Mark Yacura
Quarles & Brady, LLP
1701 Pennsylvania Avenue, NW
Washington, DC 20006-5805

Re: GRAS Notice No. GRN 000685

Dear Mr. Yacura,

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000685. We received the notice that you submitted on behalf of Probi AB (Probi) on February 6, 2017, and filed it on March 2, 2017. We received amendments to the notice on June 30, 2017, and August 30, 2017, containing additional information regarding dietary exposure estimates, specifications, and other safety information.

The subject of the notice is *Lactobacillus plantarum* strain 299v (*L. plantarum* 299v) for use as an ingredient in conventional foods at up to 1×10^{10} CFU/serving.[1] The notice informs us of Probi's view that this use of *L. plantarum* 299v is GRAS through scientific procedures.

Probi provides information about the identity and composition of *L. plantarum* 299v.[2] Probi states that *L. plantarum* 299v is a Gram-positive, lactic acid bacterium, which was isolated from healthy intestinal mucosa.

Probi describes the manufacture of and specifications for *L. plantarum* 299v. The strain is fermented under pH- and temperature-controlled, aseptic conditions and monitored for contamination. After fermentation, the broth culture is concentrated by centrifugation and cryoprotectants are added. The ingredient is packaged as a liquid concentrate, freeze-dried powder, or pellets. Probi states that all materials used in the manufacturing process are food-grade.[3] The specifications for *L. plantarum* 299v include a minimum of 5×10^{11} CFU/g and limits for microbial contaminants including total bacteria, fungi, and *Salmonella*. Probi provides batch analyses for six nonconsecutive lots to demonstrate that their production meets the intended specifications.

[1] Probi states that *L. plantarum* 299v is not intended for use in infant formula, or any meat or poultry products that are under the jurisdiction of the United States Department of Agriculture.
[2] The strain was deposited in the Deutsche Sammlung von Mikroorganismen und Zellkulturen in Germany as DSM 9843.
[3] The culture media may contain soy-derived ingredients.

Probi states that *L. plantarum* 299v is intended for use at up to 1 x 10^{10} CFU/serving as an ingredient in conventional foods, including, but not limited to, wet chilled and ambient products such as fruit drinks, yogurts, milk, and plant based products; dry chilled products; dry and shelf-stable products such as cereals, candy, bars, cookies, gums, and confectionery. Probi states that they intend for addition of *L. plantarum* 299v at up to 1 x 10^{11} CFU/serving to ensure the intended use level is maintained throughout shelf life.

Probi estimates the dietary exposure to *L. plantarum* 299v. Probi intends to use *L. plantarum* 299v as an ingredient in conventional foods at up to 1 x 10^{10} CFU/serving. Based on Probi's assumption that the strain will be added to a limited number of foods, Probi expects that consumers will only consume one serving of *L. plantarum* 299v; therefore, Probi estimates the dietary exposure of *L. plantarum* 299v at 1 x 10^{10} CFU/day.

Probi discusses published data to support the safety of consumption of *L. plantarum* 299v. Probi discusses the results of studies in animals where *L. plantarum* 299v was administered to rats, mice or pig models of acute liver injury or colitis at up to 1 x 10^{10} CFU/day and for up to 28 days. No treatment-related adverse events were reported in these studies.

Probi also describes the results of published human studies conducted to investigate the effects of consumption of *L. plantarum* 299v in healthy adults and children, as well as compromised adults and children. *L. plantarum* 299v was administered to healthy adults at up to 2 x 10^{11} CFU/day and for up to 42 days; *L. plantarum* 299v was administered to children at up to 1.4 x 10^{11} and for up to 90 days. No treatment-related adverse events were reported in these studies. Probi concludes that the studies presented support safety of ingestion of *L. plantarum* 299v up to 2 x 10^{11} CFU/day.

Probi discusses published literature demonstrating that *L. plantarum* has been isolated from the human gastrointestinal tract of healthy individuals and is present in many fermented foods with a long history of safe consumption. Additionally, Probi states that *L. plantarum* 299v has been used in food products in Europe and in dietary supplements in 25 countries without reported adverse events. Probi states that the European Food Safety Authority considered *L. plantarum* to meet Qualified Presumption of Safety (QPS) status beginning in 2007 and has maintained its status through the 2016 QPS publication.

Probi discusses the results of published and unpublished studies demonstrating that *L. plantarum* 299v is susceptible to antibiotics and lacks functional or transferable antibiotic resistance genes. Additionally, *L. plantarum* 299v does not exhibit hemolytic activity.

Probi includes the report of a panel of individuals (Probi's GRAS panel). Based on its review, Probi's GRAS panel concluded that *L. plantarum* 299v is safe under the conditions of its intended use.

Based on the totality of information discussed above, Probi concludes that *L. plantarum* 299v is GRAS under the conditions of its intended use.

Standards of Identity

In the notice, Probi states its intention to use *L. plantarum* 299v 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, and Cosmetic Act (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 as nutrient content claims and health claims). The notice raises a potential issue under these labeling provisions. In the notice, Probi cites studies that describe *L. plantarum* 299v as having certain health benefits. If products containing *L. plantarum* 299v bear any nutrient content or health claims on the label or in labeling, such claims are the 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. *L. plantarum* 299v may require labeling under the FD&C Act because the culture media may contain soy-derived protein. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. Questions related to food labeling in general should be directed to ONFL.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Probi's notice concluding that *L. plantarum* 299v 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* 299v. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* 299v, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Probi provided, as well as other information available to FDA, we have no questions at this time regarding Probi's conclusion that *L. plantarum* 299v is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* 299v 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 000685 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe -S

Digitally signed by Dennis M. Keefe -S
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Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition