U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

August 30, 2019

Thomas Berger, Ph.D.
Vice President
G-Science, Inc.
5500 Highlands Parkway
Smyrna, GA 30082

Re: GRAS Notice No. AGRN 29

Dear Dr. Berger:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 29. We received G-Science Inc.'s ("G-Science") notice on October 24, 2018. This notice was filed on December 11, 2018.

The notified substance is clinoptilolite of sedimentary origin. This notice informs us of G-Science's view that the notified clinoptilolite of sedimentary origin is GRAS, through scientific procedures, for use as an anticaking agent in diets for cattle, swine, goats, sheep, poultry, cats and dogs at a level up to 1% by weight in complete diets.

G-Science provides information about the method of manufacture and specifications of the notified clinoptilolite. The notified clinoptilolite is produced using conventional pit mining techniques, dried until the moisture is less than or equal to 6%, and milled to particle size of 0.01 – 2.5 mm. The notified clinoptilolite contains at least 80% clinoptilolite and no more than 20% clay minerals and is free of fibers and quartz. The composition of notified clinoptilolite is 62-73% SiO_2, 11-14% Al_2O_3, Si:Al ratio of 4.8-5.4, 2-5.5% CaO, 0.2-1.5% Na_2O, 0.7-2.3% Fe_2O_3, 2.2-3.4% K_2O, and 0.5-1.2% MgO. It also contains no more than 20 mg/kg Pb, 0.1 mg/kg Cd, 2 mg/kg As, 0.05 mg/kg Hg, 0.3 ng WHO-TEQ/kg dioxins, and 0.5 ng WHO-PCDD/F-PCB-TEQ/kg of total of dioxins and dioxin-like polychlorinated biphenyls (PCBs). G-Science also provides the stability and packaging information for the notified clinoptilolite.

To address the intended technical effect of the notified clinoptilolite, G-Science provides published literatures to describe the mechanisms to achieve anticaking effect and general properties of anticaking agents. The notifier compares the notified clinoptilolite to three aluminosilicates, aluminum calcium silicate (21 CFR 582.2122), sodium aluminosilicate (21 CFR 582.2727), and hydrated sodium calcium aluminosilicate (21 CFR 582.2729). These three aluminosilicate substances are GRAS when used as an anticaking agent in animal food at a level not exceeding 2% in accordance with good manufacturing or feeding practice. G-Science provides the identity and compositions of the notified clinoptilolite, and the publicly available

description and composition information for sodium aluminosilicate and aluminum calcium silicate. G-Science discusses the similarities between the notified clinoptilolite and these three aluminosilicate substances.

G-Science references the reports issued by European Food Safety Authority (EFSA) and European Commission (EC) Expert Group for Technical Advice on Organic Production (EGTOP) in which both committees have concluded that clinoptilolite of sedimentary origin has the potential to be effective as an anticaking agent in feedingstuffs. These two reports are used as corroborative information to support the intended anticaking technical effect of notified clinoptilolite in animal food.

In addition, G-Science discusses the potential interference of notified clinoptilolite with animal drug assays in medicated feeds based on published studies on interactions between clinoptilolite and few drugs and organic molecules. As a precaution, the label of the notified clinoptilolite product should include a cautionary statement regarding the potential interference with the bioavailability and assay of the animal drugs in medicated feeds.

To address the target animal safety, G-Science provides studies in: 1) Dairy and beef cattle, sheep/goats; 2) Swine; 3) Layer chickens and broiler chickens; 4) Dogs and cats; and 5) Other non-target species (rodents). G-Science also provides information on the exposure of the target animal species to the contaminants present in clinoptilolite such as heavy metals, and environmental contaminants (dioxins, dioxin-like PCBs, and radionuclides). G-Science compares the daily intake of minerals/heavy metals in animal food containing clinoptilolite at 1% with their maximum tolerated levels (MTLs) established by the National Research Council of the National Academies (NRC) in complete feeds.

G-Science lists published studies in the target species that included clinoptilolite sourced from mines where the notified clinoptilolite is obtained, and mines from other geographic locations. The studies listed in ruminants used appropriate animal models, and represent long-term clinoptilolite exposure, except in calves which were short-term studies. Most studies listed were feeding studies and some studies examined selected hematological/serum chemistry parameters. Most studies listed in swine and poultry were feeding studies, and a few of these studies examined hematological/serum chemistry, or histopathological parameters. The studies in dogs and cats evaluated palatability, and/or nutrient digestibility. These studies were short-term and did not evaluate safety parameters.

G-Science also lists studies in both target and non-target species to address the stability of clinoptilolite in gastric environments; the bioavailability of aluminum in the presence of silicon; carcinogenicity, chronic, reproductive and developmental toxicity of clinoptilolite. Studies in rodents report a non-observed adverse effect level (NOAEL) of clinoptilolite in mice of 25% in the diet (37,500 mg/kg body weight/day), and 50% in rats (25,000 mg/kg body weight/day).

To address human food safety, G-Science references a body of publications showing that clinoptilolite is stable under the physiological and chemical conditions in the digestive system of target animal species; clinoptilolite is not degraded during its passage through the gastrointestinal tract of target animals, it is essentially unabsorbed and excreted in the feces. G-Science states that there are no studies available showing that any impurities contained in clinoptilolite are

deposited in tissues of animals fed with clinoptilolite above maximum permitted levels. G-Science concludes that human exposure to residues of clinoptilolite in animal tissues is unlikely to pose a potential risk or safety issue, and there is no need to determine the estimated daily intake for human consumption for clinoptilolite.

Based on the totality of the data and information described above, G-Science concluded that clinoptilolite of sedimentary origin is GRAS for its intended use in animal food.

FDA's Evaluatin of the data and Information in G-Science's notice and other data and information available to FDA

Based on the information provided by G-Science, as well as other information available to the agency, we have no questions at this time regarding G-Science's conclusion that the use of clinoptilolite of sedimentary origin is safe for cattle, sheep, goats, broiler chickens, turkeys for meat, dogs, and cats, under the conditions of its intended use as an anticaking agent in food for these target animal species at a level of up to 1% of the complete diets. However, we have questions regarding G-Science's conclusion that the use of clinoptilolite of sedimentary origin is safe for layer chickens, under the conditions of its intended use as an anticaking agent in food for layer chickens at a level of up to 1% of the complete diet for the following reasons:

1. There is disagreement on the effects of clinoptilolite on selected parameters in studies conducted in layer chickens exposed to 1% clinoptilolite in the diet. The study by Straková *et al*. 2008, reports that long-term exposure of layers chickens to 1% clinoptilolite (80% purity) on weeks 22-68 decreased egg weight, total plasma protein, triacylglycerol, and magnesium, and increased aspartate aminotransferase (AST), erythrocytes, hemoglobin, and mean corpuscular hemoglobin concentration (MCHC). The study by Herzig *et al*. 2008 reports no adverse effects in layer chickens exposed to 1% clinoptilolite on weeks 22-68 on feed consumption/egg, egg production, egg weight, egg crude protein, calcium, magnesium, and phosphorus.

2. Layer chickens are highly susceptible to mineral imbalances. and the margin for reaching the MTL for aluminum is very low when 1% clinoptilolite is added to the diet of layer chickens. The notified clinoptilolite (which contains up to 14% aluminum) contributes approximately 74% of the MTL for aluminum in the diet of layer chicken, which does not account for the aluminum content of other feed ingredients

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 "clinoptilolite of sedimentary origin" as the common or usual name for the notified clinoptilolite.

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 G-Science's notice concluding that clinoptilolite of sedimentary origin 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 clinoptilolite of sedimentary origin. Accordingly, our response should not be construed to be a statement that foods containing clinoptilolite of sedimentary origin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice provided by G-Science, as well as other information available to FDA, we have no questions at this time regarding G-Science's conclusion that clinoptilolite of sedimentary origin is GRAS when used as an anticaking agent in food for cattle, swine, goats, sheep, broiler chickens, turkeys for meat, cats and dogs at a level up to 1% in complete diets. However, the notice does not provide a sufficient basis for a conclusion that clinoptilolite of sedimentary origin is GRAS when used as an anticaking agent in food for layer chickens at a level up to 1% of complete diet. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified clinoptilolite of sedimentary origin 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 G-Science to ensure that animal food ingredients that the firm 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 29 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. Lei Tang at 240-402-5922 or by email at lei.tang@fda.hhs.gov. Please reference AGRN 29 in any future correspondence regarding this GRAS notice.

Sincerely,

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

References

Herzig I, Strakova E, and Suchy P. Long-term application of clinoptilolite via the feed of layers and its impact on the chemical composition of long bones of pelvic limb (femur and tibiotarsus) and eggshell. *Veterinarni Medicina* 2008;53(10):550-554.

Straková E, Suchy P, Herzig I, Serman V, and Mas N. The long-term administration of a clinoptilolite-supplemented feed to layers and its effect on performance, haematological parameters and metabolic profile. *Czech Journal of Animal Science* 2008;53(5):212-218.