U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

April 6, 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 31

Dear Dr. Ligon:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 31. We received Agrivida Inc.'s ("Agrivida") notice on June 04, 2019. This notice was filed on July 15, 2019. Agrivida submitted amendments on August 27, 2019 and February 5, 2020 containing revisions on the claim of the intended use, clarifications on the generic engineering process to develop the production corn variety, and the glucanase activity assay method.

The notified substance is ground grain obtained from a corn (*Zea mays)* variety that expresses an altered AC1 beta-glucanase gene obtained from an environmental DNA library (transformation event FG259). 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 feed to decrease the viscosity of digesta in poultry consuming feed containing high amounts of soluble non-starch polysaccharides when used at 200 – 500 beta-glucanase activity units per kilograms (kg) of complete feed.

Agrivida provides a description of the genetic modifications that were performed during the development of the new corn variety (transformation event FG259) that expresses a beta-glucanase. Agrivida provides information pertaining to the molecular characterization of event FG259 and summarizes information that describes the nucleotide sequences for the flanking corn genome, genomic/inserted junction regions, and inserted nucleotides. Agrivida also addresses the transformation system, the potential production of putative protein at the junction sites between corn genome and the inserted DNA, genetic stability, and the absence of antimicrobial resistance markers in the new corn variety.

Agrivida provides information about the identity, method of manufacture, and specifications of the notified ground corn containing AC1 beta-glucanase. 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: 150-300 units of beta-glucanase activity per gram of grain, *Escherichia coli* (not detected in 10 g), and *Salmonella sp.* (not detected in 25 g). Agrivida also provides AC1 beta-glucanase activity stability, homogeneity, and packaging information for the notified substance. Based on the data provided in the GRAS notice, Agrivida has concluded that the pelleting temperature for poultry feed containing notified ground corn should not exceed 90 °C.

Agrivida provides data and information to address the identity and characteristics of the beta-glucanase enzyme expressed in the notified substance. The intended use of the notified substance is to decrease digesta viscosity in poultry. To address the functionality of the expressed beta-glucanase, Agrivida provides published empirical data and information generated using studies in broiler chickens that served as a model for the functionality of the beta-glucanase enzyme in the notified substance when added to poultry feed at 200-500 AC1 beta-glucanase units per kg feed. Pivotal evidence to establish utility of the notified substance are available in published articles by Ayres *et al.*, 2018 and 2019. Secondary supporting evidence is available based on data generated from a study by Jasek *et al.*, 2018.

To address the target animal safety, Agrivida provides publicly available information on the safety of the production host (corn) and demonstrates the similarity in the altered AC1 beta-glucanase gene sequence compared to Cel5A glucanase of *Thermotoga maritima* (NCBI accession Q9X273). Agrivida applies the decision tree analysis described by Pariza and Johnson, 2001 to support the safety of the expressed AC1 beta-glucanase. Agrivida provides the publicly available tolerance study by Broomhead *et al.* 2019, showing that inclusion of the notified substance at 5,000 U/kg feed (10X the maximum intended use level) did not affect growth, hematological or serum biochemistry parameters, or necropsy findings at day 42 of age in broilers. In addition, Agrivida cites publicly available corroborative studies by Ayres *et al*. 2018, and Jasek *et al*. 2018, showing the effect of the ACl beta-glucanase on growth parameters in poultry. Agrivida also describes that exposure of poultry to other substances that could result from the enzymatic action of the AC1 beta-glucanase would be to substances derived from the maize grain that are considered safe for food.

To address human food safety, Agrivida states that expressed AC1 beta-glucanase, like most proteins, will be metabolized during the animal's digestion into constituent amino acids and will not present a hazard to human health following consumption of poultry that consume feed containing the notified substance. Agrivida adds that it has demonstrated that the AC1 beta-glucanase enzyme is sensitive to digestion in a simulated gastric environment. Agrivida concludes that meat derived from animals that consume feed containing the notified substance 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 "beta-glucanase" as the common or usual name for the beta-glucanase produced by a corn (*Zea mays*) variety that expresses an altered AC1 beta-glucanase gene obtained from an environmental DNA library (transformation event FG259).

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 AC1 beta-glucanase gene obtained from an environmental DNA library (transformation event FG259) 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 AC1 beta-glucanase gene obtained from an environmental DNA library (transformation event FG259). 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 AC1 beta-glucanase gene obtained from an environmental DNA library (transformation event FG259), 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 amendments 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 AC1 beta-glucanase gene obtained from an environmental DNA library is GRAS under its intended conditions of use. Our evaluation only pertains to the transformation event FG259 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 AC1 beta-glucanase 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 31 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 31 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

Ayres, V., Baldwin, H.L., Li, X., Xu, H., Raab, R.M., Boney, J.W., Broomhead, J.N., and Moritz, J.S., (2018). The effect of corn-expressed carbohydrase on performance and digesta viscosity of broilers fed a high non-starch polysaccharide diet. *J. Appl. Poult. Res.* 27:499-506.

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Pariza, M.W., and Johnson, E.A., (2001). Evaluating the safety of microbial enzyme preparations used in food processing: Update for a new century. *Reg. Toxicol. Pharmacol.* 33:173-186.