February 11, 2026

BASF Corporation
Attention: Andreas Kern, Ph.D.
Senior Regulatory Affairs Manager
100 Park Avenue
Florham, NJ 92121

Re: GRAS Notice AGRN 82 – Beta-Mannanase from a *Thermothelomyces thermophilus* Strain Expressing an Altered *man1* Gene from *Trichoderma reesei*

Dear Dr. Kern:

The Food and Drug Administration's (FDA, the Agency) Center for Veterinary Medicine refers to a generally recognized as safe (GRAS) notice, dated June 17, 2025, submitted by BASF Corporation (BASF). The subject of the notice is beta-mannanase from a *Thermothelomyces thermophilus* strain expressing an altered *man1* gene from *Trichoderma reesei*, (hereafter referred to as beta-mannanase or the notified substance) to increase the digestibility of beta-mannans in complete and balanced swine diets at a use rate of 800 Thermostable Mannanase Units per kg (TMU/kg) of feed. The submission informs us of BASF's conclusion that the subject of the submission is GRAS through scientific procedures. You were notified in a letter dated July 15, 2025, that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 82. We have completed our evaluation of AGRN 82 and have no questions at this time.

To address the identity, method of manufacture, and specifications of the notified substance, BASF refers to AGRN 67 for information on enzyme identity, manufacturing processes and controls, analytical methods used to determine the mannanase activity, enzyme's pH and thermal profiles, and side activities. One mannanase unit, TMU, is defined as the amount of enzyme that produces reducing carbohydrates having a reducing power corresponding to one µmol mannose from locust bean gum (0.3 g/100 ml, final concentration in the reaction solution: 0.27 g/100 ml) in one minute under the assay conditions of 50.0 ± 0.1°C and pH 3.5. The notified substance is produced from a fermentation of a genetically engineered *Thermothelomyces thermophilus* strain followed by cell inactivation, recovery, and formulation. The production strain is absent in the produced enzyme preparation. BASF provides the same specifications for both market formulations Natupulse® TS (beige to brownish fine powder) and Natupulse® TS L (clear, brownish liquid): enzyme activity ≥8000 TMU/g, lead ≤1.0 mg/kg, aflatoxin B1 <3.0 µg/kg, ochratoxin A <5.0 µg/kg, deoxynivalenol <500 µg/kg, zearalenone <50 µg/kg, *Salmonella* not detected in 25 g, *E. coli* <1 CFU/25g, coliforms < 10 CFU/g. BASF provides stability, enzyme thermotolerance under high temperatures and during pelleting process, and packaging information.

To address molecular biology, BASF refers to AGRN 67 for a description of genetic

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modifications that were performed during development of the source strain, *Thermothelomyces thermophilus* DSM 33149, to produce the notified substance. BASF also addresses genetic stability, potential new open reading frames, and absence of antibiotic resistance markers that were used in the genetic engineering process.

To address target animal safety of the intended use of the notified substance, BASF describes enzyme identity, safety of both the production organism and donor organism, and the manufacturing process. Publicly available safety data provided in support of target animal safety of the notified substance includes a) results of a battery of toxicology studies, including a sub chronic rat study using the notified substance (Kern *et al.*, 2020) and b) a swine tolerance study that demonstrated at least a 100-fold safety factor for the intended use rate of the notified substance (Acosta *et al.*, 2025).

BASF concludes that information on the physical or other technical effect of the notified substance is not necessary because use of the notified substance to increase digestibility of beta-mannans in complete and balanced swine diets does not impact target animal safety.

To address the human food safety of the intended use of the notified substance, BASF refers to the safety narrative from AGRN 67 and includes publicly available data and information to conclude that the notified substance is an enzyme, and because enzymes are proteins, the notified substance is expected to be digested in the gastrointestinal tract of swine and converted into amino acids which are expected to be indistinguishable from the digestions of other proteins in the gastrointestinal tract.

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 firm did not provide any information to demonstrate that the notified substance functions as intended because the firm 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 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 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 the firm's notice concluding that the notified substance 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 by BASF Corporation, and other information available to the FDA, we have no questions at this time regarding BASF's conclusion that beta-mannanase from a *Thermothelomyces thermophilus* strain expressing an altered *man1* gene from *Trichoderma reesei* is GRAS for use in increasing the digestibility of beta-mannans in complete and balanced swine diets at a use rate of 800 Thermostable Mannanase Units per kilogram (TMU/kg) of feed. 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 BASF Corporation 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 82 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. Lauren Howell at animalfood-premarket@fda.hhs.gov.

Sincerely,

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

References

Acosta JP, Lee SA, Fickler A, Stein HH. Tolerance of weanling pigs and effects on growth performance of supplementing corn-soybean meal-based diets with graded levels of a novel exogenous beta-mannanase. Transl Anim Sci 2025;9:txaf061. DOI: 10.1093/tas/txaf061.

Kern A, Shanahan D, Buesen R, Geiger D. Safety evaluation of a beta-mannanase enzyme preparation produced with *Thermothelomyces thermophilus* expressing a protein-engineered beta-mannanase gene. PLoS One 2020;15(12):e0243647. DOI: 10.1371/journal.pone.0243647.