



Steven Hagens, Ph.D.
Chief Scientific Officer
Microcos B.V.
Nieuwe Kanaal 7P
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The NETHERLANDS

Re: GRAS Notice No. GRN 000757

Dear Dr. Hagens:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000757. We received Microcos B.V.'s (Microcos) notice on January 23, 2018, and filed it on February 26, 2018. Microcos submitted an amendment to the notice on May 14, 2018, providing additional information on safety and method of application.

The subject of the notice is a preparation containing two bacteriophages (EP335 and ER75) specific to *Escherichia coli* O157 (*E. coli* O157 bacteriophage preparation) for use as an antimicrobial at up to 10^9 PFU/g of beef (on beef carcasses, primals, subprimal cuts, and trimmings) to control *E. coli* O157. The notice informs us of Microcos' view that the use of *E. coli* O157 bacteriophage preparation is GRAS through scientific procedures.

Our use of the term "*E. coli* O157 bacteriophage 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 *E. coli* O157 bacteriophage preparation.

Microcos describes the identity and composition of *E. coli* O157 bacteriophage preparation as a solution containing two *E. coli* O157-specific bacteriophages, EP335 and ER75, which are produced and purified separately and mixed in equal concentrations. Microcos states the commercial product has a minimal titer of 2×10^{11} PFU/mL, and will be diluted with water at application sites to result in concentrations up to 10^9 PFU/g of food.

Microcos describes the manufacturing method for production of *E. coli* O157

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bacteriophage preparation. Microeos states that the host bacteria are incubated in a bioreactor with sterilized growth medium. Each phage (EP335 and EP75) is grown individually with the appropriate host bacteria at the appropriate temperature and time. After the phage reach a predetermined titer, the phage is separated by filtration from bacteria and cell debris. The phage suspension is then concentrated and purified by ultrafiltration. Microeos states that over 95% of cell debris, proteins, and growth medium are removed. The final *E. coli* O157 bacteriophage preparation is composed of ~19% each EP335 and EP75 and ~62% filtered sterilized water and has a resulting titer of $\sim 2 \times 10^{11}$ PFU/mL. The notifier states that all components used in the manufacturing process (including medium components, processing aids, titrants, etc.) are food grade and that the final phage mixture contains no allergens. Microeos tested batches of *E. coli* O157 bacteriophage preparation to ensure it can be manufactured to meet specifications including phage titer, sterility, and identity.

Microeos estimates the dietary exposure to *E. coli* O157 bacteriophage preparation. Microeos bases its estimate on the intended use level of *E. coli* O157 bacteriophage preparation on beef, the estimated average *per capita* daily beef consumption according to USDA, and the assumption that all cuts destined to be ground are treated with *E. coli* O157 bacteriophage preparation. Microeos estimates dietary exposure at 6 $\mu\text{g}/\text{person}/\text{day}$. Microeos considers that the use of *E. coli* O157 bacteriophage preparation is self-limiting due to the cost of the product, diminishing numbers of phage after depletion of the *E. coli* host, and degradation by environmental factors.

Microeos discusses the safety of phages in general noting that phages are ubiquitous in the environment and are present in water and foods of various origins. Phages are ubiquitous in the intestinal tracts of animals and humans and are harmless for all organisms other than the bacteria they infect. Microeos further discusses the safety of *E. coli* O157 bacteriophage preparation, specifically, noting that these phages are solely lytic phages. Finally, the *E. coli* O157 bacteriophage preparation is free of genes that encode *E. coli* virulence factors, known toxins, antibiotic resistance, or allergenic proteins.

Microeos provides data demonstrating the antimicrobial effects of the *E. coli* O157 bacteriophage preparation when applied to the surface of beef samples inoculated with *E. coli* O157.

Based on the totality of the data and information available, Microeos concludes that *E. coli* O157 bacteriophage preparation is GRAS for its intended use on beef.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000757 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 to the use of the *E. coli* O157 bacteriophage preparation as an antimicrobial spray, mist, or wash application (or a mix of these application methods) on beef carcasses, primals, subprimal cuts, and trimmings at levels up to 10⁹ PFU/g of food to control *E. coli* O157. 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, Innovations, and Management Staff (RIMS) about the use of *E. coli* O157 bacteriophage preparation on beef. 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(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 our evaluation of Microeos' notice concluding that *E. coli* O157 bacteriophage preparation is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing *E. coli* O157 bacteriophage preparation. Accordingly, our response should not be construed to be a statement that foods containing *E. coli* O157 bacteriophage preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Microeos provided, as well as other information available to FDA, we have no questions at this time regarding Microeos' conclusion that *E. coli* O157 bacteriophage preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *E. coli* O157 bacteriophage 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 000757 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

Digitally signed by
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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