Jim Lassiter
REJIMUS, Inc.
600 W. Santa Ana Blvd.
Suite 1100
Santa Ana, CA 92701

Re: GRAS Notice No. GRN 001078

Dear Mr. Lassiter:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001078. We received the notice that you submitted on behalf of Cell Biotech Co. Ltd. (CBI) on May 12, 2022, and filed it on December 14, 2022. CBI submitted amendments to the notice on April 15, 2023, April 21, 2023, June 12, 2023, June 22, 2023, June 30, 2023, August 7, 2023, October 2, 2023, and October 6, 2023, providing clarifying information about the microorganism, manufacturing method, stability, specifications, including revised heavy metal specifications, results from additional batch analyses, clarification on the dietary exposure assessment, and an updated literature search.

The subject of the notice is *Bifidobacterium bifidum* KCTC 12199BP for use as an ingredient at a level up to 10^9 colony forming units (CFU)/serving in liquid unflavored milk.[1] The notice informs us of CBI's view that this use of *B. bifidum* KCTC 12199BP is GRAS through scientific procedures.

CBI describes *B. bifidum* KCTC 12199BP as a light brown powder. CBI states that *B. bifidum* KCTC 12199BP is a non-pathogenic, non-toxigenic, non-motile, non-spore forming, Gram-positive, rod-shaped bacterium. The strain was isolated from cheese and is deposited in the strain collection of the Korean Collection for Type Cultures (KCTC) in Jeongeup-si, South Korea. CBI discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

CBI describes the manufacture of *B. bifidum* KCTC 12199BP by fermentation of a pure culture under controlled conditions. After fermentation, the bacterial culture and the fermentation media are separated by centrifugation. Following this, coating ingredients are added to water, mixed, sterilized with saturated steam, and blended with the concentrated bacterial culture and corn starch. The resulting product is quick-frozen, freeze dried, milled, and blended with corn starch to ensure a standardized cell count. CBI states that the manufacturing process is monitored for contamination, and that *B.*

[1] CBI states that *B. bifidum* KCTC 12199BP is not intended for use in infant formula, food products intended for infants and young children, or in food products under the jurisdiction of the United States Department of Agriculture.

bifidum KCTC 12199BP is manufactured under current good manufacturing practices and that all raw materials are food-grade and are used in accordance with existing U.S. authorizations.

CBI provides specifications for *B. bifidum* KCTC 12199BP that include viable cell count (≥ 10^{11} CFU/g); limits for heavy metals, including lead (≤ 0.01 mg/kg); and microorganisms, including coliforms (absent in 10 g), yeast and mold (≤ 10 CFU/g), *Escherichia coli* (absent in 1 g), *Staphylococcus aureus* (absent in 25 g), *Salmonella* serovars (absent in 25 g), and *Listeria monocytogenes* (absent in 25 g). CBI provides the results from the analyses of three non-consecutive batches to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

CBI estimates an eaters-only dietary exposure to *B. bifidum* KCTC 12199BP from the intended uses to be 8.94 x 10^8 CFU/person (p)/d at the mean and 1.85 x 10^9 CFU/p/d at the 90th percentile for the U.S. population aged 2 years or older based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES).

CBI cites published literature that documents the history of safe use of *B. bifidum* in human foods, including in fermented foods. CBI performed a literature search through April 2023 and summarizes published literature and governmental evaluations that support the safe consumption of *B. bifidum*, including *B. bifidum* KCTC 12199BP, with no serious adverse effects reported. CBI further concludes that the phenotypic characteristics of *B. bifidum* KCTC 12199BP do not pose a safety concern (i.e., production of antimicrobials, production of secondary metabolites, antibiotic resistance). CBI notes that bacteremia caused by bifidobacteria have been reported; however, these cases have occurred mainly in immunocompromised patients or those with a known medical condition. CBI explains that cases of bacteremia attributed to *B. bifidum* have not been reported.

Based on the totality of evidence, CBI concludes that *B. bifidum* KCTC 12199BP is GRAS for its intended use.

Standards of Identity

In the notice, CBI states its intention to use *B. bifidum* KCTC 12199BP in a food category for which standards of identity exist, located in Title 21 of the CFR. 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 to as nutrient content claims and health claims). If products containing *B.*

bifidum KCTC 12199BP 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 (CFSAN). 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.

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. *B. bifidum* KCTC 12199BP may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL in CFSAN.

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 CBI's notice concluding that *B. bifidum* KCTC 12199BP 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 *B. bifidum* KCTC 12199BP. Accordingly, our response should not be construed to be a statement that foods containing *B. bifidum* KCTC 12199BP, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that CBI provided, as well as other information available to FDA, we have no questions at this time regarding CBI's conclusion that *B. bifidum* KCTC 12199BP is GRAS under its intended conditions of use. This letter is not an affirmation that *B. bifidum* KCTC 12199BP 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 001078 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.10.31 13:23:22 -04'00'

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