July 8, 2019

James M. Ligon, Ph.D.
Vice President, Regulatory Affairs and Stewardship
Agrivida, Inc.
1023 Christopher Drive
Chapel Hill, NC 27517

Re: GRAS Notice No. AGRN 27

Dear Dr. Ligon:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 27. We received Agrivida Inc.'s ("Agrivida") notice on June 21, 2018 and additional information on August 21, 2018 to support the utility of the notified substance under its intended conditions of use. This notice was filed on September 6, 2018. Agrivida submitted an amendment on March 1, 2019 containing revisions on phytase activity assay method and a published study to support the intended use and target animal safety.

The notified substance is ground grain obtained from a corn (*Zea mays)* variety that expresses an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 (transformation event PY203). The phytase expressed in the notified ground corn grain is designated as Phy02 phytase. This submission informs the United States Food and Drug Administration (FDA) of Agrivida's view that the notified ground corn grain is GRAS, through scientific procedures, for use in swine feed to provide 500-4500 phytase activity units (FTU)/kg complete feed.

Agrivida previously submitted GRAS Notice AGRN 21 to inform FDA that the same ground corn (*Zea mays)* variety that expresses an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 (transformation event PY203), is GRAS, through scientific procedures, for use in poultry feed at a rate providing 250-6000 FTU/kg complete feed. On May 23, 2017, CVM issued a response letter indicating that CVM has no questions at that time regarding the notifier's conclusion that the notified ground corn grain containing Phy02 phytase is GRAS under its intended conditions of use in poultry feed.

Agrivida references the GRAS Notice AGRN 21 for detailed information pertaining to genetic characterization of engineered corn variety, transformation event PY203. In the current notice, Agrivida includes a brief description of the genetic modifications that were performed during the development of the transformation event PY203. Agrivida also summarizes information that describes the nucleotide sequence for the flanking corn genome, inserted nucleotide sequences, junction regions, and the nucleotide sequences for the inserts. Agrivida provides adequate

information to demonstrate that additional T-DNA sequences were not inserted at other locations in the corn genome.

Agrivida references the GRAS Notice AGRN 21 for detailed information pertaining to the identity and manufacturing of method of the notified ground corn grain containing Phy02 phytase (transformation event PY203). The production of the notified substance is the same agronomic practices as is typically used for the production of traditional corn, including the application of chemical fertilizers and crop protection chemicals approved for use on maize. After harvesting, the crop is shelled to produce whole corn grain, which is then dried and milled. Agrivida provides specifications for the finished product which include: 4000-7000 units of phytase activity per gram of grain, *Escherichia coli* (not detected in 10 g), and *Salmonella sp.* (not detected in 25 g). The phytase activity stability, homogeneity, and packaging information for the notified ground corn grain are provided in GRAS Notice AGRN 21. The information regarding phytase thermostability during the pelleting process provided in GRAS Notice AGRN 21 includes some inconsistent stability results for pelleting temperatures above 80°C.

To address the functionality of the expressed Phy02 phytase, Agrivida references the GRAS Notice AGRN 21 for detailed information pertaining to the identity of the Phy02 phytase enzyme expressed in the notified ground corn grain. The notifier failed to adequately establish that the kinetic parameters of the notified Phy02 phytase and the two selected commercial phytase enzymes are substantially equivalent. However, the pivotal and supporting parameters in the published study (Broomhead *et al.* 2019) show significant responses to demonstrate intended phytase function when the notified substance was added in swine diets at 500 FTU/kg feed. In addition, results of two unpublished studies conducted in swine provide corroborative evidence that the notified substance achieves the intended effect as a source of phytase activity in swine feed when added at 500 FTU/kg feed.

To address the target animal safety, Agrivida provides publicly available information on the safety of both, the production host (corn) and the gene donor (*Escherichia coli* K12 strain MG1655). Agrivida also provides an exposure assessment of swine to the notified substance resulting from its dietary inclusion at the maximum intended use level. Agrivada also provides the published study (Broomhead *et al.* 2019) to demonstrate that inclusion of the notified ground corn grain up to 4,000 FTU/kg feed did not elicit adverse effects in swine. Agrivida cites other published studies in which pigs administered diets containing 3,000-6,000 FTU/kg feed of the notified Phy02 enzyme showed no adverse effects on growth performance, bone characteristics, and nutrient digestibility in pigs. As corroborative information, Agrivida provides an unpublished tolerance study showing the inclusion of the notified ground corn grain up to 10X of the intended maximum use level did not alter growth or hematological parameters for growing pigs.

To address human food safety, Agrivida states that expressed Phy02 phytase, as with most proteins, will be metabolized during animal digestion into constituent amino acids and will not present a hazard to human health following consumption of swine consuming feed containing Phy02 phytase. The notifier adds that it has demonstrated that Phy02 phytase enzyme is sensitive to digestion in a simulated gastric environment. The notifier concludes that meat derived from

animals that consume feed treated with Phy02 phytase is safe for human consumption and does not present any human safety concerns.

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 "phytase" as the common or usual name for 6-phytase produced by a corn (*Zea mays*) variety that expresses an altered *appA* 6-phytase gene obtained from *E. coli* strain K12 (transformation event PY203).

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 Agrivida's notice concluding that ground grain obtained from a corn (*Zea mays)* variety that expresses an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 (transformation event PY203) 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 ground grain obtained from a corn (*Zea mays)* variety that expresses an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 (transformation event PY203). Accordingly, our response should not be construed to be a statement that foods containing ground grain obtained from a corn (*Zea mays)* variety that expresses an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 (transformation event PY 203), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice and amendment submitted by Agrivida, as well as other information available to FDA, we have no questions at this time regarding Agrivida's conclusion that ground grain obtained from a corn (*Zea mays*) variety expressing an altered *appA* 6-phytase gene obtained from *Escherichia coli* strain K12 is GRAS under its intended conditions of use. Our evaluation only pertains to the transformation event PY203 described in this notice. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified ground corn grain containing Phy02 phytase enzyme 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 Agrivida 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 27 is accessible to the public on our website for the Current Animal Food GRAS Notices Inventory at http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/ucm243845.htm.

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 27 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

J. N. Broomhead, P. A. Lessard, R. M. Raab, and M. B. Lanahan, Effects of feeding corn-expressed phytase on the live performance, bone characteristics, and phosphorus digestibility of nursery pigs. Journal of Animal Science, 2019, vol. 97(3), 1254-1261.