Ariane Renaud
Laboratoire Innodal
2211 Metropole Street
Longueuil, QC, J4G 1S5
CANADA

Re: GRAS Notice No. GRN 001164

Dear Ms. Renaud:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001164. We received the notice submitted by Laboratoire Innodal (Innodal) on August 25, 2023 and filed it on January 12, 2024. Innodal submitted amendments on December 11, 2023, March 12, April 12, April 16, May 17, May 21, June 5, June 17, and June 28, 2024, that clarified the manufacturing process, technical effect, specifications, intended uses, dietary exposure, and safety information.

The subject of the notice is a chemically synthesized analog of pediocin PA-1 (s-PA-1) specific to *Listeria monocytogenes* for use as an antimicrobial agent on meat and poultry, fish and shellfish, dairy products, vegetables and fruits, and grains at levels up to 5 mg/kg of food.[1] The notice informs us of Innodal's view that these uses of s-PA-1 are GRAS through scientific procedures.

Our use of the term "chemically synthesized analog of pediocin PA-1" or "s-PA-1" in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for non-standardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "chemically synthesized analog of pediocin PA-1" or "s-PA-1".

Innodal describes s-PA-1 as a white to light yellow powder, or transparent to yellowish liquid. Innodal states that s-PA-1 is chemically synthesized according to the 44-amino acid sequence of naturally-occurring bacteriocin pediocin PA-1 found in *Pediococcus*

[1] Innodal states that s-PA-1 is not intended for use in infant formula.

acidilactici, with no post-transcriptional modifications. Innodal states that the only difference between pediocin PA-1 and s-PA-1 is the substitution of methionine at position 31 with leucine.

Innodal provides a description of the manufacturing process for s-PA-1. Innodal states that s-PA-1 is produced by linear standard solid-phase peptide synthesis (SPPS) using an insoluble resin. Innodal provides a detailed description of s-PA-1 synthesis, including coupling of a single amino acid to the resin, elongation of the peptidyl chain, cleavage, and side chain deprotection. The resulting peptide is precipitated, washed, and then dried. The crude peptide is solubilized in an aqueous solution of food grade acetic acid and further purified by ultrafiltration and diafiltration. The resulting solution is either adjusted with water to the concentration of 0.25-1.5% to yield s-PA-1 in a liquid form or freeze dried to yield s-PA-1 in a powder form. Innodal states that s-PA-1 is manufactured according to current good manufacturing practice, and that all solvents and reagents used in the manufacturing process are, at a minimum, of American Chemical Society (ACS) reagent grade. Innodal also states that the solvents and reagents are removed during the manufacture of s-PA-1 by multiple washing and filtration steps.

Innodal provides specifications for s-PA-1 that include specific activity (<800 ng/mL), lead (≤0.017 mg/kg), arsenic (≤0.02 mg/kg), cadmium (≤0.008 mg/kg), mercury (≤0.01 mg/kg), and limits for microorganisms. Innodal provides the results from the analyses of three non-consecutive batches of the powder form and four non-consecutive batches of the liquid form to demonstrate that s-PA-1 can be manufactured to meet these specifications. Based on the results from stability testing, Innodal concludes that s-PA-1 in the liquid form is stable for 12 months when stored at 4 °C in a dark, sealed container.

Innodal estimates the dietary exposure to s-PA-1 from the intended uses to be 12.2 mg/person (p)/d at the mean and 24.4 mg/p/d at the pseudo-90th percentile[2] using data on per capita consumption of dairy, eggs, fruits, vegetables, grains, meat and poultry, and fish and shellfish from the United States Department of Agriculture, Economic Research Services (ERS) Food Availability (Per Capita, 2018-2021) Data System. Innodal notes that the dietary exposure to s-PA-1 from the intended uses is negligible compared to the Institute of Medicine (IOM)'s recommended dietary allowance (RDA) of protein. Therefore, Innodal concludes that the cumulative dietary exposure to protein is not expected to change as a result of the intended uses of s-PA-1.

Innodal discusses the safety of consumption of the source organism *P. acidilactici* that produces natural pediocin. *Pediococcus* spp. including *P. acidilactici* are naturally present in fermented foods, such as fermented seafood, vegetables and grains. Additionally, *P. acidilactici* in combination with two other lactic acid bacteria, is the

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[2] The pseudo-90th percentile dietary exposure approximates the dietary exposure at the 90th percentile by doubling the mean dietary exposure as described in FDA's "Guidance for Industry: Estimating Dietary Intake of Substances in Food" (https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/guidance-industry-estimating-dietary-intake-substances-food).

subject of GRN 000171.[3] Innodal discusses a published study that demonstrated that s-PA-1 was readily digested by pepsin in the simulated gastric fluid and states that no allergenic safety concerns are identified by using sequence comparison with the database Allergen Online. Innodal provides unpublished *in vitro* corroborative data demonstrating the absence of adverse effects of s-PA-1 in HIEC-6, which is a normal small intestinal epithelial cell line.

Innodal provides results demonstrating the antimicrobial effects of s-PA-1 in meat, poultry, fish and shellfish, dairy products, and vegetables.

Based on the totality of evidence, Innodal concludes that s-PA-1 is GRAS for its intended use.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 001164, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

FSIS has completed its review and has no objection to the surface application of s-PA-1 to intact poultry as a processing aid at levels of up to 5 mg/kg, and for surface application to intact raw meat, ready-to-eat (RTE) meat, and poultry products. Regarding labeling, s-PA-1 incorporated into raw and RTE comminuted meat products, RTE poultry products, and blended RTE poultry products, is required to be listed in the ingredients statement as "pediocin."

FSIS requested that we advise Innodal to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of s-PA-1 in meat, poultry and egg products. Innodol should direct such an inquiry to Stephanie Hretz, Director, RMIS, Office of Policy and Program Development, FSIS by email at Stephanie.Hretz@usda.gov.

Standard of Identity

In the notice, Innodal states its intention to use s-PA-1 in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products

[3] Lactic acid bacteria mixture (LAB mixture) consisting of *Lactobacillus acidophilus* (NP35, NP51), *Lactobacillus lactis* (NP7), and *Pediococcus acidilactici* (NP3) was the subject of GRN 000171. We evaluated this notice and responded in a letter dated December 7, 2005 stating that we had no questions at the time regarding the notifier's GRAS conclusion.

may be used in a standardized food only if it is permitted by the applicable standard of identity.

Section 301(ll) of the 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 Innodal's notice concluding that s-PA-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 s-PA-1. Accordingly, our response should not be construed to be a statement that foods containing s-PA-1, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Innodal provided, as well as other information available to FDA, we have no questions at this time regarding Innodal's conclusion that s-PA-1 is GRAS under its intended conditions of use. This letter is not an affirmation that s-PA-1 is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001164 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.08.07 14:43:58 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
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