December 21, 2022

Kristi Smedley, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Rd.
Woodbridge, VA 22192

Re: Animal Generally Recognized as Safe Notice No. 58 – Alpha-Lipoic Acid

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 March 16, 2022, submitted by Hill's Pet Nutrition, Inc. (Hill's or the notifier). The subject of the submission is alpha-lipoic acid to be used as a nutritive antioxidant in food for adult dogs, included at a rate up to 150 ppm. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. Following an initial evaluation, you were notified in a letter dated May 2, 2022 that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 58. We have completed our evaluation of AGRN 58.

To address the chemistry, manufacturing and controls of the notified substance, the notifier provides information about the identity, method of manufacture, and specifications of the notified substance. The notified substance is synthesized using a chemical reaction that converts dihydrolipoic acid to alpha-lipoic acid in the presence of a catalyst followed by multiple steps of centrifugation, purification, and crystallization. The finished alpha-lipoic acid is a racemic mixture of R- and S-enantiomers (dl-forms). It is intended to be used as a nutritive antioxidant in foods for adult, non-gestating, non-lactating dogs at concentrations up to 150 ppm. The notifier provides specifications for the finished product which include: purity of alpha-lipoic acid in the range of 97-102%, loss on drying ≤ 0.2% , residual solvent cyclohexane ≤ 1000 ppm, residual solvent ethyl acetate ≤ 1000 ppm, residual solvent toluene ≤ 50 ppm, melting point 60-62 °C, arsenic ≤ 1.0 ppm, cadmium ≤ 0.5 ppm, lead ≤ 0.5 ppm, mercury ≤ 0.1 ppm, β-lipoic acid ≤ 0.10%, 6,8-epitrihio-octanoic acid ≤ 0.1%, single unknown impurities ≤ 0.10% each, sum of all impurities ≤ 0.3%, and polymers ≤ 1%. The notifier also provides stability, homogeneity, and packaging information for the notified substance. Data from stability studies are provided for both the notified alpha-lipoic acid and for alpha-lipoic acid in dog foods. The notifier further provides a procedure and validation results of an analytical method for the determination of the notified substance in extruded dog foods.

To address target animal safety (TAS) of the intended use of the notified substance, the notice summarizes information regarding relevant safety studies in the published literature, including the results of a pivotal 6-month feeding study in dogs.

Most of the toxicology studies reviewed in the notice were conducted with rats and mice receiving alpha-lipoic acid in dosage form rather than incorporated into a complete dog food and thus are limited to support TAS in dogs. However, several sources conducted dosage studies in dogs administering 0 to 87.7 mg/kg BW/day of alpha-lipoic acid. None of the included studies

revealed any toxicological concerns that would suggest the notified substance may pose a TAS risk when fed to dogs under the conditions of intended use.

The pivotal TAS data come from the 6-month feeding study in which dogs consumed alpha-lipoic acid incorporated into dry kibble diets at concentrations of 0, 50 ppm, 150 ppm, and 300 ppm (as-fed; Anthony et al., 2021). Data pertaining to digestibility, fecal consistency, hematology, serum chemistry, food intake, body weight, and physical examinations were collected. All concentrations of alpha-lipoic acid were generally well-tolerated, and all measured parameters remained within normal limits. The pivotal study supports the use of the notified substance as a safe nutritive antioxidant in food for non-gestating, non-lactating adult dogs.

To address the utility of the notified substance, 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 nutritive antioxidant in food for non-gestating, non-lactating adult dogs at an inclusion amount not to exceed 150 ppm of the diet on an as-fed basis does not impact target animal safety.

The Association of American Feed Control Officials 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 "alpha-lipoic acid" as the common or usual name for the notified substance.

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. The notifier 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, alpha-lipoic acid, 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 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 Hill's notice, concluding that the notified substance, alpha-lipoic acid as a nutritive antioxidant in food for adult dogs, included at a rate up to 150 ppm 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 submitted on behalf of Hill's Pet Nutrition, Inc. as well as other information available to FDA, we have no questions at this time regarding their conclusion that alpha-lipoic acid as a nutritive antioxidant in food for adult dogs, included at a rate up to 150 ppm is GRAS. Unless noted above, our evaluation did not address other provisions of the FD&C Act. As always, it is the continuing responsibility of Hill's Pet Nutrition, Inc. 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 58 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 or comments, please contact Ms. Megan Hall at (301) 796-3801 or at megan.hall@fda.hhs.gov. Refer to AGRN 58 in any future correspondence regarding this notice.

Sincerely,

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

Reference:

Anthony RM, et al., 2021, "Alpha-Lipoic Acid is an Effective Nutritive Antioxidant for Healthy Adult Dogs." *Animals*. 11, 274.