December 5, 2011

Ms. Diane Loiselle
Vice President – Safety, Regulatory & Quality
Hill's Pet Nutrition
400 SW 8th Street
Topeka, Kansas 66603

Re: GRAS Notice No. AGRN 000-003

Dear Ms. Loiselle:

The Food and Drug Administration (FDA) is responding to the notice, dated January 4, 2011, that you submitted 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 January 10, 2011, filed it on February 8, 2011, and designated it as GRAS Notice No. AGRN 000-003.

The subject of your notice is α-lipoic acid. The notice informs FDA of the view of Hill's Pet Nutrition that α-lipoic acid is GRAS, through scientific procedures, for use as an ingredient in dry foods for adult dogs (i.e., at least 1 year old) at levels up to 150 ppm (150 mg/kg food or 0.0150%) as a cellular antioxidant and cofactor of enzymes involved in the metabolism of carbohydrates and amino acids.

FDA has evaluated the information that Hill's Pet Nutrition discusses in its GRAS notice as well as other data and information that are available to the agency. As discussed more fully below, the notice does not provide a sufficient basis for a determination that α-lipoic acid is GRAS under the conditions of its intended use in animal food.

Data and information that Hill's Pet Nutrition presents to support its GRAS determination

Hill's provides information regarding common name of the ingredient, conditions of use, specifications and product analyses, analysis of lots, physical description, general method of manufacture, method validation, and stability information. Public information included general manufacturing methods and analytical methods.

Hill's provides information regarding conditions of intended use of α-lipoic acid in the target species (adult dog), estimated intakes, summaries and references to information pertaining to the use of the substance in target and non-target species of animals, discussion of potential unfavorable information in relation to Hill's determination, and an Expert Panel Review consensus document. The discussion also covers the role of α-lipoic acid in major metabolic pathways and a brief summary of the uptake, metabolism, and elimination of α-lipoic acid. Hill's discusses the potential intended use of α-lipoic acid such as the cellular antioxidant effect and enzyme cofactor function that are part of the GRAS exemption claim. In addition, Hill's also provides other potential biological or physiological effects of α-lipoic acid that are not part of the intended use presented by Hill's in its GRAS exemption claim.

Hill's provides published target animal safety information regarding oral-dose kinetics, genotoxicity, toxicity in mice, toxicity in rats (including acute, subacute/subchronic, chronic, and reproductive and developmental toxicity), toxicity in dogs, and Expert Panel Review consensus document. The pivotal publication reporting the partial safety results (the first 6 months of data) of α-lipoic acid in a 12-month, repeated-dose dog safety study published in Summer 2002 (Zicker et al., 2002) was provided.

FDA's evaluation of the data and information in Hill's Pet Nutrition notice

FDA has the following comments regarding manufacturing chemistry:

1. CVM has no questions at this time regarding this information about α-lipoic acid for use as an ingredient in dry foods for adult dogs (i.e., at least 1 year old) at levels up to 150 ppm (150 mg/kg food or 0.0150%) as a cellular antioxidant and cofactor of enzymes involved in the metabolism of carbohydrates and amino acids, which supports Hill's Pet Nutrition determination that the use of α-lipoic acid is GRAS under the conditions of its intended use(s).

FDA has the following comments regarding demonstration of intended use:

2. Hill's describes the role antioxidant systems have in combating the effect of ROS (reactive oxygen species) and thus, limiting cellular damage from oxidative reactions. Hill's suggests that these antioxidants decline with increasing age in multiple animal species; however, no references are provided to support this statement. Hill's also cites published experimental data to demonstrate that addition of α-lipoic acid to the diet helps improve cellular antioxidant function but several of these studies were conducted in disease models and thus, are not suitable to support the intended use of α-lipoic acid as an animal food. Several studies examined the effect of injected α-lipoic acid in rodents which is also not appropriate, although oral absorption of α-lipoic acid has been demonstrated in dogs. Hill's also cites studies where the impact of α-lipoic acid in the diet was not assessed using parameters that addressed an effect on antioxidant function. Hill's also discusses that experimental data from several rodent studies where α-lipoic acid was fed, demonstrate an antioxidant function of the molecule. However, these studies used the biologically active enantiomer of α-lipoic acid at significantly higher levels than that proposed by Hill's for adult canine diets.

3. The pivotal study presented by Hill's is the paper by Zicker et al. (2002), where adult dogs were fed α-lipoic acid for 3 months at the rate of 150, 1500, 3000, and 4500 ppm in the diet, and the ratio of GSH:GSSG in lymphocytes was used as the pivotal marker to assess oxidative stress. Results of the study indicate a significant overall effect ($P=0.024$) of treatment diets on the GSH:GSSG ratio, with significant differences in the GSH:GSSG ratio observed only for the lowest (150 ppm) and highest inclusion rates (4500 ppm) of α-lipoic acid compared to the change in ratio observed over the experimental period in dogs fed the basal diet alone. An NRC

expert committee (NRC, 2006)[1] found this study, among others, to be inconclusive and that there was a lack of data to establish specific recommendations other than for essential vitamins and minerals that are components of antioxidants. Hill's also presents a study by Paetau-Robinson et al. (2008) where diets containing α-lipoic acid along with vitamins C and E, and three commercial adult dog diets were fed to older dogs and oxidative stress was assessed using multiple markers for oxidative status. However, this study design is flawed as the effect of α-lipoic acid is confounded by the levels of added vitamins C and E in the test diets. A more recent Zicker et al. (2010)[2] abstract suggests that α-lipoic acid can significantly increase the GSH:GSSG ratio when dogs are fed dry food supplemented with α-lipoic acid at 50, 100, 150, and 300 ppm. However, this abstract information is not sufficient on its own to support the stated intended use of α-lipoic acid. Based on the information present in the GRAS notice submitted by Hill's and other information available to the agency, the intended use of α-lipoic acid in dry food for adult dogs at the rate of 150 ppm as an intracellular antioxidant is not adequately supported by the scientific literature.

4. Hill's provides a summary of the role of α-lipoic acid as a cofactor of some of the major enzyme systems in the body, specifically pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). However, Hill's does not present data and information demonstrating a need to supplement α-lipoic acid in the diets of adult dogs in order to maintain the functioning of these enzyme systems. Neither biological marker(s) nor target parameter(s) are identified, and studies are not present or referenced to establish that addition of α-lipoic acid to the diet results in alteration in the reaction pathways catalyzed by these enzymes, thus supporting the need for dietary addition of α-lipoic acid over and above what is available from other diet ingredients and endogenous synthesis. Thus Hill's claim regarding the intended use of α-lipoic acid as a "cofactor of enzymes" is not adequately supported by the scientific literature.

5. In addition, the GRAS Notice contains additional proposed claims which are not present in the GRAS exemption claim signed by Hill's. These statements have not been evaluated as they are not part of the GRAS exemption claim and thus, no conclusions can be drawn about them based on the current GRAS notice submitted by Hill's. In the narrative of the GRAS notice, attempts were made to associate the use of α-lipoic acid and its effects on prevention or mitigation of disease conditions such as cancer, neurodegenerative diseases, and even cognitive dysfunction. These uses of α-lipoic acid would cause α-lipoic acid to be a drug under the Federal Food, Drug, and Cosmetic Act, not a food.

[1] National Research Council. 2006. Nutrient Requirements of Dogs and Cats. pp 347. National Academy Press: Washington, D.C.
[2] Zicker, S. C., Jewell, D. E., Joshi, D., and Davidson, S. (2010) J. Vet. Int. Med. 24(3), pp 772, Abst# 331

FDA has the following comments regarding target animal safety:

6. Hill's presents the findings in the paper by Zicker et al. (2002) as a pivotal study to demonstrate target animal safety. Based on other data and information that are available to the agency, we have questions regarding the study design and the implementation of the study protocol used to support this published article. Significant deficiencies were noted in the 12-month study sponsored by your organization as conducted by your contractor. These deficiencies included, but are not limited to, the lack of uniformity of study system, the identity of contributing scientists, the appended contributing scientific reports (analytical chemistry, clinical pathology, etc.) to the study final report, the oversight by study director and quality assurance on the study sample analysis, etc. conducted at your organization. Based on this data and information, we have questions regarding the safety conclusions of this study.

7. Hill's failed to provide sufficient peer-reviewed and published safety data or information addressing the impact of α-lipoic acid on fertility, sexual behavior, and reproductive performance of adult dogs; survivability of embryos in pregnant female dogs; and fetal and prenatal and perinatal development of the young. The Expert Panel addressed this issue theoretically and did not base the safety determination on scientific data or published information. 21 CFR 570.30(b) requires the same quality and quantity of evidence needed for a food additive petition. This information is of the type that would be required in a food additive petition.

8. The effects noted in improving induced animal disease models, such as diabetic condition of rats induced by streptozocin or testicular toxicity induced by cyclophosphamide, as specified by the Expert Panel can not be used to support the safety of the intended use for animal food ingredients.

We have the following administrative recommendations regarding the notice:

9. The notice should include consecutive page numbers throughout the entire notice.

Conclusions

FDA has evaluated the data and information in AGRN 000-003 as well as other available information. The notice does not provide a sufficient basis for a determination that α-lipoic acid is GRAS under the conditions of its intended use in animal food.

In accordance with the Federal Register notice announcing the CVM Pilot Program, a copy of the text of this letter responding to AGRN 000-003, and 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 "Animal & Veterinary" topic to the "Products" section to the "Animal Food & Feeds" to the "Generally Recognized as Safe (GRAS) Notifications" page where the Animal Food GRAS Inventory is listed.

If you have any questions about this letter, please contact Dr. M. Thomas Hendricks at 240-453-6869 or by email at thomas.hendricks@fda.hhs.gov. Please reference AGRN 000-003 in any future correspondence regarding this submission. If Hill's Pet Nutrition wishes to have FDA consider any new information that Hill's Pet Nutrition submits regarding α-lipoic acid, the appropriate mechanism would be for the notifier to submit, in accordance with proposed 21 CFR 570.36, a complete GRAS notice. FDA would assign a new file number to a new notice regarding α-lipoic acid.

Sincerely,

Sharon A. Benz, Ph.D., PAS
Director
Division of Animal Feeds
Center for Veterinary Medicine