



Amy Clewell, ND, DABT
Vice President, Scientific and Regulatory Affairs
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000847

Dear Ms. Clewell:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000847. We received the notice you submitted on behalf of ProBiotix Health Ltd. (ProBiotix) dated February 21, 2019, and filed it on May 1, 2019.

The subject of the notice is *Lactobacillus plantarum* ECGC 13110402 (*L. plantarum* ECGC 13110402) for use as an ingredient in conventional foods (excluding infant formula and foods under the jurisdiction of the United States Department of Agriculture (USDA)) at levels up to 1×10^{10} colony forming units (CFU) per serving. The notice informs us of ProBiotix's view that this use of *L. plantarum* ECGC 13110402 is GRAS through scientific procedures.

ProBiotix provides information about the identity of *L. plantarum* ECGC 13110402. ProBiotix describes *L. plantarum* ECGC 13110402 as a fine and smooth granulated powder. ProBiotix states that *L. plantarum* ECGC 13110402 is a Gram-positive, rod-shaped bacterium, which is deposited at the European Culture General Collection under accession number ECGC 13110402. ProBiotix discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity.

ProBiotix describes the manufacture of *L. plantarum* ECGC 13110402. ProBiotix states that the strain is produced by fermentation of a pure culture under controlled conditions. After fermentation, the bacterial cells are concentrated by centrifugation and cryoprotectants (water, organic salts, sugars, and carbohydrates) are added. The concentrate is freeze-dried, and the pellets are milled to produce the powder. ProBiotix states that *L. plantarum* ECGC 13110402 is manufactured in accordance with current good manufacturing practices using food-grade materials. ProBiotix states that *L. plantarum* ECGC 13110402 does not contain any major allergens.

ProBiotix provides specifications for *L. plantarum* ECGC 13110402. These include a minimum cell count of 2×10^{11} CFU and limits for other microorganisms, including non-

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lactic acid bacteria (≤ 5000 CFU/g), coliforms (< 10 CFU/10 g), total yeast and molds (< 100 CFU/g), and *Escherichia coli* and Salmonella (absent in 25 g). ProBiotix provides results of analyses of three non-consecutive batches to demonstrate that *L. plantarum* ECGC 13110402 can be produced to meet the specifications. Additionally, ProBiotix provides data to demonstrate that *L. plantarum* ECGC 13110402 is stable for up to 18 months when stored at temperatures of 5 °C and 25 °C.

ProBiotix estimates dietary exposure to *L. plantarum* ECGC 13110402 from its use in conventional foods.¹ ProBiotix intends to use *L. plantarum* ECGC 13110402 in foods at levels up to 1×10^{10} CFU/serving. Based on the assumptions that males ≥ 51 years old consume the highest number of servings of food per day (d) (18.2 servings/d), and that 100% of food servings contain *L. plantarum* ECGC 13110402, ProBiotix estimates maximum dietary exposure for males ≥ 51 years old to be 1.82×10^{11} CFU/d or 2.6×10^9 CFU/kg body weight (bw)/d. ProBiotix states that since *L. plantarum* ECGC 13110402 will not be added to foods where standards of identity preclude its use, or in foods under USDA jurisdiction, a more realistic estimate of dietary exposure for males ≥ 51 years old, based on 50% of food servings containing *L. plantarum* ECGC 13110402, would be 9.1×10^{10} CFU/d, or 1.3×10^9 CFU/kg bw/d.

ProBiotix discusses information to support the safety of *L. plantarum* ECGC 13110402. ProBiotix discusses the results of published animal toxicity studies on *L. plantarum* strains including studies summarized in GRNs 000685² and 000722³ and states that no treatment-related adverse effects were reported in these studies. ProBiotix states that an updated literature search was also conducted through February 2019, which did not identify any studies that report safety concerns. ProBiotix also discusses several clinical studies where *L. plantarum* strains were consumed by children and adults, including a study where *L. plantarum* ECGC 13110402 was consumed by healthy adults. ProBiotix states that the results of these studies demonstrated that *L. plantarum* ECGC 13110402 is well tolerated at levels up to 2×10^{11} CFU/day. To further support the safety of *L. plantarum* ECGC 13110402, ProBiotix describes the long history of safe use of *L. plantarum* strains in fermented human foods. Additionally, ProBiotix states that analysis of *L. plantarum* strain ECGC 13110402 genome did not detect any known genes encoding antibiotic resistance or virulence factors.

ProBiotix notes that the European Food Safety Authority concluded *L. plantarum* met the Qualified Presumption of Safety status in 2007, and has maintained this status. Additionally, ProBiotix states that *L. plantarum* is included in the International Dairy Federation inventory of microbial food cultures with a documented use in human foods.

1 ProBiotix states that its intended uses for *L. plantarum* ECGC 13110402 in some foods would be substitutional for uses of other *L. plantarum* strains listed in GRNs 000685 and 000722.

2 GRN 000685 describes the use of *L. plantarum* strain 299v as an ingredient in conventional foods. FDA evaluated this notice and responded in a letter dated October 31, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

3 GRN 000722 describes the use of *L. plantarum* strain Lp-115 as an ingredient in conventional foods. FDA evaluated this notice and responded in a letter dated February 16, 2018, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Based on the totality of information discussed above, ProBiotix concludes that *L. plantarum* ECGC 13110402 is GRAS under the conditions of its intended use.

Standards of Identity

In the notice, ProBiotix states its intention to use *L. plantarum* ECGC 13110402 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 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). The notice raises a potential issue under these labeling provisions. In the notice, ProBiotix cites studies that describe *L. plantarum* ECGC 13110402 as having certain health benefits. If products containing *L. plantarum* 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 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.

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 ProBiotix's notice concluding that *L. plantarum* ECGC 13110402 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. plantarum*. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* ECGC 13110402, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that ProBiotix provided, as well as other information available to FDA, we have no questions at this time regarding ProBiotix's conclusion that *L. plantarum* ECGC 13110402 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* ECGC 13110402 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 000847 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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Susan Carlson, Ph.D.
Director
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