



James La Marta, Ph.D.  
Splitrock Regulatory Solutions, LLC  
107 Decker Road  
Boonton, NJ 07005

Re: GRAS Notice No. GRN 001112

Dear Dr. La Marta:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001112. We received the notice that you submitted on behalf of BiomEdit, LLC (BiomEdit) on July 4, 2022, and filed it on April 14, 2023. BiomEdit submitted amendments on June 23, 2023, August 11, 2023, and September 13, 2023, that clarified the manufacturing process, specifications, batch analyses, intended use, stability, dietary exposure, and safety information.

The subject of the notice is *Limosilactobacillus reuteri* ATCC PTA-126787 and *L. reuteri* ATCC PTA-126788 (*L. reuteri* ATCC PTA-126787 and ATCC PTA-126788), in combination, in a 1:1 ratio on a colony forming unit (CFU) basis, for use as an ingredient at a maximum level of  $1 \times 10^{10}$  CFU/serving in cream cheese, natural cheese, processed cheese and spreads; sour cream; “energy” bars, granola bars, and meal replacement bars; ice cream, frozen yogurt and novelties; yogurt and yogurt drinks; flavored milk, fermented milk, and milk drinks; meal-replacement beverages; soy-based beverages; and refrigerated fruit and vegetable beverages.<sup>1</sup> The notice informs us of BiomEdit’s view that these uses of *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 are GRAS through scientific procedures.

BiomEdit describes *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 as an off-white to dull orange colored powder. BiomEdit states that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 are Gram-positive, non-spore forming, and non-motile bacteria. The strains were isolated from a single chicken cecum and have been deposited in the American Type Culture Collection (ATCC), with deposit numbers ATCC PTA-126787 and ATCC PTA-126788, respectively. BiomEdit describes the taxonomic analysis for the identity of the strains. BiomEdit also discusses the results of genomic analyses to confirm the strains’ identity and states

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<sup>1</sup> BiomEdit states that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is not intended for use in infant formula or in products under the jurisdiction of the United States Department of Agriculture.

that the strains are not genetically modified. BiomEdit discusses the results of phenotypic and genotypic characterization performed on *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788, and concludes that no genes encoding virulence factors, toxins, antimicrobial resistance proteins, hemolysin or biogenic amines were identified, and that the strains are non-pathogenic and non-toxicogenic.

BiomEdit describes the manufacture of *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 by fermentation of a pure culture of each strain under controlled conditions. BiomEdit states that the two strains are fermented independently. After fermentation, the cells are separated from the fermentation medium and concentrated by centrifugation, and then lyophilized in the presence of cryoprotectants and milled into a powder. The two individual strains are then blended in a 1:1 ratio on a CFU basis to obtain the final *L. reuteri* ingredient. BiomEdit states that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is manufactured under current good manufacturing practices using food-grade raw materials and that all processing aids used in the manufacturing process are used in accordance with applicable U.S. regulations or are GRAS for their respective uses. BiomEdit states that the fermentation medium does not contain any ingredients nor derivatives of major allergens.

BiomEdit provides specifications for *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 that include total cell count ( $\geq 2.6 \times 10^9$  CFU/g), and limits for microorganisms, including *Escherichia coli* (absent in 10 g), *Salmonella* serovars (absent in 25 g), *Staphylococcus aureus* (absent in 25 g), and heavy metals, including lead ( $\leq 0.2$  mg/kg). BiomEdit provides the results from the analyses of three non-consecutive batches to demonstrate that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 can be manufactured to meet these specifications. BiomEdit provides the results of stability studies and states that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is stable for 9 months at 5 °C and ambient humidity when stored in sealed containers.

BiomEdit estimates the dietary exposure to *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 from the intended uses based on the maximum use level of  $1 \times 10^{10}$  CFU/serving of food and the average consumption of 20 servings/person (p)/d. Based on the assumption that the highest number of servings that may contain *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is 10 servings/p/d, BiomEdit estimates the dietary exposure to *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 to be no more than  $1 \times 10^{11}$  CFU/p/d.

BiomEdit discusses data and information used to support the safety of *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788, including a history of safe use of *L. reuteri* species in fermented and non-fermented milk products, salami, sour dough, fermented molasses, and fruit juices. BiomEdit incorporates into their notice and provides summaries of the information pertaining to the safety of the *L. reuteri* strains discussed

in GRNs 000254, 000410, and 000440.<sup>2</sup> BiomEdit summarizes published animal and human studies on *L. reuteri*. BiomEdit states that no adverse effects were reported from the consumption of the *L. reuteri* strains according to the published clinical studies. BiomEdit also provides a report of an unpublished 28-day rodent study with *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788, and describes no adverse effects or translocation of the organisms to other organs. BiomEdit conducted a literature search through June 2022 to identify available safety information relevant to *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788. BiomEdit did not identify any safety concerns or information that would contradict its GRAS conclusion.

Based on the totality of the data and information, BiomEdit concludes that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is GRAS for its intended use.

### **Standards of Identity**

In the notice, BiomEdit states its intention to use *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

### **Potential Labeling Issues**

Under section 403(a) of the Federal Food, Drug, & Cosmetic (FD&C) Act, a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and 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 (OFAS) did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

### **Potential Requirement for a Color Additive Petition**

There is no GRAS provision for color additives. In the notice, BiomEdit notes that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is an off white to dull orange colored powder. As such, the use of *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21

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<sup>2</sup> *L. reuteri* DSM17938 was the subject of GRNs 000254 and 000410. *L. reuteri* NCIMB 30242 was the subject of GRN 000440. We evaluated these notices and responded in letters dated November 18, 2008, March 26, 2012, and February 12, 2013, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 001112 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

### **Section 301(ll) of the 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 BiomEdit's notice concluding that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 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 *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788. Accordingly, our response should not be construed to be a statement that foods containing *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that BiomEdit provided, as well as other information available to FDA, we have no questions at this time regarding BiomEdit's conclusion that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. reuteri* ATCC PTA-126787 and ATCC PTA-126788 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 001112 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

**Susan J.  
Carlson -S**

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