December 23, 2022

Cara Welch, Ph.D.
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CFSAN/FDA
Via email: cara.welch@fda.hhs.gov

Re: *Pinellia ternata* as a source of ephedrine

Hello Cara,

I'm writing to follow up on the topic of FDA's 2/23/2022 Warning Letter to Princess Lifestyles LLC, a matter we discussed during our most recent phone call, on November 21, 2022.

This Warning Letter alleges, among other details, that the company's Stomaisu product is an adulterated dietary supplement under 21 U.S.C. 342(f)(1)(A) because, citing 21 CFR 119.1, it "presents an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use." In support of this allegation, the Warning Letter cites the presence of the dietary ingredient *Pinellia ternata*, which, according to the letter, "contains ephedrine alkaloids." The Warning Letter does not reference any testing or analysis of the Stomaisu product, or results of any such testing or analysis, to confirm that the product, in fact, contains ephedrine alkaloids.

If based solely on the presence of *Pinellia ternata* in the product, FDA's allegation in the Warning Letter that the Stomaisu product is adulterated under 21 U.S.C. 342(f)(1)(A) per 21 CFR 119.1 would appear to be improper. 21 CFR 119.1 ("Dietary supplements containing ephedrine alkaloids") states that dietary supplements containing ephedrine alkaloids are adulterated because FDA has concluded they present a significant or unreasonable risk of illness or injury. While the preamble to FDA's final rule asserts, citing a single article (Oshio et al., 1978), that "[o]ther plant sources that contain ephedrine alkaloids include … *Pinellia ternata* (Thunb.) Makino," by its text the regulation itself deems products adulterated only when they actually "contain[] ephedrine alkaloids." See 69 Fed. Reg. 6788, 6789 (Feb. 11, 2004). It should be acknowledged that the preamble also includes the following statement: "We use the term 'dietary supplements containing ephedrine alkaloids' in this final rule to refer to dietary supplements containing botanical sources of ephedrine alkaloids." Id. n.1. However, the controlling regulatory text at 21 CFR 119.1 does not include any such definition for "dietary supplements containing ephedrine alkaloids." Thus, it appears that FDA cannot definitively

conclude that such a dietary supplement product is adulterated under 21 U.S.C. 342(f)(1)(A) based on 21 CFR 119.1, absent confirmation of actual presence of ephedrine alkaloids in such product.

Testing confirming the actual presence of ephedrine alkaloids would seem necessary not only based on the text of the regulation but also based on the existing scientific debate regarding whether *Pinellia ternata* actually contains ephedrine alkaloids. In 2004, FDA relied on Oshio et al. (1978), which reported extracting l-ephedrine hydrochloride from material described as *Pinellia ternata* tuber with a 20 ppm yield. Importantly, the published paper did not reference the method used by the authors to confirm the identity of the botanical substance used in the reported experiment. A later-published analysis by Fang et al. (2019) of a single sample of *Pinellia ternata* (with the plant part and method of identification not provided) reported extracting ephedrine with a 5.5 ppm yield. More recent research by Yahagi et al. (2021) reported non-detection of ephedrine at a detection limit of 0.5 parts per billion in analyses of 55 samples of *Pinellia ternata* tuber. The Yahadi study tried, but failed, to duplicate the findings of the Oshio and Fang studies, and also included DNA analysis to confirm the identity of the materials tested in this research. The totality of the published literature therefore calls into question FDA's 2004 statement that "[o]ther plant sources that contain ephedrine alkaloids include … *Pinellia ternata* (Thunb.) Makino."

I will greatly appreciate your attention to this matter, including an internal inquiry into whether ORA actually confirmed the presence of ephedrine alkaloids to support the Warning Letter's adulteration allegation, and, if not, any ideas or suggestions on how to prevent a recurrence of this apparent misapplication of 21 CFR 119.1 in future Warning Letters (or otherwise).

Thank you for revisiting this subject and any assistance or information you can provide. And please let me know if you would like to schedule a time to discuss this further.

Sincerely,

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References:

Fang L, Xie J, Lin L, Tian M, and Row KH. 2020. Multi-phase extraction of ephedrine from *Pinellia ternata* and herbal medicine using molecular imprinted polymer coated ionic liquid-based silica. *Phytochem Anal* 31:242–251. https://doi.org/10.1002/pca.2888

Oshio H, Tsukui M, and Matsuoka T. 1978. Isolation of *l*-Ephedrine From "Pinelliae Tuber." *Chem Pharm Bull* (Tokyo) 26:2096–2097.

Yahagi T, Atsumi T, Mano S et al. 2021. Quality evaluation of Pinellia tuber by LC-TOF/MS targeted to ephedrine. *J Nat Med* 75:692–698. https://doi.org/10.1007/s11418-021-01485-2