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

Re: GRAS Notice No. GRN 000672

Dear Dr. Sulakvelidze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000672. We received the notice, dated October 4, 2016, that you submitted under the format of the agency's final rule (81 FR 54960; August 17, 2016; Substances Generally Recognized as Safe (GRAS)) on October 5, 2016, and filed it on October 13, 2016. We received amendments containing additional safety information on November 23, 2016, February 24, 2017, and March 07, 2017.

The subject of the notice is a preparation containing five bacterial monophages specific to *Shigella* spp. (Shigella phage preparation) for use as an antimicrobial agent on ready-to-eat-meat and poultry, fish (including smoked fish), shellfish, fresh and processed fruits and vegetables, and dairy products including cheese at levels up to 1×10^8 plaque forming units (PFU)/g food. The notice informs us of the view of Intralytix, Inc. (Intralytix) that this use of Shigella phage preparation is GRAS through scientific procedures.

Our use of the term, "Shigella phage preparation," 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 nonstandardized 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. We did not consult with ONFL regarding the appropriate common or usual name for Shigella phage preparation.

Intralytix describes the identity and composition of Shigella phage preparation as a fluid suspension of five double-stranded DNA lytic phages specific to *Shigella* spp., designated SHFML-11, SHFML-26, SHBML-50-1, SHSML-52-1, and SHSML-45, present in approximately equal amounts at a minimum total lytic titer of 1×10^{10} PFU/mL. Intralytix states that for application, the preparation is diluted in water, yielding a working solution with a lytic titer of ca. 1×10^9 PFU/mL. The application process ensures that the final concentration on food is no greater than 1×10^8 PFU/g.

Intralytix describes the method of manufacture for Shigella phage preparation. Each individual phage suspension is prepared through aerobic fermentation of the host *Shigella sonnei* strain Sh.s43 and infection with the desired phage. The suspension is filtered, concentrated, washed, and filter sterilized. The individual phages are combined and diluted with sodium chloride as necessary to produce a final suspension containing approximately equal titers of each phage.

Intralytix uses restriction fragment length polymorphism to verify the identities of the component phages. Intralytix estimates the shelf life of Shigella phage preparation at one year under dark, ultraviolet-light protected storage conditions at 2−6°C.

Intralytix provides specifications for Shigella phage preparation including lytic titer, bacterial sterility, limits on endotoxin (≤25,000 Endotoxin Units (EU)/mL at standard working concentration of ca. 1×10^9 PFU/mL), and phage component identity. Intralytix also provides the results of lot analyses and typical composition of Shigella phage preparation. Typical values are provided for total nitrogen (3.5 mg/L) and total organic carbon (18.7 mg/L).

Intralytix estimates the dietary exposure to Shigella phage preparation. Using food availability (per capita) data from the U.S. Department of Agriculture, Economic Research Service, Intralytix estimates that 1891 g of target foods are consumed per person per day, based on per capita intakes of all poultry and red meat, all fish and shellfish, all fruits and vegetables (processed and unprocessed), and all dairy. Intralytix assumes 100% market saturation of the intended use of Shigella phage preparation in the notified food categories, yielding a total exposure of 1.9×10^{11} PFU/person(p)/day(d). Using the estimated dietary exposure to Shigella phage preparation and maximum level of endotoxin permitted by the specification, Intralytix estimates dietary exposure to endotoxin to be 4.7×10^6 EU/p/d. Intralytix notes that the amount of endotoxin from the intended use of Shigella phage preparation would constitute 0.95% of the dietary exposure to endotoxin from saliva (5×10^8 EU/p/d) and therefore would be safe. Intralytix states that levels of Shigella phage preparation in foods would be self-limiting due to the cost of the product, depletion of the Shigella host, and susceptibility to environmental factors.

Intralytix presents results of six studies in which cooked beef, cooked chicken, smoked salmon, honeydew melon, lettuce, and yogurt were inoculated with *S. sonnei* and treated with Shigella phage preparation. Intralytix concludes that Shigella phage preparation reduces the levels of *S. sonnei* on all foods tested, accomplishing its intended effect.

Intralytix discusses the safety of phages in general as well as the safety of Shigella phage preparation itself. Intralytix notes that the peer-reviewed scientific literature extensively documents that lytic phages, which lyse host bacteria without integrating into the host genome, pose no safety hazards to humans. Phages are ubiquitous in the environment, food, and in human and animal guts and oral cavities. Because they are present on all fresh, unprocessed food, and in drinking water, they are consumed on a daily basis. Intralytix considers the safe use of phages for almost 100 years and their specificity to particular bacterial species and strains to support their safety. Intralytix considers that bacteriophages would not have deleterious effects on the human microbiota because of this specificity.

Intralytix states that, based on DNA sequencing and bioinformatics comparisons of the individual phage genome sequences to known sequences, the phages are free of undesirable genes, including genes encoding bacterial toxins or antibiotic resistance genes. Further, the estimated exposure to phages from Shigella phage preparation by the consumer is low. Intralytix notes that the particular phages were obtained from the environment, where phages are ubiquitous. Intralytix cites a published study in which Shigella phage preparation was administered to mice for up to 28 days without notable impact on microflora and without side effects.

Based on publicly available information, Intralytix concludes Shigella phage preparation is GRAS for its intended use in food.

Standards of Identity

In the notice, Intralytix states its intention to use Shigella 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 000672 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 Shigella phage preparation as an antimicrobial spray application on ready-to-eat meat and poultry at levels up to 1×10^8 PFU/g.

FSIS requested that we advise you to seek regulatory guidance from its Risk, Innovations, and Management Staff (RIMS) about the use of Shigella phage preparation in meat and poultry products. You should direct such an inquiry to Dr. William K. Shaw Jr., Director, RIMS, Office of Policy and Program Development, FSIS by email at William.Shaw@fsis.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 Shigella 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 Shigella phage preparation. Accordingly, our response should not be construed to be a statement that foods containing Shigella 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 Shigella phage preparation is GRAS under its intended conditions of use. This letter is not an affirmation that Shigella 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 000672 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042713, cn=Michael A. Adams -S
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Dennis M. Keefe, Ph.D.
Director
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cc: William K. Shaw Jr., Ph.D.
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