



Kristi O. Smedley, PhD
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Rd.
Woodbridge, VA 22192

Re: GRAS Notice No. GRN 001215

Dear Dr. Smedley:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001215. We received FINK TEC GmbH (FINK)'s notice on July 22, 2024, and filed it on November 5, 2024. FINK submitted amendments to the notice on January 27, 2025, February 24, 2025, April 9, 2025, and May 22, 2025, clarifying the identity, intended uses, manufacturing process, analytical methods, dietary exposure, and safety.

The subject of the notice is bacteriophage (phage) preparation specific to *Listeria monocytogenes* (*Listeria* phage preparation) for use as an antimicrobial on intact red meat, including carcasses, primals, and subprimals, fruits, vegetables, fish, and milk products¹ at levels ranging from 10⁶ to 10⁷ plaque forming units (PFU)/g of food. The notice informs us of FINK's view that these uses of *Listeria* phage preparation are GRAS through scientific procedures.

FINK describes the *Listeria* phage preparation as a colorless to light yellowish liquid that consists of one strictly lytic, double-stranded DNA phage specific to *Listeria monocytogenes*. FINK states that the phage is deposited in the Leibniz Institute DSMZ – German Collection of Microorganisms and Cultures under the deposit designation number DSM 33309. FINK explains that the phage was characterized using Next-Generation-Sequencing. FINK states that the lytic activity of *Listeria* phage preparation was tested against 96 *L. monocytogenes* strains and lytic activity was shown for 89.6% of the tested strains.

FINK describes the manufacturing process of *Listeria* phage preparation. FINK states that the phage preparation is produced using a non-pathogenic and non-toxicogenic bacterial host (*Listeria innocua* DSM 33311), noting that the host strain does not produce listeriolysin O. FINK explains that the fermentation process occurs in a contained, sterile environment using an aerobic fermentation process. The *L. innocua* host strain is grown to a target optical density before the bacteriophage is added at a predetermined multiplicity of infection. FINK states that after the fermentation process is complete, the lysate is centrifuged followed by filtration by to remove host cells.

¹ FINK states that *Listeria* phage preparation is not intended for use in infant formula.

Afterwards, the lysate undergoes a second filtration step where the growth medium is exchanged for phosphate buffered saline. The bacteriophage solution undergoes a final filtration step and sterilization. FINK states that *Listeria* phage preparation is diluted with water at the application site to a concentration between 10^6 and 10^7 PFU/mL. FINK states that none of the materials used during the manufacturing process are derived from major allergens. FINK states that *Listeria* phage preparation is manufactured in accordance with good manufacturing practices and that all raw materials and processing aids used are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for the intended use, or are the subject of an effective food contact notification.

FINK provides specifications for *Listeria* phage preparation, including concentration (between 10^9 and 5×10^{10} PFU/mL); limits for microorganisms, including total plate count (<500 colony forming units (CFU)/g), yeast and mold (<100 CFU/g), *Enterobacteriaceae* (<100 CFU/g), *Staphylococcus* spp. (<10 CFU/g), *Salmonella* serovars (not detectable in 25 g), and *L. monocytogenes* (not detectable in 25 g); and a limit for lead (<0.01 mg/L). FINK provides the results from the analyses of three non-consecutive batches to demonstrate that *Listeria* phage preparation can be manufactured to meet the specifications. FINK states that *Listeria* phage preparation has a shelf life of 6 months when stored at 2-10 °C in a dark, UV-protected area.

FINK estimates the dietary exposure to *Listeria* phage preparation based on the maximum use level of 1×10^7 PFU/g of food and the average per capita food availability reported in the Food Availability (Per Capita) Data System (Economic Research Service, U.S. Department of Agriculture, 2019). FINK estimates the dietary exposure to *Listeria* phage preparation from the intended uses to be 4 µg/person/d.

FINK discusses the safety of phages in general, stating that phages are abundant in the environment. FINK notes that phages are found in the gut of mammals and humans and are consumed in various foods. FINK explains the difference between lytic and temperate phages, stating that lytic phages lack the genes responsible for lysogenic conversion. FINK notes that infection of a host bacterium by a lytic phage results in the death of the bacterial host. FINK states that genomic analysis of the phage in *Listeria* phage preparation confirms that it is strictly lytic. FINK discusses analyses of the phage genome, stating that the phage contains no virulence or toxin genes, no antibiotic resistance markers, no genes coding for proteins with allergenic properties, nor any other genes that pose a safety concern. FINK conducted a literature search through April 2025 and states that no new information contradicting their GRAS conclusion was identified.

FINK provides data demonstrating the antimicrobial effects of *Listeria* phage preparation when applied to raw beef, lettuce, cheese, and raw salmon at an application titer of 10^7 PFU/cm².

Based on data and information provided in the submission, FINK concludes that *Listeria* phage preparation is GRAS for its intended use.

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

Standards of Identity

In the notice, FINK states its intention to use *Listeria* phage preparation in a food category 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

As provided under 21 CFR 170.270, during our evaluation of GRN 001215, 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 use of *Listeria* phage preparation as an antimicrobial on intact red meat, including carcasses, primals, subprimals, and Siluriformes fish, up to a level of 10^7 plaque-forming units (PFU)/g of food. Regarding labeling, FSIS would consider the substance a processing aid that does not require labeling under the accepted above conditions of use.

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

Conclusions

Based on the information that FINK provided, as well as other information available to FDA, we have no questions at this time regarding FINK's conclusion that *Listeria* phage preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *Listeria* 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 001215 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.

Carlson -S

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Susan J. Carlson -S

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Susan J. Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Pre-Market Additive Safety

Office of Food Chemical Safety, Dietary
Supplements, and Innovation

Human Foods Program

cc: Stephanie Hretz, M.P.H., C.P.H.

Director

Risk Management and Innovations Staff

Office of Policy and Program Development