



Kristi O. Smedley, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Road
Woodbridge, VA 22192

Re: GRAS Notice No. GRN 000775

Dear Dr. Smedley:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000775. We received the notice that you submitted on behalf of Nomad Bioscience GmbH (Nomad) on April 2, 2018, and filed it on April 30, 2018.

The subject of the notice is a preparation containing one or more colicin proteins produced in *Nicotiana benthamiana* (colicin preparations) for use as an antimicrobial agent on fresh and processed vegetables, fruits, and meats at 1-10 mg/kg. The notice informs us of Nomad's view that these uses of colicin preparations are GRAS, through scientific procedures.

Our use of "colicin preparations" 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. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "colicin preparations."

Nomad describes four *N. benthamiana*-produced colicin proteins intended for use singly or in combination in colicin preparations: colicin M, colicin K, colicin U, and colicin Ib. Nomad states these *N. benthamiana*-produced colicins can also be used with food plant species-produced colicins that were the subjects of GRN 000593 and GRN 000676.¹

Nomad describes the method of manufacture of colicin preparations by referring to the processes described in GRN 000593; specifically, each recombinant colicin protein is

¹ GRN 000593 and GRN 000676 describe the use of colicin preparations produced in spinach, red beet and lettuce on fresh and processed fruits and vegetables, and meat, respectively. FDA evaluated these notices and responded in letters dated December 18, 2015, and May 15, 2017, stating that we had no questions at that time regarding Nomad's GRAS conclusions.

produced in *N. benthamiana*. Briefly, *Tobacco mosaic virus* or *Potato virus X* was engineered to contain one colicin-producing gene, which was introduced into *N. benthamiana*. Each colicin containing clone is incubated for five to ten days to allow for colicin accumulation, then leaves and stems are homogenized. After removing insoluble material, protein is enriched by a series of acid precipitation, centrifugation, and filtration steps. When using *N. benthamiana* as the host plant, an additional ion-exchange chromatography step is employed to reduce the level of host alkaloids.² Nomad intends to offer colicin preparations from *N. benthamiana* with a target purity of at least 70%. Nomad states that it manufactures colicin preparations according to current good manufacturing practices. All raw materials and processing aids used are food grade.

Nomad provides food grade specifications for colicin isolate preparations from *N. benthamiana*. Specifications include limits for total heavy metals (<30 mg/kg), lead (<5 mg/kg), microorganisms, nicotine (<75 ng/mg), anabasine (<15 ng/mg), acceptance criteria for specific activity, physical properties, and stability (>6 months). Nomad provides results of batch analyses to demonstrate that colicins produced in *N. benthamiana* can be manufactured to meet specifications.

Nomad estimates dietary exposure to colicins from all sources, which are identical to the estimates provided in GRN 000676. Dietary exposure to colicins from intended uses on produce is estimated at 4.1 mg/person/day (mg/p/d) based on the maximum application rate of 10 mg/kg. Dietary exposure to colicins from intended uses on red meats is estimated at 1.5 mg/p/d based on estimated daily consumption of 150 g red meat/p/d. Nomad also notes that cooking meats to recommended temperatures would destroy colicins.

Nomad references the published data and information contained in the previous notices for colicins (GRN 000593 and GRN 000676) and recently published data from 2017 to support the safe use of the colicins produced in *N. benthamiana*. Nomad notes that colicins are rapidly degraded by gastrointestinal enzymes and are not expected to have allergenic potential.

Nomad provides data from its own studies and from published scientific literature demonstrating the bacteriocidal effects of colicins produced in *N. benthamiana* when applied to red meat.

Based on the totality of data and information available, Nomad concludes that the intended use of colicin preparations produced from *N. benthamiana* is GRAS.

Some Uses May Require Regulatory Actions by the United States Environmental Protection Agency (EPA)

Antimicrobial agents used on raw agricultural commodities may require registration as

² Nomad notes that the plant-derived biomass remaining after colicin protein extraction is discarded.

pesticides with EPA under the Federal Insecticide, Fungicide, and Rodenticide Act. FDA's evaluation of this GRAS notice does not relieve the obligation to register colicin preparations as a pesticide for uses regulated by EPA. For information about the regulatory status of your product when used as a pesticide, please contact EPA's Office of Pesticide Products, Antimicrobial Division.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000775 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 colicin preparations as an antimicrobial spray application on meat products at levels of 1 – 10 mg/kg.

FSIS requested that we advise you to seek regulatory guidance from its Risk, Innovations, and Management Staff (RIMS) about the use colicin preparations on meats. You should direct such an inquiry to Ms. Valeria Green, Acting Director, RIMS, Office of Policy and Program Development, FSIS by email at Valeria.Green@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 Nomad's notice concluding that colicin preparations are GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing colicin preparations. Accordingly, our response should not be construed to be a statement that foods containing colicin preparations, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Nomad provided, as well as other information available to FDA, we have no questions at this time regarding Nomad's conclusion that colicin preparations are GRAS under its intended conditions of use. This letter is not an

affirmation that colicin preparations are 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 000775 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M.
Keefe -S

Digitally signed by Dennis
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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety
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cc: Valeria Green
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