient that has complied with notification and safety requirements for dietary supplements as required by Food, Drug and Cosmetic Act of 1994" [sic].[1] *See* Industrial Chemicals, LLC Announces New NDIN-Compliant Product, Mitrasafe(TM) – A Kratom Based Dietary Ingredient, *available at* http://www.nasdaq.com/press-release/industrial-chemicals-llc-announces-new-ndincompliant-product-mitrasafetm--a-kratom-based-dietary-20171227-00334. This statement is repeated on your client's website. *See* http://www.mitrasafe.us/industrial-chemical-llc-announces-new-ndin-compliant-product-mitrasafe-a-kratom-based-dietary-ingredient/.

Your client's website, www.mitrasafe.us, also contains a number of other inaccurate and misleading statements. For example, on a page titled "Regulatory Compliance," the website states (among other

[1] It appears that you meant to reference either the Federal Food, Drug, and Cosmetic Act (the "FD&C Act"), or the Dietary Supplement Health and Education Act of 1994 ("DSHEA").

things) that Mitrasafe "has complied with the regulatory framework as required by Food, Drug and Cosmetic Act of 1994." *See* http://www.mitrasafe.us/regulatory-compliance/. A page titled "Mitrasafe Development" states that "Industrial Chemical, LLC has met the challenge and succeeded, bringing compliance, proven safety, and credibility to the Kratom industry with the first 21 CFR 190.6 compliant NDIN for Mitrasafe". *See* http://www.mitrasafe.us/summary-of-kratom/. For the reasons discussed above and in the Response Letter, these statements are not accurate.

Your client's website states that Mitrasafe will be available on February 28, 2018, both in bulk and as a finished product called "Max Relax." *See* http://www.mitrasafe.us/. In the absence of a history of use or other evidence of safety establishing that Mitrasafe, when used under the conditions recommended or suggested in the labeling of Max Relax or any other dietary supplements that contain Mitrasafe, will reasonably be expected to be safe, those products are adulterated under 21 U.S.C. §§ 342(f)(1)(B) and 350b(a) because they contain 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). FDA is aware of no history of use or other evidence of safety establishing that Mitrasafe will reasonably be expected to be safe when used under the conditions set forth in your client's NDI notification, or under any other conditions of use.

Mitrasafe is also a drug within the meaning of section 201(g) of the FD&C Act [21 U.S.C. § 321(g)], because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Your client's website states that "Mitrasafe™ offers the benefits of Kratom in a pure extract format that is water soluble and ready for use in all types of dietary supplements." http://www.mitrasafe.us/summary-of-kratom/. The website then describes the "8 Impressive Benefits of Kratom Leaves." Examples of the many claims on your client's website showing that Mitrasafe is intended for use as a drug include:

- "natural substitute for opium"
  "morphine-like effects"
- "used as a method of curing addiction for hundreds of years"
  "also helps to cover withdrawal symptoms"
- "lower blood pressure"
- "prevent diabetes"
  "diabetes treatment … effectively prevent[] the dangerous peaks and troughs that diabetics face"
- "analgesic properties"
  "pain relief" – described on the website as "[o]ne of the most obvious and widely known effects of kratom leaves"

- "an alternative, natural solution" for "sufferers of Chronic Fatigue Syndrome";
- "widely used … for people who suffer from … depression [and] anxiety";
- "reduce inflammation throughout the body, including the blood vessels and arteries" and "prevent more serious heart conditions, such as atherosclerosis, heart attacks, and strokes"

See http://www.mitrasafe.us/8-impressive-benefits-of-kratom-leaves/.

Mitrasafe is not generally recognized as safe and effective for the above-referenced uses and, therefore, the product is a "new drug" under 21 U.S.C. § 321(p). New drugs may not be legally introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in 21 U.S.C. §§ 331(d) and 355(a). FDA approves a new drug on the basis of scientific data and information demonstrating that the drug is safe and effective.

A drug is misbranded under 21 U.S.C. § 352(f)(1) if the drug fails to bear adequate directions for its intended use. "Adequate directions for use" means directions under which a layperson can use a drug safely and for the purposes for which it is intended. 21 C.F.R. § 201.5. Prescription drugs, as defined in 21 U.S.C. § 353(b)(1)(A), can only be used safely at the direction, and under the supervision, of a licensed practitioner.

Mitrasafe is intended for treatment of one or more diseases that are not amenable to self-diagnosis or treatment without the supervision of a licensed practitioner. Therefore, it is impossible to write adequate directions for a layperson to use your product safely for its intended purposes. In addition, Mitrasafe does not qualify for a regulatory exemption from the requirement to bear adequate directions for use in its labeling. *See* 21 C.F.R. § 201.115. Because Mitrasafe fails to bear adequate directions for its intended use, the product is misbranded under 21 U.S.C. § 352(f)(1). Introducing an unapproved new drug and/or a misbranded drug into interstate commerce is prohibited under 21 U.S.C. §§ 331(a) and (d).

We request that you advise us in writing, before February 28, 2018, as to your client's intention to market Mitrasafe and products containing Mitrasafe. If you believe that your client's products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration. Any additional safety information not in your original new dietary ingredient (NDI) notification should be submitted in the form of a new NDI notification under 21 C.F.R. § 190.6. Please submit your response to Dr. Fred Hines, Consumer Safety Officer, Evaluation and Research Staff, at fred.hines@fda.hhs.gov.

Sincerely,

/s/

Steven J. Tave
Director, Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition

cc: David Derian, INI Botanicals (via electronic mail only)
Andrew Krause, Industrial Chemicals, LLC (via electronic mail only)