U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

January 29, 2021

GRAS Notice No. AGRN 37

Mr. William Turney
DSM Nutritional Products
45 Waterview Boulevard
Parsippany, NJ 07054

Dear Mr. Turney:

The Food and Drug Administration, (FDA) Center for Veterinary Medicine (CVM or we) completed our evaluation of animal GRAS notice number (AGRN) 37. We received Veramaris USA LLC's (Veramaris or the notifier), a joint venture of DSM Nutritional Products, LLC and Evonik Industries, notice, dated March 19, 2020, received March 26. The notice was filed on June 29, 2020. Veramaris submitted an amendment to the notice on December 4 to address issues regarding information on utility of notified substance.

The notified substance is marine microalgae oil from *Schizochytrium sp.* The notice informs the FDA of Veramaris' view that marine microalgae oil from *Schizochytrium sp.* is GRAS, through scientific procedures, for use as a source of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in canned and dry/extruded cat food at an intended use rate not to exceed 1.5% wt/wt of the diet on a dry matter basis.

Veramaris provides information about the identity, method of manufacture, specifications, analytical methods, contaminants, and stability of the notified marine microalgae oil from *Schizochytrium sp*. To address manufacturing chemistry of the notified substance, the notifier provides information about the identity, method of manufacture, specifications, analytical methods, contaminants, and stability. The notified substance is manufactured using the *Schizochytrium sp*. in a fed-batch culture fermentation. The notifier states that molecular biology techniques demonstrate that the organism is microalgae. The parent strain, ATCC PTA-10208, underwent three successive mutagenesis steps using a standard UV exposure procedure and the production strain was selected after screening for oil production ability and DHA:EPA ratio. The microalgae do not produce toxins such as domoic acid and prymnesin. The manufacturing process for marine microalgae oil from *Schizochytrium sp*. consists of fermentation, cell lysis, recovery of the oil phase (broth concentration, demulsification, centrifugation), oil drying, and packaging. The notifier provided specifications for the marine microalgae oil and has provided its composition and fatty acid profile. The notifier provided a finished ingredient specification of the algal oil along with test method and acceptance criteria: Color (orange to golden brown), DHA+EPA (min. 500 mg/g), DHA (min. 250 mg/g), EPA (min. 100 mg/g), free fatty acids (max.

5%), moisture (max. 0.75%), crude fat (min. 92%), peroxide value (max. 0.5 meq/kg). The commercial product is composed of the marine microalgae oil (min. 98.85%) with added mixed tocopherols (max. 0.15% (1500 ppm)).

Veramaris submitted publicly available information to support the safety of the intended use of marine microalgae oil from *Schizochytrium sp.* as a nutritional source of EPA and DHA in cat food. DHA and EPA are long-chain polyunsaturated omega-3 fatty acids (PUFAs) that have a range of physiological roles in feline health and nutrition and are particularly important for perinatal development of the neural and visual systems. Both the National Research Council (NRC) and the Association of American Feed Control Officials (AAFCO) have established a dietary minimum concentration of EPA+DHA at 0.01% on a dry matter basis for growing and reproducing cats. Many commercial cat foods meet or exceed this requirement through the use of fish oil in the formulation, and marine microalgae oil is meant to serve as a source of DHA and EPA to replace fish oil. Marine microalgae oil is intended to be used in canned and dry cat foods at a concentration not to exceed 1.5% wt/wt of the diet on a dry matter basis. The notice contains a review of publicly available literature examining the feline metabolism of long-chain PUFAs, their functions, and their proposed health benefits. These studies provide supplemental information that supports the underlying assumption that DHA and EPA are important to include in cat diets. The pivotal data to support the utility of the notified substance comes from a sequential gestation-lactation-growth feeding study sponsored by the notifier, which is included in the notice as well as publicly available in a published report. In the sequential gestation-lactation-growth feeding study, female cats were fed a diet containing at various concentrations (0, 0.75%, 1.5%, and 3% wt/wt dry matter basis) starting before mating and continuing throughout gestation and lactation. The selected kittens from these females continued on their mothers' diet until 32 weeks of age. Plasma concentrations of DHA and EPA in the treatment groups of both the adult cats and kittens increased with dietary concentration of the notified substance relative to the control group at all time points, which supports the conclusion that the notified substance provides a bioavailable source of DHA and EPA when the notified substance is incorporated into cat diets.

To address target animal safety, Veramaris provided publicly available information to support the safety of the intended use of marine algal oil produced from *Schizochytrium sp.* as a nutritional source of DHA and EPA in cat food for all life stages at up to 1.5% wt/wt of the diet. Many of the cat studies are non-pivotal but are supportive studies investigating the possible therapeutic benefits of DHA and EPA in the cat diet, rather than safety. Most studies use fish oil as a source of DHA and EPA and are short-term, nutritional or translational research studies with small numbers of animals per treatment group. The lack of long-term safety studies for the use of DHA and EPA in cat food has prevented the NRC from setting a safe upper limit for DHA + EPA in cat diets. Long-term exposure to excess amounts of dietary DHA and EPA is more likely to cause adverse effects than short term or intermittent exposures. To further explore the safety of DHA and EPA, the notifier conducted a safety study during the life stages of gestation, lactation, and growth with cats over a continuous 41-week period that was published by Vuorinen *et al.,* 2020. Adult cats and kittens were fed diets using marine algal oil as a source of DHA and EPA (AOCED). The four test diets were formulated with 0% (0X control), 0.75% (0.5X), 1.5% (1X) and 3.0% (2X) AOCED that contained 0.06, 0.41, 0.82, and 1.62% DHA + EPA/kg of diet, respectively, on a dry matter basis. The average dietary intake of AOCED

across the 0.5X, 1X, and 2X treatment groups ranged from 132 to 926 mg/kg BW/day for the queens and 264 to 3905 mg/kg BW/day for kittens.

The AAFCO publishes in their Official Publication a list of names and definitions for accepted feed ingredients. FDA recognizes these names as being the "common or usual" names for feed ingredients. FDA recognizes the name "marine microalgae oil" as the common or usual name for the notified marine microalgae oil from *Schizochytrium sp.*

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Veramaris' notice, concluding that marine microalgae oil from *Schizochytrium sp.* is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing marine microalgae oil from *Schizochytrium sp.* Accordingly, our response should not be construed to be a statement that foods containing marine microalgae oil from *Schizochytrium sp.* if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice and amendment submitted by Veramaris, as well as other information available to FDA, we have no questions at this time regarding Veramaris' conclusion that marine microalgae oil from *Schizochytrium sp.* is GRAS when used as a source of DHA and EPA in canned and dry/extruded cat food at an intended use rate not to exceed 1.5% wt/wt of the diet on a dry matter basis. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified marine microalgae oil from *Schizochytrium sp.* in cat food under Title 21 of the *Code of Federal Regulations* (21 CFR), part 570.35. Unless noted above, our evaluation did not address other provisions of the FD&C Act. As always, it is the continuing responsibility of Veramaris to ensure that animal food ingredients that it markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with 21 CFR 570.275(b)(2), the text of this letter responding to AGRN 37 is accessible to the public on our website for the Current Animal Food GRAS Notices Inventory at https://www.fda.gov/animal-veterinary/generally-recognized-safe-gras-notification-program/current-animal-food-gras-notices-inventory.

If you have any questions about this letter, please contact Ms. Wasima Wahid at (240) 402-5758 or by e-mail at wasima.wahid@fda.hhs.gov. Please reference AGRN 37 in any future correspondence regarding this GRAS notice.

Sincerely,

/s/

Timothy Schell, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine