



April 15, 2020

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 32

Dear Dr. Ligon:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 32. We received Agrivida Inc.'s ("Agrivida") notice on June 19, 2019 and additional information on July 18, 2019 to support the utility of the notified substance under its intended conditions of use. This notice was filed on July 24, 2019. Agrivida submitted an amendment on February 11, 2020 containing clarifications on the genetic engineering process to develop the production corn strain.

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 PY1203). 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 poultry and swine feed to increase the digestibility of phytin-bound phosphorous or to increase phosphorous availability from phytase. The intended use level is to provide 250-6000 phytase activity units (FTU) per kilogram (kg) of complete poultry feed and 500-4500 (FTU/kg complete swine feed.

Agrivida previously submitted GRAS Notices AGRN 21 and AGRN 27. The notified substance in both AGRN 21 and 27 is ground grain obtained from a corn (*Zea mays*) variety that expresses an altered *appa* 6-phytase gene obtained from *Escherichia coli* strain K12 using a different transformation event, maize event PY203. In GRAS Notice AGRN 21 and 27, the notifier informs FDA that the notified ground corn grain is GRAS, through scientific procedures, for use in poultry and swine feed, respectively. On May 23, 2017 and July 8, 2019, CVM issued response letters indicating that CVM had no questions at that time regarding the notifier's conclusion that the notified ground corn grain containing Phy02 phytase derived from event PY203 is GRAS under its intended conditions of use in poultry and swine feeds, respectively.

In the current notice, the notified substance is ground corn grain derived from transformation event PY1203 to express a phytase enzyme. The same *appa* phytase gene from *Escherichia coli*

strain K12 has been codon optimized for maize, resulting in about 3-fold higher phytase expression compared to event PY203 (AGRN 21 and 27). The intended use level of ground corn derived from event PY1203 is the same as that of ground corn derived from event PY203 (AGRN 21 and 27).

Agrivida includes a description of the genetic modifications that were performed during the development of the genetically engineered corn variety, event PY1203. Agrivida provides information to describe the nucleotide sequences that were present in the T-DNA. The submitted information also describes the nucleotide sequences for the flanking corn genome, genomic/inserted nucleotide sequences, junction regions, and inserted nucleotide sequences. Agrivida provides information to demonstrate that additional T-DNA sequences were not inserted at other locations in the corn genome. Agrivida also addresses the transformation system, the potential production of putative proteins, genetic stability, and the absence of antimicrobial resistance markers in the new corn variety.

Agrivida provides information about the method of manufacture and specifications of the notified substance. 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: 9000-12000 units of phytase activity per gram of grain, *Escherichia coli* (not detected in 10 g), and *Salmonella sp.* (not detected in 25 g). Agrivida has concluded that the stability of the Phy02 phytase in ground corn derived from event PY1203 is as stable as the Phy02 phytase activity of ground corn derived from event PY203 (AGRN 21 and 27). 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 derived from event PY1203, Agrivida submits summary data and information comparing the phytase enzymes expressed by both events PY1203 and PY203, addressing enzyme specific activity, kinetic properties, thermostability, pH activity profile, molecular weight, immunoreactivity, predicted amino acid sequence, and N-terminal sequence analysis. Agrivida concludes that the phytase enzymes expressed in the corn derived from events PY1203 and PY203 are identical. In addition, the intended use levels of the ground corn derived from event PY1203 provide the same levels of phytase activities as the ground corn derived from event PY203 in poultry feed (AGRN 21) and swine feed (AGRN 27). Therefore, Agrivida references functionality data included in GRAS notices AGRN 21 and AGRN 27 to support the intended technical effect of the ground corn expressing Phy02 phytase derived from event PY1203 for poultry and swine, respectively.

To address the target animal safety, Agrivida indicates that the phytase enzymes expressed in the corn derived from event PY1203 and PY203 are identical, and the maximum intended use level of the ground corn derived from event PY1203 is the same as the maximum use level of the ground corn derived from event PY203 in poultry feed (AGRN 21) and swine feed (AGRN 27), respectively. Therefore, Agrivida references the target animal safety data and information included in AGRN 21 and AGRN 27 for the use of ground corn expressing the phytase derived

from event PY203 for poultry and swine, respectively, to support the target animal safety assessment of the phytase expressed by event PY1203.

To address human food safety, Agrivida referenced the information included in GRAS notice AGRN 27 for the use of ground corn grain expressing the phytase derived from event PY203 in swine to support the human food safety of the phytase derived from event PY1203 in both poultry and swine feeds.

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 PY1203).

Section 301(II) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(II) 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(II)(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 PY1203) is GRAS under its intended conditions of use, we did not consider whether section 301(II) 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 PY1203). 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 PY1203), if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

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 PY1203 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 32 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 32 in any future correspondence regarding this GRAS notice.

Sincerely,

/s/

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