



Tyler Homer
OmniLytics, Inc.
9100 South 500 West
Sandy, UT 84070

Re: GRAS Notice No. GRN 000752

Dear Mr. Homer:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000752. We received the notice you submitted on behalf of Phagelux (Canada) Inc. (Phagelux) on January 3, 2018, and filed it on January 9, 2018. In an amendment dated March 7, 2018, Phagelux provided more information on product formulation and quality control procedures. In an amendment dated May 10, 2018, Phagelux provided a safety data sheet and clarified the conditions of use for the product.

The subject of the notice is a preparation containing two bacterial monophages (BP-63 and LVR 16-A) specific to *Salmonella enterica* (*Salmonella* phage preparation) for use as an antimicrobial agent to control *Salmonella* in food (including meat, poultry, and egg products) when applied at up to 10^8 plaque-forming units (PFU)/g of food. The notice informs us of Phagelux's view that these uses of *Salmonella* phage preparation are GRAS through scientific procedures.

Phagelux describes *Salmonella* phage preparation as an opalescent liquid consisting of two monophages (BP-63 and LVR 16-A) that are produced and purified separately and mixed in equal concentrations. The *Salmonella* phage preparation has a minimum titer of 10^{10} PFU/mL. Phagelux states that this suspension is a concentrated form that is diluted with water at the application sites to provide a maximum application rate of 10^8 PFU/g of food.

Phagelux describes the method of manufacture for *Salmonella* phage preparation. Both monophages are produced using nonpathogenic bacterial hosts (*Escherichia coli* 12-869E for monophage BP-63 and *S. enterica* 17-37A for LVR 16-A). Phagelux states that the *E. coli* production strain tested negative for the presence of Shiga toxins stx1 and stx2, while the *S. enterica* production strain lacks pathogenicity islands SPI-1 and SPI-2. The production hosts were sensitive to all antibiotics tested apart from *E. coli* 12-869E, which was resistant to penicillin. Phagelux states that all materials used in the manufacture of *Salmonella* phage preparation are safe for use in food and that the final preparation does not contain any known allergens.

The two monophages are produced separately using aerobic fermentation. Each host bacterium is grown to a desired concentration before each monophage is added at a

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predetermined multiplicity of infection. After fermentation, the culture is filtered, washed and concentrated by tangential flow filtration. The concentrated product is filter-sterilized and diluted to a titer of 10^{10} PFU/mL. The individual monophage solutions are then blended together, filter-sterilized, packaged, and refrigerated.

Phagelux describes specifications for *Salmonella* phage preparation that include an analysis of the potency ($>10^{10}$ PFU/mL); identity (using PCR analysis and matching the results with reference profiles) and sterility (no bacterial growth after 7 days). Phagelux discusses the results from an analysis of three batches of the *Salmonella* phage preparation that examine the physical and chemical composition.

Phagelux estimates the dietary exposure to *Salmonella* phage preparation based on consumption data for the food categories of its intended use. Phagelux estimates that the average *per capita* consumption of these food categories is 727.3 g/person/day based on data from the Economic Research Service of the USDA (2017). To estimate dietary exposure to the *Salmonella* phage preparation, Phagelux assumes that all the relevant foods are treated with *Salmonella* phage preparation at applied at a rate of 10^8 PFU/g of food. This scenario results into a dietary exposure of 7.27×10^{10} PFU/person/day.

Phagelux discusses the safety of use of *Salmonella* phage preparation. Phagelux states that phages are ubiquitous in the environment and the human body. Phagelux also states that humans consume phages via various foods; hence phages are found in the human digestive system. Phagelux states that the biology of lytic phages has been extensively studied and documented. Phagelux notes that most lytic phages display very limited host range even among specific bacteria and bacteria strains, and lytic phages have a reduced potential for bacterial development of resistance. Citing a published repeat dose study, Phagelux states that there were no adverse effects when large numbers of phages were administered orally to children with acute bacterial diarrhea. Phagelux also cites published studies that show that there were not observed adverse effects from topical application of phages. Phagelux reports that the proposed exposure of its *Salmonella* phage preparation is equivalent to similar phage products that are already on the market.

Phagelux provides data from its own studies demonstrating the antimicrobial effects of *Salmonella* phage preparation when applied to a variety of foods (raw chicken breast, spinach, crab, pre-cut apples, deli sliced honey baked ham, eggs, salmon, and ground beef) at 10^8 PFU/g.

Based on the totality of information discussed above, Phagelux concludes that *Salmonella* phage preparation is GRAS for its intended use.

Standards of Identity

In the notice, Phagelux states its intention to use *Salmonella* phage preparation in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products

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

Use in Products under USDA Jurisdiction

During its evaluation of GRN 000752, FDA consulted with the Risk, Innovations, and Management Staff (RIMS) of the Food Safety and Inspection Service (FSIS) of USDA. Under the Federal Meat Inspection Act, Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS is responsible for determining the efficacy and suitability of food ingredients in meat, poultry, and egg products as well as prescribing safe conditions of use. Suitability relates to the effectiveness of the ingredient in performing the intended purpose of use and the assurance that the conditions of use will not result in an adulterated product, or one that misleads consumers.

FSIS has reviewed the information and has no objection to the use of the *Salmonella* phage preparation specific to *S. enterica* as an antimicrobial agent to control *Salmonella* when applied to egg products and the surfaces of ready to eat meat and poultry products, and meat and poultry carcasses and parts at up to 10⁸ PFU/g. No labeling statement is required when used under the accepted conditions of use.

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 Phagelux's notice concluding that the *Salmonella* phage preparation 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 *Salmonella* phage preparation. Accordingly, our response should not be construed to be a statement that foods containing *Salmonella* phage preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Phagelux provided, as well as other information available to FDA, we have no questions at this time regarding Phagelux's conclusion that *Salmonella* phage preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *Salmonella* phage preparation 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 000752 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A.

Adams -S


Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

 Digitally signed by Michael A.
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cc: William K. Shaw Jr., Ph.D.
Director
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