



Kevin O. Gillies
Consulting Services, LLC
1759 Grape Street
Denver, CO 80220

Re: GRAS Notice No. GRN 000724

Dear Mr. Gillies:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000724. We received FINK TEC GmbH's (FINK TEC) notice on August 17, 2017, and filed it on September 25, 2017. FINK TEC submitted an amendment clarifying the intended use level of the substance on March 5, 2018.

The subject of the notice is a preparation containing six bacterial phages specific to shiga toxin-producing *Escherichia coli* (*E. coli* phage preparation) for use as an antimicrobial on beef carcasses to control shiga-toxin producing *E. coli* at levels up to 1.5×10^{11} phage particles per carcass. The notice informs us of the view of FINK TEC that this use of *E. coli* phage preparation is GRAS through scientific procedures.

FINK TEC describes the identity and composition of *E. coli* phage preparation as a colorless suspension of six lytic phages specific to shiga toxin-producing *E. coli* O157:H7 and non-O157:H7 shiga toxin producing *E. coli*. The notifier intends to produce commercial preparations containing subsets of six phages from a group of twelve such phages. The twelve phages are designated, DSM 103290 (AB27), DSM 104013 (TB49), DSM 104014 (TB120), DSM 104015 (KRA2), DSM 104016 (TB69), DSM 104018 (BO1), DSM 104019 (EW2), DSM 104020 (TB6A), DSM 104021 (GWF), DSM 104022 (HAM53), DSM 104023 (MP75), and DSM 104017 (TB11). Eleven of the preparation phages belong to the family Myoviridae, one bacteriophage to the family of Podoviridae (DSM 104017 (TB11)). FINK TEC states that for application, the preparation is diluted in water, yielding a working solution ranging in concentration from 10^5 to 10^7 plaque forming units per mL (PFU/mL) as applied. The application process ensures that the final concentration on food is no greater than 1.5×10^{11} phage particles per carcass.

FINK TEK describes the method of manufacture for *E. coli* phage preparation. Each phage is produced by aerobic fermentation of a non-pathogenic host strain, *E. coli* CCUG 29188 or *E. coli* MG1655 inoculated with the appropriate starter virion. Specifically, in each phage production lot, the non-pathogenic host strain is grown at 37°C, and then infected with the appropriate phage inoculum preparation once a target cell concentration is reached. The combination is incubated with aeration and mixing. After fermentation and lysis are complete, as determined by optical density, the phage lysate is assayed to determine the concentration of the phage progeny. The lysate is centrifuged and processed to remove unbroken and whole-cell debris, small molecules from the fermentation media, and finally sterilized. The resulting single phage suspension is then stored at 4°C and blended with other phage suspensions to create a multi phage suspension that is again filter sterilized during preparation of the final product, and finally stored at 4 °C.

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FINK TEC provides specifications for *E. coli* phage preparation including phage titer, bacterial sterility, and identity by PCR verification. FINK TEC notes that *E. coli* phage preparations meet or exceed typical food ingredient quality control specifications. FINK TEC provides batch analyses from three non-contiguous production lots confirming the ability to comply with these specifications.

FINK TEC estimates the dietary exposure to *E. coli* phage preparation. FINK TEC bases its estimate on the intended use level of *E. coli* phage preparation on beef carcasses, the typical weight of a dressed beef carcass, and an estimate of average *per capita* daily beef consumption. FINK TEC states that estimated dietary exposure for the general population is 0.0082 µg/person/d. FINK TEC notes that this is a conservative estimate that assumes retention of 100 percent of the applied *E. coli* phage preparation to carcasses, although FINK TEC estimates that 90 percent does not adhere to the carcass. Further, FINK TEC assumes that all beef in the United States would be treated with *E. coli* phage preparation. FINK TEC states that the use of *E. coli* phage preparation is self-limiting due to the cost of the product, diminishing numbers of phage after depletion of the *E. coli* host, and susceptibility to environmental factors that lower the number of active phage with time.

FINK TEC discusses the safety of phages in general noting that phages are ubiquitous in the environment and thus humans are continuously exposed to them. The gut of mammals and humans is an especially rich source of phages, many of which have been consumed on a daily basis via various foods. FINK TEC also notes that existing safety studies on phages have reported finding no adverse effects in humans or animals. FINK TEC 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. Finally, the *E. coli* phage preparation phages are free of genes that encode *E. coli* virulence factors, known toxins, antibiotic resistance, or allergenic proteins.

FINK TEC summarizes studies in humans and animals on *E. coli*-specific phages where no adverse effects to dietary phages have been observed. These studies reported no adverse effects as well no significant effects on the composition of gut microflora in these studies, as measured by commensal *E. coli* fecal counts and 16rRNA gene sequencing in test subjects.

FINK TEC provides data from its own studies demonstrating the antimicrobial effects on *E. coli* O157:H7, both in laboratory studies and when applied to red meat.

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

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000724, we coordinated with the Food Safety and Inspection Service (FSIS) of the USDA. 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 *E. coli* phage preparation as

an antimicrobial spray application on beef carcasses at levels of 1×10^{11} phage particles per carcass. No labeling statement is required when used under the accepted conditions of use.

FSIS requested that you direct any additional questions regarding regulatory guidance from its Risk, Innovations, and Management Staff (RIMS) about the use of *E. coli* phage preparation in meat, poultry, and egg products 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(II) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(II) 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(II)(1)-(4) applies. In its review of FINK TEC's notice that *E. coli* phage preparation is GRAS for the intended uses, we did not consider whether section 301(II) or any of its exemptions apply to foods containing *E. coli* phage preparation. Accordingly, this response should not be construed to be a statement that foods that contain *E. coli* phage preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that FINK TEC provided, as well as other information available to FDA, we have no questions at this time regarding FINK TEC'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 000724 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams Digitally signed by Michael A. Adams -S
Date: 2018.04.10 10:54:41 -04'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
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cc: William K. Shaw Jr., Ph.D.
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