September 24, 2020

Mr. William Turney
Head of Regulatory Affairs and Product Quality Management
DSM Nutritional Products
45 Waterview Boulevard
Parsippany, New Jersey 07054

Re: GRAS Notice No. AGRN 36

Dear Mr. Turney:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 36. We received Veramaris USA LLC ("Veramaris") notice on December 3, 2019. The notice was filed on January 2, 2020. Veramaris submitted an amendment to the notice on July 14, 2020 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 dog 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 notifier states that the marine 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 provides specifications for the marine microalgae oil and its composition and fatty acid profile. The notifier provides a finished ingredient specification of the algal oil along with

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test method and acceptance criteria: Color (orange to golden), 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 provides information to address the intended use of the notified substance as a source of DHA and EPA in dog food. DHA and EPA are long-chain polyunsaturated omega-3 fatty acids that have a range of physiological roles in canine nutrition and are particularly important for fetal and neonatal development of the neural and visual systems. Both the National Research Council and the Association of American Feed Control Officials have established a dietary minimum concentration of EPA+DHA at 0.05% on a dry matter basis for growing and reproducing dogs. Many commercial dog foods meet or exceed this requirement through the use of fish oil in the formulation, and the notifier states that marine microalgae oil is meant to serve as a more sustainable source of DHA and EPA to replace fish oil. Marine microalgae oil is intended to be used in canned and dry dog foods at a concentration not to exceed 1.5% of the diet on a dry matter basis. The notice contains a review of publicly available literature examining the canine metabolism of long chain polyunsaturated fatty acids and their bioavailability from dietary sources. These studies provide supplemental information that supports the underlying assumption that DHA and EPA are bioavailable. The pivotal data to support the utility of the notified substance comes from a Gestation-Lactation-Growth feeding study sponsored by the firm, which is included in the notice as well as publicly available in a published report. In the Gestation-Lactation-Growth feeding study, female dogs were fed a diet containing marine microalgae oil at various concentrations (0, 0.75%, 1.5%, and 3%; dry matter basis) starting at mating and continuing throughout gestation and lactation. The selected puppies from these females continued on their mothers' diet until 34 weeks of age. Plasma concentrations of DHA and EPA in the treatment groups of both the adults and puppies increased over time and with diet concentration relative to the control group, which supports the conclusion that the notified substance provides a bioavailable source of DHA and EPA when the notified substance is incorporated into dog diets.

To address the target animal safety, 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 dog food. Most of these pivotal studies were short-term, nutritional studies and contained elements of safety, such as hematology and clinical chemistry parameters. However, prolonged exposure to excess amounts of dietary DHA and EPA is more likely to cause adverse effects. To further explore the safety of DHA and EPA, the notifier conducted a target animal safety study during the life stages of gestation, lactation, and growth over a continuous 43-week period, which is also publicly available (Dahms et al., 2019). Adult dogs and puppies were fed diets using the notified substance as a source of DHA and EPA. The notified substance contained 13% EPA and 47% DHA and was incorporated into 4 diets at use rates of 0% (0X control), 0.75% (0.5X), 1.5% (1X), and 3.0% (2X), providing 0.12, 0.44, 0.83, and 1.69% EPA + DHA/kg of diet, respectively, on a dry matter basis. Absolute quantities of EPA + DHA expressed on a per kg BW basis compared to published safe upper limits of 370 mg EPA + DHA/kg BW/day for adult dogs and 770 mg EPA + DHA/kg BW/day for puppies were:

- The 0.75% (0.5X) diet provided 179 mg EPA + DHA/kg BW/day to adult dogs from the notified substance, and an average of 130 and 134 mg/kg BW/day for male and female puppies, respectively.

- The 1.5% (1X) diet provided 358 mg EPA + DHA/kg BW/day to adult dogs from the notified substance, and an average of 244 and 246 mg/kg BW/day for male and female, respectively, to growing puppies.

- The 3.0% (2X) diet provided 697 mg EPA + DHA/kg BW/day to adult dogs from the notified substance, and 547 mg/kg BW/day for male and female, respectively, to growing puppies.

The Association of American Feed Control Officials (AAFCO) publishes 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 dog 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 dog food under 21 CFR 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 36 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 Dr. Manisha Das at 240-402-5920 or by email at Manisha.Das@fda.hhs.gov. Please reference AGRN 36 in any future correspondence regarding this GRAS notice.

Sincerely,

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