Alexander Sulakvelidze, Ph.D.
Intralytix, Inc.
701 E Pratt St.
Baltimore, MD 21202

Re: GRAS Notice No. GRN 000834

Dear Dr. Sulakvelidze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000834. We received Intralytix Inc.'s notice on December 20, 2018, and filed it on March 7, 2019. Intralytix submitted amendments to the notice on May 3, 2019, and August 27, 2019, providing additional information on safety and application.

The subject of the notice is preparations containing three to eight bacteriophages (phage) specific to Shiga toxin-producing *Escherichia coli* (STEC; *E. coli* phage preparation) for use as antimicrobial treatments on meat, poultry, fruits, vegetables, dairy products (including cheese), fish, and other seafood at a level of no greater than 10^8 plaque-forming units (PFU)/g of food. The notice informs us of Intralytix's view that these uses of *E. coli* phage preparation are GRAS through scientific procedures.

Intralytix describes the identity of three of the phages, designated ECML-117, ECML-359 and ECML-363, as double-stranded DNA lytic phages specific to STEC, which are individually prepared and purified.[1] Intralytix states that for application, the preparation is diluted with water, yielding a working solution 10^9 PFU/mL as applied. The application process ensures that the final concentration on food is no greater than 10^8 PFU/g of food.

Intralytix describes the method of manufacture for *E. coli* phage preparation. Each phage is produced by aerobic fermentation of a *E. coli* inoculated with the appropriate starter virion. Specifically, in each phage production lot, the non-pathogenic host strain is grown under the appropriate conditions and is then infected with the appropriate phage inoculum preparation once a predetermined titer is reached. After fermentation and lysis are complete, the lysate is clarified by filtration, concentration, followed by sterilization. The resulting single phage suspension is blended with other phage suspensions to create a multi-phage suspension that is again filter sterilized during preparation of the final product and stored at 2-6°C.

[1] The notifier intends to produce *E. coli* phage preparations containing a mixture of three to eight double-stranded DNA lytic phages specific to STEC, and subject to the same manufacturing and safety standards in GRN 000834.

Intralytix estimates the dietary exposure to *E. coli* phage preparation. Intralytix bases its estimate on the intended use level of *E. coli* phage preparation on meat and poultry (ground, whole, ready-to-eat), fruits and vegetables (fresh and processed), dairy products (including cheese), fish and other seafood, and using the estimated average *per capita* daily consumption according to the U.S. Department of Agriculture. Intralytix estimates dietary exposure at 70 μg/person/day from consumption of the target foods. Intralytix considers that the use of *E. coli* phage preparation is self-limiting, diminishing numbers of phage after depletion of the *E. coli* host, and degradation by environmental factors.

Intralytix discusses the safety of phages in general noting that phages are ubiquitous in the environment, are present in water and foods of various origins, and humans are continually exposed to them. Phages are ubiquitous in the intestinal tracts of animals and humans and are harmless for all organisms other than the bacteria they infect. Intralytix further discusses the safety of *E. coli* phage preparation, specifically, noting that these phages are solely lytic phages that lack the genes responsible for lysogeny and therefore gene transfer from the phages. Furthermore, Intralytix summarizes the results of published studies involving administration of phages to humans, including at-risk groups, such as the immunocompromised. From these studies, Intralytix concludes that no negative outcomes are associated with use of phages in humans. Finally, the *E. coli* phage preparation is free of genes that encode known toxins, antibiotic resistance, or 16s ribosomal RNA.

Intralytix provides data demonstrating the antimicrobial effects of the *E. coli* phage preparation when applied to meat and poultry (ground, whole, ready-to-eat), fruits and vegetables (fresh and processed), dairy products (including cheese), fish and other seafood inoculated with *E. coli Ec*229. Intralytix concludes that *E. coli* phage preparation reduces the levels of *E. coli Ec*229 on all foods tested, accomplishing its intended effect.

Based on the totality of the data and information available, Intralytix concludes that *E. coli* phage preparation is GRAS for its intended use in food.

Standards of Identity

In the notice, Intralytix states its intention to use *E. coli* phage preparation 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 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 000834 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 evaluation and has no objection of the use of *E. coli* phage preparation as an antimicrobial for the treatment of meat (including Silurifomes fish) and poultry products at 10^8 PFU/g of treated food. FSIS advises that no labeling statement is required when used under the accepted 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 *E. coli* phage preparation in meat and poultry products. You should direct such an inquiry to Dr. Melvin Carter, Director, RMIS, Office of Policy and Program Development, FSIS by email at Melvin.Carter@usda.gov.

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

Conclusions

Based on the information that Intralytix provided, as well as other information available to FDA, we have no questions at this time regarding Intralytix's conclusion that *E. coli* phage preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *E. coli* 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 000834 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
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Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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cc: Melvin Carter, Ph.D.
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