July 2, 2025

ToxStrategies, LLC
Attention: Jennifer Hinerman, Ph.D.
Senior Scientist 1
23501 Cinco Ranch Blvd.
Suite H210
Katy, TX 77494

Re: GRAS Notice AGRN 73 – Xylooligosaccharides

Dear Dr. Hinerman:

The Food and Drug Administration's (FDA, the Agency) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated July 31, 2024, submitted on behalf of your client Rayonier Advanced Materials, Inc. (Rayonier or the notifier). The subject of the notice is xylooligosaccharides (hereafter referred to as xylooligosaccharides or the notified substance) for use as a source of fermentable fiber in poultry, swine, and fish when included at up to 3%. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. On September 23, 2024, CVM received an amendment from the notifier clarifying the safety as pertaining to the utility of the substance. You were notified in a letter dated October 2, 2024 that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 73.

CVM asked the notifier in a January 29, 2025 email to provide an amendment with additional information to address questions identified during the review of the notice. The notifier submitted a February 12, 2025 amendment to address these questions. In a May 29, 2025 meeting CVM asked for further clarifications and requested an updated amendment. The notifier submitted a June 3, 2025 amendment to address these questions and to amend the intended use to be a source of xylooligosaccharides for poultry, swine, and fish in complete feed when included at up to 1%. We have completed our evaluation of AGRN 73 and have no questions at this time.

To address the identity, method of manufacture, and specifications of the notified substance, the notifier provides information on its identity and components, manufacturing process and controls, and the analytical methods to establish the specifications. The notified substance is a coproduct of cellulose production from hardwood trees. The wood chips undergo prehydrolysis, dissolving lignin, and serial washing and extractions. The resulting purified cellulose with residual xylan-rich hemicelluloses is dissolved, concentrated, and purified via filtration processes to remove the cellulose fibers. The remaining xylooligosaccharides solution is then neutralized with acid. An optional enzymatic hydrolysis may be used to reduce the degree of polymerization of xylooligosaccharides. Final liquid xylooligosaccharides is dried and packaged. The notifier provides specifications for the notified substance: total xylooligosaccharides (! 70%), xylose (7%), moisture (10%), sodium chloride (15%), sodium caseinate (3%), and inactivated enzyme if enzymatic hydrolysis is employed in the manufacturing process. The xylooligosaccharides in the notified substance have the degree of

U.S. Food and Drug Administration
MPN 2, Room E429
12225 Wilkins Avenue
Rockville, MD 20852
www.fda.gov

polymerization (DP) ranges between 2 to 30 xylose units, specifically DP 2-6 (20-65%), DP 7-10 (30%), DP 10-30 (40%). In addition, the notifier provides analytical data for potential contaminants, including microbials, mycotoxins, and heavy metals, from three non-consecutive lots of final products. The notifier also provides stability and packaging information for the notified xylooligosaccharides.

To address the utility of the notified substance, notifier concludes that the utility of the notified substance as a source of xylooligosaccharides does not impact the safety of the target animals when the substance is used at the 1% of the complete feed. CVM does not have questions on this conclusion. Parts of the notice indicate that the notified substance may provide energy, fermentable fiber, and support for normal intestinal health and microbiota populations. However, the utility of the notified substance as a source of energy, fermentable fiber or any other function is not evaluated in this review.

To address the target animal safety of the intended use of the notified substance, the notifier provides a) 18 published studies evaluating the use of xylooligosaccharides in broiler chicken feed; b) four published studies with xylooligosaccharides added to the feed of laying hens; c) 12 published studies with xylooligosaccharides used in swine feed; d) 15 published studies on the effects of xylooligosaccharides supplementation in the feed of a variety of fish species; and e) results of experiments evaluating acute and chronic toxicity of xylooligosaccharides in rodents and dogs.

To address the human food safety associated with the intended use of the notified substance, the notifier refers to data and information in several GRAS notices allowing the use of xylooligosaccharides in human food (GRN 343, GRN 458, GRN 816) and data and information leading to a European Food Safety Authority report (Safety of xylo-oligosaccharides (XOS) as a novel food pursuant to Regulation (EU) 2015/2283) establishing the safety of xylooligosaccharides in human food and explains that xylooligosaccharides will be fermented by microbial flora in the intestinal tract to produce short-chain fatty acids. The fermentation products will be metabolized by the animal and their microbiota to intermediates and metabolic end-products typical of any food containing indigestible carbohydrates.

Section 403(a) of the Federal Food, Drug, and Cosmetic Act

Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular. Rayonier Advanced Materials Inc. has concluded that the intended use of xylooligosaccharides would not be expected to impact safety. Therefore, CVM did not evaluate whether xylooligosaccharides would achieve the effect claimed for it. However, please note that if products containing xylooligosaccharides 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

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 Rayonier's notice, as amended, concluding that xylooligosaccharides for use as a

source of fermentable fiber in poultry, swine, and fish when included at up to 1% 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 xylooilgosachharides if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

CONCLUSION

Based on the information contained in the notice, as amended, submitted on behalf of Rayonier Advanced Materials, Inc., and other information available to the FDA, we have no questions at this time regarding the notifier's conclusion that xylooligosaccharides is GRAS under the intended conditions of use. 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 Rayonier Advanced Materials, Inc. to ensure that animal food ingredients that the notifier 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 73 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-notificationprogram/current-animal-food-gras-notices-inventory.

If you have any questions or comments, please contact Ms. Wasima Wahid at animalfood-premarket@fda.hhs.gov.

Sincerely,

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