Sheng-Hung Huang
Glac Biotech Co. Ltd.
3F-2, No. 17, Guoji Rd.
Xinshi Dist., Tainan City 74442
TAIWAN

Re: GRAS Notice No. GRN 001130

Dear Mr. Huang:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001130. We received the notice from Glac Biotech Co. Ltd. (Glac Biotech) on February 9, 2023, and filed it on May 11, 2023. Glac Biotech submitted amendments on June 9, 2023, and August 18, 2023, that provided additional information regarding the strain identity, manufacturing process, specifications, analytical methods, intended use, and safety.

The subject of the notice is *Lactobacillus rhamnosus* CGMCC 21225 for use as an ingredient at a maximum level of 1 x 10^9 colony forming units (CFU)/serving in "energy" and "sports" drinks; flavored, carbonated, "enhanced," and "fortified" waters; meal replacement, protein, and nutritional drinks; bottled tea; fruit juices, drinks, nectars, ades, and smoothies; breakfast cereals; cheeses; chewing gum; buttermilk; plain fermented milks; flavored milks, milk drinks and mixes; milk shakes; evaporated, condensed, and dry milks; yogurt and yogurt drinks; milk-based gelatins, puddings, and fillings; soy milk, soy-based drinks, and soy-based protein products; bars (cereal, granola, "energy," protein, and meal replacement); soft and hard candies; and cereals, fruits, vegetables, and fruit juices intended for infants (>4 months) and young children.[1] The notice informs us of Glac Biotech's view that these uses of *L. rhamnosus* CGMCC 21225 are GRAS through scientific procedures.

Glac Biotech describes *L. rhamnosus* CGMCC 21225 as a light yellow to light brown colored powder. Glac Biotech states that *L. rhamnosus* CGMCC 21225 is a Gram-positive, rod-shaped, non-spore forming, and non-motile bacterium. The strain was isolated from infant feces and has been deposited in the China General Microbiological Culture Collection Center (CGMCC), with deposit number 21225. Glac Biotech describes the taxonomic analysis for the identity of the strain. Glac

[1] Glac Biotech states that *L. rhamnosus* CGMCC 21225 is not intended for use in infant formula or other foods targeted to infants less than 4 months of age, products under the jurisdiction of the United States Department of Agriculture, alcoholic beverages, or foods where standards of identity do not permit its addition.

Biotech also discusses the results of genomic analyses to confirm the strain's identity and states that the strain is not genetically modified. Glac Biotech discusses the results of phenotypic and genotypic characterization performed on *L. rhamnosus* CGMCC 21225 and concludes that no virulence factors, toxins, or transferable antibiotic resistance genes were identified, and that the strain is non-pathogenic and non-toxigenic.

Glac Biotech describes the manufacture of *L. rhamnosus* CGMCC 21225 by fermentation of a pure culture under controlled conditions. After fermentation, the cells are separated from the fermentation medium and concentrated by centrifugation, lyophilized, and then mixed with maltodextrin before packing. Glac Biotech states that *L. rhamnosus* CGMCC 21225 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.

Glac Biotech provides specifications for *L. rhamnosus* CGMCC 21225 that include total cell count ($\geq 1.0 \times 10^{11}$ CFU/g), and limits for moisture (≤ 7 %), microorganisms, including *Escherichia coli* (negative in 50 g), *Salmonella* serovars (negative in 25 g), *Staphylococcus aureus* (negative in 50 g), and heavy metals, including lead (≤ 0.1 mg/kg). Glac Biotech provides the results from the analyses of three non-consecutive batches to demonstrate that *L. rhamnosus* CGMCC 21225 can be manufactured to meet these specifications. Glac Biotech provides the results of stability studies and states that *L. rhamnosus* CGMCC 21225 is stable for 24 months at -20 °C and 4 °C, and for 3 months at 25 °C with 60% relative humidity.

Glac Biotech provides the dietary exposure to *L. rhamnosus* CGMCC 21225 from the intended uses based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). Glac Biotech estimates the mean and 90th percentile eaters-only dietary exposure to *L. rhamnosus* CGMCC 21225 for the U.S. population aged 2 years and older to be 2.9×10^9 CFU/person (p)/d and 6.3×10^9 CFU/p/d, respectively. Further, Glac Biotech states that the intended uses of *L. rhamnosus* CGMCC 21225 are substitutional for current uses of other *L. rhamnosus* strains.

Glac Biotech discusses data and information used to support the safety of *L. rhamnosus* CGMCC 21225, including the gastrointestinal colonization and survival, translocation from the gastrointestinal tract to circulation and extraintestinal sites, and opportunistic infections for other *L. rhamnosus* strains. Glac Biotech summarizes published animal and human studies on *L. rhamnosus* CGMCC 21225. Glac Biotech describes no adverse effects in the 90-day rat study at the highest dose tested. In the human studies, they conclude that the observed adverse events were unrelated to the strain.

Based on the totality of the data and information, Glac Biotech concludes that *L. rhamnosus* CGMCC 21225 is GRAS for its intended use.

Standards of Identity

In the notice, Glac Biotech states its intention to use *L. rhamnosus* CGMCC 21225 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. rhamnosus* CGMCC 21225 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.

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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. *L. rhamnosus* CGMCC 21225 requires labeling under the FD&C Act because it contains protein derived from milk and soy.

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 Glac Biotech's notice concluding that *L. rhamnosus* CGMCC 21225 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. rhamnosus* CGMCC 21225. Accordingly, our response should not be construed to be a statement that foods containing *L. rhamnosus* CGMCC 21225, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Glac Biotech provided, as well as other information available to FDA, we have no questions at this time regarding Glac Biotech's conclusion that *L. rhamnosus* CGMCC 21225 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. rhamnosus* CGMCC 21225 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 001130 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.09.28 16:48:55 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition