Xin Tao
Baker McKenzie
815 Connecticut Avenue, NW
Washington, DC 20006

Re: GRAS Notice No. GRN 001134

Dear Mr. Tao:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001134. We received the notice that you submitted on behalf of Qingdao Phagepharm Bio-Tech Co., Ltd (Qingdao) on December 2, 2022, and filed it on June 8, 2023. Qingdao submitted an amendment to the notice on October 13, 2023, providing clarifying information on the identity, intended use, manufacturing process, specifications, and safety.

The subject of the notice is a bacteriophage (phage) preparation specific to *Salmonella enterica* serovars (*Salmonella* phage preparation) for use as an antimicrobial on chicken prior to being ground at levels up to 2×10^8 plaque forming units (PFU)/g of food. The notice informs us of Qingdao's view that this use of *Salmonella* phage preparation is GRAS through scientific procedures.

Qingdao describes *Salmonella* phage preparation as a clear translucent liquid that consists of one strictly lytic, double-stranded DNA phage specific to *Salmonella enterica* serovars. Qingdao states that the phage is deposited in the China General Microbiological Culture Collection Center under the deposit designation number CGMCC No. 45256. Qingdao explains that the phage was characterized using full-genome sequencing and electron microscopy. Qingdao states that the lytic activity of *Salmonella* phage preparation was tested against 85 *Salmonella enterica* strains and that lytic activity was shown for 90% of the tested strains.

Qingdao describes the manufacturing process of *Salmonella* phage preparation. The phage preparation is produced using a non-pathogenic and non-toxigenic bacterial host (*Salmonella* Enteritidis strain C1106). Qingdao states that the host strain was tested for its sensitivity to antibiotics and was sensitive to all antibiotics tested except for erythromycin, polymyxin, and rifampicin. Qingdao notes that the host strain is not capable of genetic transfer.

The phage is produced by aerobic fermentation of the production strain. The production strain is grown to a target optical density before the phage stock is added at a predetermined multiplicity of infection and incubated under aerobic conditions.

Qingdao states that after incubation, the culture is centrifuged to remove the production strain and purified through micro- and sterile filtration. Qingdao states that ultra-filtration is then used to wash the phages with phosphate-buffered saline. Qingdao explains that residual endotoxins are further removed during clarification and extensive washing of the phage preparation. Qingdao states that the *Salmonella* phage preparation is diluted with sterile water, resulting in a concentration of 1×10^{10} PFU/mL. Qingdao states that all raw materials used in the manufacture of *Salmonella* phage preparation are food grade, are used in accordance with U.S. regulations, or were concluded to be GRAS for their respective uses.

Qingdao provides specifications for *Salmonella* phage preparation, including concentration ($>10^{10}$ PFU/mL), limits for bacterial sterility (no growth detected after 7 days), endotoxin (<2500 EU/mL), and heavy metals, including lead (<0.02 mg/kg). Qingdao provides the results from the analyses of three non-consecutive batches to demonstrate that *Salmonella* phage preparation can be manufactured to conform with the provided specifications.

Qingdao estimates the dietary exposure to *Salmonella* phage preparation based on the maximum use level of 2×10^8 plaque forming units (PFU)/g of food and the eaters-only consumption of chicken meat as reported in the Food Commodity Intake Database.[1] Qingdao estimates the 90th percentile eaters-only dietary exposure to *Salmonella* phage preparation from the intended uses to be 1×10^{-6} g/p/d.

Qingdao discusses the safety of phages in general, stating that phages are ubiquitous in the environment and constantly consumed and released by humans. Qingdao explains the differences between lytic and temperate phages, stating that lytic phages generally do not cross species or genus boundaries and will not affect desired bacteria in foods, commensals in the gastrointestinal tract, or bacterial flora in the environment. Further, Qingdao states that lytic phages are normal commensals of humans and animals, and lytic phages can be used to lyse specific pathogens without disturbing normal bacterial flora, posing no risk to anything other than their specific bacterial host. Qingdao concludes that lytic phages are therefore safe for humans. Qingdao discusses bioinformatic analysis performed on *Salmonella* phage preparation and states that the phage genome does not contain any virulence or undesired[2] genes.

Qingdao provides data demonstrating antimicrobial effects of *Salmonella* phage preparation when applied to chicken prior to being ground at 2×10^8 PFU/g of food.

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

[1] https://fcid.foodrisk.org/

[2] In an amendment dated October 13, 2023, Qingdao states that "undesired" genes refers to antibiotic resistance genes, integrase genes, and lysogenic genes.

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 Qingdao's 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).

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 001134, 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 raw chicken trim prior to grinding up to a level of 2×10^8 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 *Salmonella* 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 Qingdao provided, as well as other information available to FDA, we have no questions at this time regarding Qingdao'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 001134 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 J. Carlson, Ph.D.
Director
Division of Food Ingredients
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cc: Stephanie Hretz, MPH, CPH
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