U.S. FOOD & DRUG ADMINISTRATION

February 3, 2025

Center for Regulatory Services, Inc.
Attention: Kristi Smedley, Ph.D.
1536 Canoe House Road
Jamaica, VA 23079

Re: GRAS Notice AGRN 69 – Oxidized beta-Carotene

Dear Dr. Smedley:

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated April 9, 2024, submitted on behalf of your client, Avivagen, Inc., (Avivagen or the notifier). The subject of the notice is oxidized beta-carotene (hereafter referred to as oxidized beta-carotene or the notified substance), to be used as a source of oxidized beta-carotene in food for poultry and swine at a maximum inclusion level of 25 ppm and in food for dairy cattle at a maximum inclusion level of 300 mg per head per day. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. You were notified in a letter dated May 16, 2024, that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 69. On September 10, 2024, CVM received an amendment from the notifier containing additional information. We have completed our evaluation of AGRN 69 and have no questions at this time regarding the conclusion for use of the notified substance in food for poultry (except laying hens), swine, and dairy cattle.

To address the identity, method of manufacture, and specifications of the notified substance, the notifier describes the composition, characterization, manufacturing process and controls, and analytical methods used to establish the specifications of the notified substance. The notified substance is manufactured by complete autoxidation of pure synthetic beta-carotene with air under controlled reaction conditions. The produced notified substance is a complex mixture of beta-carotene oxygen copolymer and apocarotenoid compounds. Oxidized beta-carotene contains a marker compound geronic acid 0.85 ± 0.25% (w/w) and is absent of residual unoxidized beta-carotene. The market formulation contains oxidized beta-carotene 10 ± 1% (w/w). The notifier also provides stability, mixability, and packaging information for the notified substance.

To address target animal safety of the intended use of the notified substance, the notifier provides the following: a) published studies in broiler chickens and swine fed the notified substance at levels of up to 8 ppm; b) corroborative non-published studies in broiler chickens, swine, and dairy cattle fed the notified substance in commercial conditions, and non-published studies on the target animal safety of the notified substance on dogs and cats as supportive evidence for swine; c) data showing the content of oxidized beta-carotene in common ingredients used in animal food such as alfalfa, grass, and gains; d) the estimated exposure resulting from the intended use of the notified substance in the target species; e) published studies on the uptake of oxidized beta-carotene in mice and a toxicological battery of studies in

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rodents that includes acute and subchronic studies and genotoxicity data gathered from in vitro and in vivo studies; and f) information on the safety of the notified substance marketed for dogs and cats over a period of 13 years as supportive evidence for the other species.

The notifier estimates the safe level of exposure to the target species using the no observed adverse effect level (NOAEL) from a rodent subchronic study and compares it to the estimated exposure to oxidized beta-carotene resulting from the intended use of the notified substance in the target species.

The notifier concludes that information on the physical or other technical effect of the notified substance is not necessary because use of the notified substance as a source of oxidized beta-carotene does not impact target animal safety.

To address the human food safety of the intended use of the notified substance, the notifier provides the following: a) data on the level of the notified substance present in some human products with a high content of beta-carotene; b) published studies on the uptake of the notified substance in mice and a toxicological battery of studies in rodents that includes acute and subchronic studies and genotoxicity data gathered from in vitro and in vivo studies; and c) the estimated exposure in humans to the notified substance resulting from the consumption of animal tissues or milk containing oxidized beta-carotene residues.

However, we have questions regarding the notifier's conclusion that the use of the notified substance is safe for use in food for laying hens, under the conditions of its intended use as a source of oxidized beta-carotene at a rate of up to 25 ppm for the following reason:

> The notifier did not provide information to support the potential residues of the notified substance in eggs, and there is limited information available on the metabolism of oxidized beta-carotene in laying hens and its potential to accumulate in eggs.

Section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular. Avivagen did not provide any information to demonstrate that the notified substance functions as intended because the notifier concluded that the intended use would not be expected to impact safety. Therefore, we did not evaluate whether the notified substance would achieve the effect claimed for it. However, please note that if products containing the notified substance bear any claims on the label or in labeling regarding the function of the notified substance, these claims should be supported by appropriate data and information. FDA may take enforcement action if any claims on labels or labeling are found to be false or misleading.

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 Avivagen's notice, as amended, concluding that oxidized beta-carotene as a source of oxidized beta-carotene in food for poultry and swine at a maximum inclusion level of up to 25 ppm and in food for dairy cattle at a maximum inclusion level of 300 mg per head per

day of complete feed 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 the notified substance. Accordingly, our response should not be construed to be a statement that foods containing the notified substance if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice, as amended, submitted by Avivagen, Inc., and other information available to the FDA, we have no questions at this time regarding the notifier's conclusion that oxidized beta-carotene is GRAS as a source of oxidized beta-carotene in food for poultry (except laying hens) and swine at a maximum inclusion level of up to 25 ppm and in food for dairy cattle at a maximum inclusion level of 300 mg per head per day. However, the notice does not provide a sufficient basis for a conclusion that oxidized beta-carotene is GRAS under the condition of its intended use in food for laying hens. The Agency has not made its own determination regarding the GRAS status of the intended use of the notified substance in animal 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 Avivagen, Inc., to ensure that animal food ingredients that the notifier 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 69 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-notificationprogram/current-animal-food-gras-notices-inventory.

If you have any questions or comments, please contact Ms. Lauren Howell at 240-402-8012 or at Lauren.Howell@fda.hhs.gov.

Sincerely,

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