

June 4, 2015

Dr. James La Marta
DSM Nutritional Products, Inc.
45 Waterview Boulevard
Parsippany, New Jersey 07054

Re: GRAS Notice No. AGRN 000-017

Dear Dr. La Marta:

The Food and Drug Administration (FDA) is responding to the notice, dated June 27, 2014 that you submitted on behalf of DSM Nutritional Products, Inc. (“DSM”) under FDA’s Center for Veterinary Medicine (CVM) Pilot Program for substances generally recognized as safe (GRAS) added to food for animals (See 75 FR 31800; June 4, 2010). FDA’s Center for Veterinary Medicine received the notice on July 1, 2014, filed it on July 22, 2014 and designated it as GRAS Notice No. AGRN 000-017.

The subject of your notice is canthaxanthin produced synthetically by oxidation of β -carotene. The notice informs FDA of the view of DSM that canthaxanthin is GRAS, through scientific procedures, as a nutritive antioxidant to support the development of chicks at levels of 6 ppm of complete feed. The intended target animal species and production class includes only breeder chickens.

DSM provides information about the identity, specifications, method of manufacture, and conditions of use of canthaxanthin (CAS number 514-78-3).

DSM provides information about the synthesis of canthaxanthin and its optimized manufacturing process which is tightly controlled. The notified substance is produced synthetically by oxidation of β -carotene via an optimized process based upon the method described in the color additive petition (CAP) of 1971. Following the synthesis, the substance is purified and isolated and excipient materials are added for formulation. DSM states that all the substances used in the manufacture and formulation of the final product are suitable for use in animal feed and comply with regulations of FDA, listed in the Official Publication of the American Association of Feed Control Officials (AAFCO OP), or have been determined by DSM to be GRAS for the intended use. DSM includes raw ingredients and final product specifications. DSM includes analytical methodology to determine canthaxanthin content of the final product, which is added to breeder chicken feeds, as well as the canthaxanthin content in pre-mixes and final complete feed. DSM also provides stability, homogeneity, and packaging information for canthaxanthin.

DSM provides specifications for canthaxanthin, which are the same as those listed in 21 CFR 73.75. DSM provides finished product specifications for canthaxanthin as follows: physical state, solid; 1% solution in chloroform, complete and clear; melting range (decomposition), 207 °C to 212 °C (corrected); loss on drying, max 0.2%; residue on ignition, max 0.2%; total

carotenoids other than trans-canthaxanthin, max 5%; lead, max 10 ppm; arsenic, max 3 ppm; mercury, max 1 ppm; assay, 96 to 101%.

DSM provides published information to support the intended use of canthaxanthin as a nutritive antioxidant to support the development of chicks at 6 ppm in complete breeder chicken feeds. For empirical evidence, DSM includes reports and discussions pertaining to three pivotal studies (Surai et al. 2003, Robert et al. 2007, and Zhang et al. 2011) conducted in breeder chickens that evaluated one or more of the pivotal parameters including MDA/TBARS (malondialdehyde/thiobarbituric acid reactive substances) content, TAC (total antioxidant content), or SOD (superoxide dismutase) content and one additional study (Rosa et al. 2012). The results of these studies in general demonstrate that hatching eggs, incubated eggs/developing chicks, and newly hatched chicks are subject to oxidative insults. Supplementation of canthaxanthin in diets of breeder chickens results in significant favorable responses in pivotal parameters, such as decrease in MDA/TBARS content, or increase in TAC or SOD content in hatching eggs, and developing or newly hatched chicks, specifically selected to assess the nutritive antioxidant effect of canthaxanthin against these oxidative challenges.

To address human food safety, the notice states that the safety of canthaxanthin, which has been available in the market place for over forty years as a color additive, has been reviewed by numerous competent authorities. DSM states that the notified substance meets the specifications stated in 21 CFR 73.75. DSM states that the safety profile of canthaxanthin was evaluated several times by the FDA, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Commission Scientific Committee on Food (SCF), and the European Food Safety Authority (EFSA). Also, a comprehensive evaluation of public toxicity and ADME studies were reviewed by the United States International Life Sciences Institute (ILSI).

To address target animal safety, DSM provided a narrative and corresponding references summarizing canthaxanthin safety including the history of use, metabolism in poultry, several feeding studies, and one target animal study in female breeding chickens. DSM listed three unpublished studies previously submitted to the FDA in CAP 101. Overall, the results of the tolerance studies show that the inclusion of canthaxanthin at a rate of 6 ppm in complete breeder chicken feeds for 10-24 weeks exerts a favorable response or no effects on breeder chicken growth or production parameters. The calculated estimated daily intake for canthaxanthin in female breeding chickens resulting from exposure to canthaxanthin in the diet at the proposed use level provides a safety margin greater than 10-fold for the development of alterations in the electroretinography and formation of canthaxanthin crystals observed in the human retina.

Based on the information provided by DSM, as well as other information available to FDA, the agency has no questions at this time regarding DSM's conclusion that canthaxanthin is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of canthaxanthin. As always, it is the continuing responsibility of DSM to ensure that animal food ingredients that the firm markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

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 and usual” names for feed ingredients. FDA recognizes the name “canthaxanthin” as the common and usual name for canthaxanthin produced synthetically by oxidation of β -carotene.

In addition, in our review of DSM’s notice for canthaxanthin, FDA did not review whether food containing canthaxanthin would violate section 301(II) of the Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. 331(II)], or whether any of the exemptions in section 301(II) apply to foods containing canthaxanthin. Section 301(II) of the FDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FDCA, 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(II) (1)-(4) applies.

In accordance with the Federal Register notice announcing the CVM Pilot Program, a copy of the text of this letter, as well as a copy of the information in this notice that conforms to the information described in your GRAS exemption claim is available for public review and copying via the FDA home page at <http://www.fda.gov>. To view or obtain an electronic copy of this information, follow the hyperlinks from the “Safe Feed” webpage (www.fda.gov/safefeed) under the Seek Ingredient Approval section to “Generally Recognized as Safe (GRAS) Notification Program” where the Animal Food GRAS Inventory is listed.

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-000017 in any future correspondence regarding this submission.

Sincerely,

/s/

Daniel G. McChesney, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine

References:

- Robert, F, Panheleux-Le Bastard, M, Hamelin, C, and C Boulard. 2007. Effects of canthaxanthin supplementation in the ROSS breeder diet on oxidative stress of chicks. Report published in World Poultry Science Association, Proceedings of the 16th European Symposium on Poultry Nutrition, Strasbourg, France, 731-734.
- Rosa, AP, Scher, A, Sorbara, JOB, Boemo, LS, Forgiarini, J, and A Londero. 2012. Effects of canthaxanthin on the productive and reproductive performance of broiler breeders. Poultry Science 91 (3): 660-666.

Surai, AP, Surai, PF, Steinberg, W, Wakeman, WG, Speake, BK, and NHC Sparks. 2003. Effect of canthaxanthin content of the maternal diet on the antioxidant system of the developing chick. *British Poultry Science* 44 (4): 612-619.

Zhang, W, Zhang, KY, Ding, XM, Bai, SP, Hernandez, JM, Yao, B, and Q Zhu. 2011. Influence of canthaxanthin on broiler breeder reproduction, chick quality, and performance. *Poultry Science* 90 (7): 1516-1522.