Edith Chow, Ph.D.
Gum Products International
1255 Journey's End Circle
Newmarket, Ontario L3Y 8T7
CANADA

Re: GRAS Notice No. GRN 000917

Dear Dr. Chow:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000917. We received Gum Products International's (Gum Products) GRAS notice on March 5, 2020 and filed it on April 24, 2020. Gum Products submitted amendments to the notice on June 25, 2020, July 15, 2020, and July 28, 2020, providing additional information regarding manufacturing specifications, safety information, clarification on the intended use, and data supporting the intended use as an antimicrobial.

The subject of the notice is a preparation containing three bacteriophages (phage) specific to *Salmonella enterica* serovars (*Salmonella* phage preparation) for use as an antimicrobial at levels of up to 2 x $10^8$ plaque-forming units (PFU)/g of food, on intact poultry, intact red meat, eggs, fruits, vegetables, fish (excluding Siluriformes (catfish)), and shellfish. The notice informs us of Gum Products' view that these uses of *Salmonella* phage preparation are GRAS through scientific procedures.

Gum Products describes *Salmonella* phage preparation as a clear translucent liquid, consisting of three double-stranded DNA lytic monophages (Phi_16, Phi_78, and Phi_87) specific to *S. enterica* serovars, that are produced and purified separately, and then subsequently mixed. Gum Products states that the preparation is diluted in sterile water, yielding a minimum total phage concentration of 1 x $10^{10}$ PFU/mL, ensuring a final concentration no greater than 2 x $10^8$ PFU/g of food.

Gum Products describes the method of manufacture for *Salmonella* phage preparation. The monophages are produced using a non-pathogenic bacterial host (*Salmonella* Typhimurium strain LB5000). Gum Products states that *S.* Typhimurium strain LB5000 is commercially available.[1] Gum Products states that the host strain was tested for its sensitivity to antibiotics and was sensitive to all six tested. Gum Products states

[1] Gum Products states that *S.* Typhimurium strain LB5000 is available from the *Salmonella* Genetic Stock Centre at the University of Calgary, Canada.

that all materials used in the manufacture of *Salmonella* phage preparation are food grade.

The three monophages are produced individually by aerobic fermentation. The host strain is grown to a desired concentration before each monophage stock is added at a predetermined multiplicity of infection. After fermentation and lysis are complete, the lysate is clarified by micro- and sterile filtration, washed with phosphate-buffered saline, and concentrated by ultra-filtration. The purity of each monophage production is monitored by quantitative PCR to keep contamination low.[2] Each monophage is tested for concentration, purity, endotoxin, and sterility prior to blending them together, diluting to a total monophage concentration of $1 \times 10^{10}$ PFU/mL, and storing at 2-8°C.

Gum Products provides the following specifications for *Salmonella* phage preparation: concentration (> $10^{10}$ PFU/mL), endotoxin (< 25,000 EU/mL), sterility (no bacterial growth after >14 days), Kjeldahl nitrogen (20 mg/L), organic carbon (250 mg/L), and heavy metals including lead (0.01 µg/g). Gum Products provides the results from three non-consecutive lots to demonstrate that *Salmonella* phage preparation can be manufactured to conform with the provided specifications.

Gum Products estimates the dietary exposure to *Salmonella* phage preparation by using 558 g/person (p)/day (d) as the average *per capita* consumption of food (USDA Food Availability Data System, 2017). Based on the assumptions that all the foods listed above are treated with the *Salmonella* phage preparation at the maximum use level of $2 \times 10^8$ PFU/g food, and that all the available food in the categories the antimicrobial is intended for, is consumed, Gum Products estimates dietary exposure to the *Salmonella* phage preparation to be $1.2 \times 10^{11}$ PFU/p/d.

Gum Products discusses the safety of phages in general, noting that phages are the most ubiquitous entity on Earth and can be found anywhere bacteria exist, including human mouths and stomachs. Further, Gum Products states that humans are in contact with and consume phages constantly. Gum Products states that the three phages in *Salmonella* phage preparation are strictly lytic, and notes that lytic phages are obligate intracellular parasites that target only specific species of bacteria and have no effect on other bacteria, human, animal, or plant cells. Gum Products states that numerous studies have demonstrated that consumption of phages is harmless to humans and animals and cites published studies showing no effects on humans or rats following consumption of phages. Gum Products notes that other commercially available phage preparations have GRAS status and its *Salmonella* phage preparation is equivalent to these products.[3] Gum Products states that the three phages in *Salmonella* phage preparation do not contain any virulence or undesired genes.

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[2] Gum Products describes "contaminant phages" as presence of any one, two or three of the three *Salmonella* phages (Phi_16, Phi_78, Phi_87) in a production lot designated for production of a different *Salmonella* phage.

[3] Gum Products references GRNs 000218, 000435, 000468, 000528, and 000603. We evaluated these GRNs, and responded in letters respectively dated June 22, 2007, February 22, 2013, December 23, 2013, December 23, 2014, and July 28, 2016, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

Gum Products provides data demonstrating the antimicrobial effects of *Salmonella* phage preparation when applied to poultry (skin-on chicken drumstick, skinless chicken breast), red meat (boneless inside round steak), eggs, fruits (pre-cut apples), fish (salmon), and shellfish (shelled shrimp) at 2 x $10^8$ PFU/g of food.

Based on the data and information provided in the submission, Gum Products concludes that *Salmonella* phage preparation is GRAS for its intended uses.

**Allergen Labeling**

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. *Salmonella* phage preparation may require labeling under the FD&C Act because it may contain protein derived from soybeans. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in the Office of Food Additive Safety. Questions related to food labeling in general should be directed to the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition.

**Use in Products under USDA Jurisdiction**

As provided under 21 CFR 170.270, during our evaluation of GRN 000917, 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 *Salmonella* phage preparation as an antimicrobial on intact red meat and intact poultry products at a level of up to 2 x $10^8$ PFU/g of food. Regarding labeling, FSIS would consider the substance a processing aid that does not require labeling under the requested 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 *Salmonella* phage preparation in meat, poultry, and egg 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@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 Gum Products' notice concluding that *Salmonella* 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 *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(ll).

**Conclusions**

Based on the information that Gum Products provided, as well as other information available to FDA, we have no questions at this time regarding Gum Products' 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 000917 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
Office of Food Additive Safety
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cc: Melvin Carter, Ph.D.
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