U.S. FOOD & DRUG ADMINISTRATION

NutraSteward Ltd.
Attention: Elizabeth Lewis, Ph.D.
Scientific & Regulatory Advisor
Frederick House
Johnston, Pembrokeshire SA62 3AQ
United Kingdom

Re: GRAS Notice AGRN 72 – Synthetic Sodium Aluminosilicate

Dear Dr. Lewis:

The Food and Drug Administration's (FDA, the Agency) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated July 24, 2024, submitted on behalf of your client, Protekta, Inc. (Protekta or the notifier). The subject of the notice is synthetic sodium aluminosilicate (hereafter referred to as synthetic sodium aluminosilicate or the notified substance) as a calcium and phosphorus absorber in periparturient dairy cattle when included in a top-dress or total mixed ration at 400 grams (g) synthetic sodium aluminosilicate /head/day for up to 14 days immediately prior to calving. 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 August 19, 2024 that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 72. On December 9, 2024, CVM received an amendment from the notifier containing chemistry, manufacturing, and controls information to address questions identified during evaluation of the notice. We have completed our evaluation of AGRN 72 and have no questions at this time.

To address the identity, method of manufacture, and specifications of the notified substance, the notifier provides composition, characterization, manufacturing process and controls, and analytical methods used to establish the specifications of the notified substance. The theoretical mineral composition is Na_2O: Al_2O_3: SiO_2: H_2O in the ratio 6 : 6 : 12 : 27. The notified substance is manufactured by reacting a hot mixture of silica sand and sodium hydroxide with a hot mixture of alumina and sodium hydroxide, followed by filtering and spray drying the slurry. The notifier provides specifications for synthetic sodium aluminosilicate with test methods and the following acceptance criteria: appearance odorless white crystalline powder, composition 17.0 to 20.0% Na_2O, 28.0 to 32.0% Al_2O_3, and 32.0 to 37.0% SiO_2, arsenic ≤ 5 milligrams/kilogram (mg/kg), cadmium ≤ 1 mg/kg, lead ≤ 2 mg/kg, and mercury ≤ 0.1 mg/kg. The notifier also tests for dioxins, polychlorinated biphenyls (PCBs), dioxin-like PCBs, and non-dioxin-like PCBs in the produced synthetic sodium aluminosilicate.

To address the utility of the of the notified substance, the notice provides one published paper regarding the in vitro binding capacity of synthetic sodium aluminosilicate in rumen fluid, and 12 published papers related to utility of synthetic sodium aluminosilicate as an aid to maintain calcium balance in periparturient dairy cows through the binding of calcium and phosphorus. All papers utilized the notified substance with the chemical formula $Na_{12}Al_{12}Si_{12}O_{48} \cdot 27\ H_2O$. Three papers utilized Protekta's market formulation, X-Zelit. One paper used a different, yet similar market formulation, where the notified substance was combined with carriers and other

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components. Four papers used raw synthetic sodium aluminosilicate. Four papers were excluded from consideration due to the paper being written in German, confounding use of synthetic sodium aluminosilicate in the postpartum period, no statistical analysis of the data, and/or the included papers did not match the journal citation. Response variables that were not directly related to nutrition (e.g., immune function, disease incidence, reproductive performance, inflammation) were not considered in this evaluation. The notified substance and not the market formulation was evaluated. The evaluated publications demonstrate that the notified substance sufficiently bound dietary calcium and phosphorus to support utility of the intended use of the notified substance.

To address the target animal safety of the intended use of the notified substance, the notifier provides published literature providing evidence about the metabolic fate of sodium aluminosilicate in ruminants and published feeding studies in which synthetic sodium aluminosilicate was used to supplement the diet of periparturient cows for periods of 14 to 40 days before the expected calving date.

The primary toxicological studies were undertaken by Gloxhuber et al. (1983) using synthetic sodium aluminosilicate in rats and mice, including metabolism, sub-chronic, and a combined chronic and carcinogenicity study. In unpublished studies, the notified substance or an unspecified form of sodium aluminum silicate were administered to rats in 14-day repeat dose and 90-day sub-chronic experiments. These studies investigated the potential for renal toxicity observed in the sub chronic experiment. Sodium aluminosilicate was not associated with adverse systemic effects after oral administration. The notified substance was also not associated with any toxicological effects on the mother, embryonic, or fetal development in teratogenicity studies.

The feeding studies identified in the published literature indicate that the notified substance leads to decreased prepartum dry matter intake (DMI), and decreased blood magnesium and phosphorus during the periparturient period compared to control cows. However, blood magnesium and phosphorus concentrations did not fall below lower physiological limits. In addition, DMI and blood magnesium and phosphorus concentrations returned to normal levels typically within four to seven days post-calving.

To address the human food safety of the intended use of the notified substance, the notifier provides four published papers on the metabolic fate of aluminum to support that aluminum is efficiently cleared from the body via the kidneys and that no accumulation of aluminum in milk is expected to occur. The notice also refers to a published feeding study in which synthetic sodium aluminosilicate was used to supplement the diet of periparturient cows.

To corroborate the safety of milk from periparturient cows receiving the notified substance, the notifier references an unpublished study that included three treatment groups (10 cows/group) fed diets supplemented with 0, 250, or 500 g synthetic sodium aluminosilicate/head/day for an undefined period of time prior to calving. The study observed no significant differences in milk aluminum concentrations at seven- and 14-days post-calving between control and treatment groups. The notifier also provided corroborative data from two unpublished aluminum milk concentration analyses collected post-calving from dairy cows in commercial trials feeding 320-400 g synthetic sodium aluminosilicate/head/day for approximately 14 to 21 days prior to calving. The data indicate no numerical differences in mean values between cows supplemented with synthetic sodium aluminosilicate and control cows.

Section 301(ll) of the Federal Food, Drug, and Cosmetic 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 Protekta's notice, as amended, concluding that synthetic sodium aluminosilicate as a calcium and phosphorus absorber in periparturient dairy cattle when included in a top-dress or total mixed ration at 400 grams synthetic sodium aluminosilicate/head/day for up to 14 days immediately prior to calving 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 synthetic sodium aluminosilicate, 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 on behalf of Protekta, Inc., and other information available to the FDA, we have no questions at this time regarding the notifier's conclusion that synthetic sodium aluminosilicate is GRAS under the intended conditions of use. The Agency has not, however, 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 Protekta, 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 72 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. Megan Hall at animalfood-premarket@fda.hhs.gov.

Sincerely,

/s/
Jeanette B. Murphy, M.S.
Acting Director
Office of Surveillance and Compliance
Center for Veterinary Medicine

Electronic Signature Addendum for Submission ID

M-000153-N-0001-DF-AA

Signing Authority (Role)	Letter Date
Jeanette Murphy: Office Director - Acting	5/8/2025

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