



James Heimbach, Ph.D.
JHeimbach, LLC
923 Water Street #66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 001108

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001108. We received the notice that you submitted on behalf of Advanced Enzyme Technologies, Ltd. (AET, they) on September 21, 2022 and filed it on February 28, 2023. AET submitted amendments on May 6, July 18, August 8, and August 15, 2023 that clarified the manufacturing process, specifications, intended use, and provided additional safety information.

The subject of the notice is *Lactiplantibacillus plantarum* strain MCC 0537 (*L. plantarum* MCC 0537) for use as an ingredient at up to 1×10^{10} colony forming units (CFU)/serving in yogurt and other milk-based products, dairy alternatives, soy products, fruit drinks, frostings, frozen dairy desserts and mixes, fruit and water ices, chewing gum, condiments, herbs, seeds, spices, seasoning blends, extracts, and flavorings, nuts and nut products, plant-protein products, cereals, processed fruits, processed vegetables and vegetable juices, snack foods, and toppings.¹ The notice informs us of AET's view that these uses of *L. plantarum* MCC 0537 are GRAS through scientific procedures.

AET describes *L. plantarum* MCC 0537 as an off-white to brown colored powder. AET states that *L. plantarum* MCC 0537 is a Gram-positive, rod-shaped, non-motile bacterium. The strain was isolated from fermented milk and has been deposited in the National Centre for Microbial Resources (NCMR), India, with deposit number MCC 0537. AET describes the taxonomic analysis for the strain identity. They conduct genotypic characterization utilizing BLAST analysis of the 16S rRNA and *pheS* gene, whole genome sequencing, homology search on the Comprehensive Antibiotic Resistance Database (CARD) for antibiotic resistance,

¹ AET states that *L. plantarum* MCC 0537 is not intended for use in infant formula, any products under the jurisdiction of the United States Department of Agriculture, foods for which standards of identity preclude its use, or in alcoholic beverages.

search of the Virulence Factor Database for virulence factors, and other genomic searches for biogenic amine production, mobile elements, putatively adverse metabolites and Clustered Regularly Interspaces Short Palindromic Repeats (CRISPR). AET also discusses the results of phenotypic analysis on biochemical tests, antibiotic resistance, cytotoxicity, antimicrobial activity, production of enterotoxin and D-lactic acid. AET states that *L. plantarum* MCC 0537 is non-pathogenic, non-toxicogenic, is not genetically engineered, does not produce biogenic amines and has a CRISPR system to promote genome stability.

AET describes the manufacture of *L. plantarum* MCC 0537 by fermentation of a pure culture under controlled conditions. After fermentation, the *L. plantarum* MCC 0537 cells are separated from the medium and concentrated by centrifugation, washed, and then lyophilized. AET states that *L. plantarum* MCC 0537 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, are GRAS for their respective uses, or are the subject of an effective food contact notification.

AET provides specifications for *L. plantarum* MCC 0537 that include limits for total cell count ($\geq 4.0 \times 10^{11}$ CFU/g), microorganisms, including *Escherichia coli* (absent in 10 g), *Salmonella* serovars (absent in 10 g), *Staphylococcus aureus* (absent in 1 g), and heavy metals, including lead (< 0.1 mg/kg). AET provides the results from the analyses of three non-consecutive batches to demonstrate that *L. plantarum* MCC 0537 can be manufactured to meet these specifications. AET provides the results of stability studies and states that *L. plantarum* MCC 0537 is stable for 18 months at 5 ± 3 °C in double low-density polyethylene (LDPE) bags stored in high-density polyethylene (HDPE) drums.

AET states that males aged 51 years and older consume the highest number of servings of food per day at 18.2 servings/d. AET estimates dietary exposure to *L. plantarum* MCC 0537 from the intended uses to be 1.82×10^{11} CFU/person (p)/d based on the presumption that all servings of food would contain *L. plantarum* MCC 0537 at the maximum use level of 1×10^{10} CFU/serving.

AET discusses data and information used to support the safety of *L. plantarum* MCC 0537, including a history of safe use of *L. plantarum* species in fermented foods, such as cheese, kefir, sauerkraut, meat, vegetables, and beverages. AET incorporates into their notice and provides summaries of the information pertaining to the safety of the *L. plantarum* strains discussed in GRNs 000685, 000722, and 00847.² AET also summarizes published animal and human studies on *L. plantarum*. AET states that no serious adverse events were reported in animal studies. For human studies using *L. plantarum* at levels up to 4.5×10^{11} CFU/d, AET describes either no serious adverse events or that the adverse events were mild and were judged to be unrelated to the

² *L. plantarum* 299V, LP-115 and ECGC13110402 were the subjects of GRNs 000685, 000722 and 000847, respectively. We evaluated these notices and responded in letters dated October 31, 2017, February 16, 2018, and September 30, 2019, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

dietary intervention.

Based on the totality of the data and information, AET concludes that *L. plantarum* MCC 0537 is GRAS for its intended use.

Standards of Identity

In the notice, AET states its intention to use *L. plantarum* MCC 0537 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. plantarum* MCC 0537 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 AET's notice concluding that *L. plantarum* MCC 0537 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* MCC 0537. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* MCC 0537, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that AET provided, as well as other information available to FDA, we have no questions at this time regarding AET's conclusion that *L. plantarum* MCC 0537 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* MCC 0537 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 001108 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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Susan J. Carlson, Ph.D.
Director
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