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

May 31, 2024

Dr. Elizabeth Lewis
Scientific & Regulatory Advisor
NutraSteward, Ltd.
Frederick House, Hayston View, Johnstown
Pembrokeshire SA62 3AQ
United Kingdom

Re: Animal Generally Recognized as Safe Notice No. 63 - Purified Yeast Cell Wall

Dear Dr. Lewis:

The Food and Drug Administration's Center for Veterinary Medicine (we) refers to a generally recognized as safe (GRAS) notice dated August 31, 2023, received on September 14, 2023, submitted on behalf of your client, Phileo, Division of S.I. Lesaffre, (Phileo or the notifier). The subject of the submission is purified yeast cell wall as a source of beta-glucans in food for all animal species at a use level depending on the animal species and life stage. The submission informs us of the notifier's conclusion that the notified substance is GRAS for use as a source of beta-glucans in all species and life stages when included at 0.125 to 1.2 g/kg complete feed or 0.05 to 10 g/head/day depending on the species and category of animal through scientific procedures. Following an initial evaluation, you were notified in a letter dated October 4, 2023 that the GRAS notice was acceptable for filing, and the notice was designated as AGRN 63. We have completed our evaluation of AGRN 63 and have no questions at this time.

To address the identity, method of manufacture, and specifications of the notified substance, the notifier describes manufacture and process controls, composition, and analytical methods used to determine the contents of β-glucan and other constituents. The notified substance is produced in three stages consisting of the fermentation of non-genetically engineered *Saccharomyces cerevisiae* to yield a cream yeast, autolysis of the cream yeast, and extraction and purification of the β-glucan component of the *S. cerevisiae* cell wall. The notifier provides specifications for the notified substance as follows: β-glucans: ≥50%; Fat: ≤20%, Crude Protein: ≤8%; Ash: ≤10%; Mannans: ≤5%; Moisture: ≤6%; Lead: <1 mg/kg; Arsenic: <1 mg/kg; Cadmium: <0.5 mg/kg; Mercury: <0.1 mg/kg; Mesophilic aerobic flora: <5,000 CFU[1]/g; Yeast and molds: <100 CFU/g; Coliforms: <100 CFU/g; *Escherichia coli*: <10 CFU/g; Salmonella: Absent in 25 g. The notifier has also provided stability and packaging information.

To address the target animal safety of the intended use of the notified substance, the notifier describes/provides publicly available information on the: a) estimated exposure to animals, b) history of safe use of yeast products in animal feed; c) safety of the *S. cerevisiae* source; d) use of yeast cell wall ingredients in poultry, swine, aquaculture, cattle, sheep, rabbits, cats, and dogs; and e) toxicological information for purified yeast cell wall.

[1] Colony forming unit

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The notifier provides a statement recognizing intake of the substance will be self-limiting on the basis that there are detrimental physiological effects associated with the intake of excessive levels of fermentable fiber.

The notifier provides publicly available studies in broiler chickens, laying hens, sows and weaned piglets, salmonid fish, non-salmonid fish, shrimp, pre-ruminating calves and beef cattle, ewes and lambs, rabbits, cats, and dogs all of which were fed yeast cell wall-based ingredients. The studies identified evaluated impacts on digestibility, performance parameters, lactation/milk production, blood chemistry and hematological analyses, and/or survivability. These studies demonstrated either no impact or an improvement ($P \leq 0.05$) for these measures in animals receiving yeast cell wall-based ingredients as compared with untreated control animals, except for pre-ruminating calves. Pre-ruminating calves fed a diet of milk-replacer containing 0.0034% purified yeast cell wall with 70% beta-glucans content exhibited reduced feed intake and a depression in blood parameters. However, these observations occurred only at the end of the study, with no differences being seen during the previous collection points. Furthermore, no significant differences were observed in body weight or gain to feed ratio.

The notifier also provides a narrative based on physiological similarities to support extrapolation of the studies in broiler chickens to support all poultry species and classes, in fish and shrimp to support all aquaculture species, in beef cattle and sheep to support all ruminant species, in poultry, swine, cattle, and dogs to support equine species and further support cats, and in each of the aforementioned species to collectively support all animal species.

The notifier supports the information in target animal species with a history of safe use of whole yeast ingredients (no separation or removal of the yeast cell wall from other components during their manufacturing) within the United States, and the use of purified yeast cell wall in Canada and the European Union (EU). The notifier also provides a battery of toxicology studies utilizing beta-glucans derived from yeast and mushroom sources to further support the safe use of the notified substance in animal food.

To address the human food safety of the intended use of the notified substance, the notifier describes how beta-glucans are not digested or absorbed to any significant extent by animals. Furthermore, the other minor components will be metabolized by animals according to well-established pathways and are not expected to have any significant impact on the composition or quality of animal products. Thus, no residues will deposit in animal products under the conditions of intended use of the notified substance or its metabolites which may pose a safety concern to humans consuming animal products. Additionally, the notifier provided studies that had previously been evaluated by The European Food Safety Authority (EFSA) and the FDA as part of novel foods and GRAS notifications for beta-glucans rich ingredients for use in human food(s).

The Association of American Feed Control Officials publishes in their Official Publication 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 “purified yeast cell wall” as the common or usual name for the notified substance.

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

Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular. The notifier did not provide any information to demonstrate that the notified substance functions as intended because the notifier concluded that the intended use would not

be expected to impact safety. Therefore, we did not evaluate whether the notified substance, purified yeast cell wall, would achieve the effect claimed for it. However, please note that if products containing the notified substance, purified yeast cell wall, 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 (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 Phileo's, Division of S.I.Lesaffre, notice, concluding that purified yeast cell wall as a source of beta-glucans in all species and life stages when included at 0.125 to 1.2 g/kg complete feed or 0.05 to 10 g/head/day depending on the species and category of animal 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 purified yeast cell wall. Accordingly, our response should not be construed to be a statement that foods containing purified yeast cell wall, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice submitted by Phileo, Division of S.I.Lesaffre, and other information available to the FDA, we have no questions at this time regarding the notifier's conclusion that purified yeast cell wall 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 Phileo 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 63 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 Ms. Megan Hall at 301-796-3801 or at megan.hall@fda.hhs.gov.

Sincerely,

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