May 6, 2014

Dr. James LaMarta
DSM Nutritional Products, Inc.
45 Waterview Boulevard
Parsippany, New Jersey 07054

Re: GRAS Notice No. AGRN 000-015

Dear Dr. LaMarta:

The Food and Drug Administration (FDA) is responding to the notice, dated July 8, 2013 that you submitted on behalf of DSM Nutritional Products, Inc. ("DSM") 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 July 11, 2013, filed it on August 8, 2013 and designated it as GRAS Notice No. AGRN 000015.

The subject of your notice is a 6-phytase enzyme produced by an *Aspergillus oryzae* strain expressing a synthetic gene coding for a 6-phytase from *Citrobacter braakii* ("phytase"). The notice informs FDA of the view of DSM that phytase is GRAS, through scientific procedures, to increase the digestibility of phytin-bound phosphorous or to increase phosphorous availability from phytate in swine diets when fed at the rate of 500-4000 FYT/kg feed (phytase enzyme units). The intended target animal species is swine.

DSM incorporated by reference AGRN 000014, which is the same phytase for use in poultry. In AGRN 000014, you provided information about the identity, specifications, method of manufacture, conditions of use of phytase, and information about the genetic engineering of the source organism, *Aspergillus oryzae*. The finished product specifications are the same as those indicated in AGRN 000014. Information regarding human food safety was also incorporated by reference to AGRN 000014.

DSM provides published and unpublished information to support the intended use of the phytase to increase phosphorous availability when added at the rate of 500-4000 FYT/kg feed. Eight unpublished study reports were included to support functionality: three studies in weanling pigs, four studies in growing swine, and one study in lactating sows. DSM provided a reference to a published study (Almeida and Stein, 2011) as supporting information to address the functionality of the notified phytase.

To address target animal safety, DSM summarized data that established safety of the production organism and summarized published *in vitro* and *in vivo* toxicology studies which were described in AGRN 000014. In the present notice, DSM summarized published and unpublished tolerance studies in swine that were fed up to 10 times the recommended level, measured in phytase units. Pivotal published articles to support safety of the notified phytase for its intended use were Lichtenberg, et al. (2011) and Guggenbuhl, et al. (2012).

Based on the information provided by DSM, as well as other information available to FDA, the agency has no questions at this time regarding DSM's conclusion that this phytase is GRAS under the stated intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of this phytase. As always, it is the continuing responsibility of DSM to ensure that food ingredients that the firm markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

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 and usual" names for feed ingredients. FDA recognizes the name "phytase" as the common and usual name for 6-phytase produced by an *Aspergillus oryzae* strain expressing a synthetic gene coding for a 6-phytase from *Citrobacter braakii* included in animal food.

In addition, in our review of DSM's notice for phytase, FDA did not review whether food containing phytase would violate section 301(ll) of the Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. 331(ll)], or whether any of the exemptions in section 301(ll) apply to foods containing phytase. Section 301(ll) of the FDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FDCA, 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. *See* section 301(ll) of the FDCA.

In accordance with the Federal Register notice announcing the CVM Pilot Program, a copy of the text of this letter, as well as 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 "Safe Feed" webpage (www.fda.gov/safefeed) under the Seek Ingredient Approval section to "Generally Recognized as Safe (GRAS) Notification Program" where the Animal Food GRAS Inventory is listed.

If you have any questions about this letter, please contact Dr. Andrea Krause at 240-276-9768 or by email at andrea.krause@fda.hhs.gov. Please reference AGRN 000015 in any future correspondence regarding this submission.

Sincerely,

/s/

Daniel G. McChesney, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine

References

Almeida FN and HH Stein. 2012. Effects of graded levels of microbial phytase on the standardized total tract digestibility of phosphorus in corn and corn coproducts fed to pigs. Journal of Animal Science 90:1262-1269.

Guggenbuhl P, D Torrallardona, I Cechova, C Simoes Nunes, Y Wache, F Fru, J Broz. 2012. The Efficacy of a Novel Microbial 6-Phytase Expressed in *Aspergillus oryzae* on the Performance and Phosphorus Utilization in Swine. Journal of Animal Science Advances 2: 438-452.

Lichtenberg, J, PB Pedersen, SG Elvig-Joergensen, LK Skov, CL Olsen, and LV Glitsoe. 2011. Toxicological Studies On A Novel Phytase Expressed From Synthetic Genes in *Aspergillus oryzae*. Regulatory Toxicology and Pharmacology 60: 401-410.