U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Xuecong Liu
Bioflag Co., Ltd
No.2 JingYi Road
Development Zone, Huai'an
Jiangsu Province 223001
CHINA

Re: GRAS Notice No. GRN 001235

Dear Xuecong Liu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001235. We received Bioflag Co., Ltd (Bioflag)'s notice on July 12, 2024, and filed it on March 12, 2025. Bioflag submitted amendments to the notice on June 17, 2025, August 4, 2025, August 27, 2025, and August 28, 2025, clarifying the manufacturing process, analytical data, specifications, dietary exposure, and safety narrative.

The subject of the notice is *Bifidobacterium lactis* CCTCC M 2014588 for use as an ingredient at a maximum level of 10^9 colony forming units (CFU) per serving in "energy" and sports drinks; enhanced, flavored, carbonated, and fortified water; bottled tea; meal replacement, protein, and nutritional beverages; ready-to-eat (RTE) and hot breakfast cereals; cheeses; chewing gum; milk-based desserts; bars (cereal, granola, "energy," protein, meal replacement, and soy-based); hard candy; buttermilk, plain fermented milk, flavored milk, milk drinks and mixes, milk shakes, evaporated, condensed, and dry milk; yogurt and yogurt drinks; soy milk, soy-based drinks, soy-based products and plant-based protein products; fruit juices and nectars, fruit drinks, ades, and smoothies; soft candy; and baby foods (dry instant, prepared, ready-to-serve and RTE cereals, strained fruits or vegetables, and fruit juices), excluding infant formula, alcoholic beverages, and products under the jurisdiction of the United States Department of Agriculture. The notice informs us of Bioflag's view that these uses of *B. lactis* CCTCC M 2014588 are GRAS through scientific procedures.

Bioflag discusses the identity of *B. lactis* CCTCC M 2014588 and describes it as a white to light brown powder. Bioflag states that *B. lactis* CCTCC M 2014588 was isolated from human breast milk. Bioflag states that 16S-23S rRNA intergenic spacer, 23S rRNA gene sequencing, and whole genome sequencing were performed to confirm the strain's identity. Bioflag states that *B. lactis* CCTCC M 2014588 is non-pathogenic, non-toxigenic, and is deposited in the China Center for Type Culture Collection (CCTCC) under CCTCC M 2014588. Bioflag states that the strain is not genetically engineered.

Bioflag describes the manufacturing process for *B. lactis* CCTCC M 2014588, stating that it is produced using an optimized microbial fermentation process in a sterile,

controlled environment. After fermentation, the cells are isolated by centrifugation, lyophilized, and mixed with maltodextrin. Bioflag states that *B. lactis* CCTCC M 2014588 is manufactured in accordance with current good manufacturing practices and that all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

Bioflag provides specifications for *B. lactis* CCTCC M 2014588 that include *B. lactis* CCTCC M 2014588 (≥3.0 x 10^{11} CFU/g), and limits for moisture (≤ 8%), water activity (≤ 0.35), heavy metals, including lead (<0.2 mg/kg), and microorganisms, including yeast and mold (<100 CFU/g), *Salmonella* serovars (negative/g), *Listeria monocytogenes* (negative/25 g), and *Cronobacter sakazakii* (negative/g). Bioflag provides the results from the analyses of three non-consecutive batches to demonstrate that *B. lactis* CCTCC M 2014588 can be manufactured to meet these specifications. Bioflag states that *B. lactis* CCTCC M 2014588 is stable for up to 36 months at –20 °C when stored in the original sealed package.

Bioflag estimates an eaters-only dietary exposure to *B. lactis* CCTCC M 2014588 from the intended uses to be 2.94 x 10^9 CFU/person (p)/d (0.05 x 10^9 CFU/kg body weight (bw)/d) at the mean and 6.27 x 10^9 CFU/p/d (0.11 x 10^9 CFU/kg bw/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). Bioflag states that the intended uses of *B. lactis* CCTCC M 2014588 are substitutional to current uses of other *B. lactis* strains and therefore, not expected to significantly increase dietary exposure to *B. lactis* strains.

Bioflag discusses data and information used to support the safety of *B. lactis* CCTCC M 2014588. Bioflag incorporates into their notice and provides summaries of the information pertaining to the safety of *B. lactis* discussed in GRNs 000952, 000872, and 000856.[1] Bioflag also cites a published clinical study in which infants consumed *B. lactis* CCTCC M 2014588 and states that no adverse events were reported. Bioflag discusses the results of genotypic and phenotypic analyses and states no genes encoding virulence factors and toxigenicity were identified in the genome of *B. lactis* CCTCC M 2014588 and the strain is susceptible to most antibiotics. Bioflag states that genomic analysis identified sequence mutations that confer resistance to elfamycin and mupirocin, and phenotypic analysis showed that *B. lactis* CCTCC M 2014588 is resistant to gentamycin. Bioflag explains that resistance to these antibiotics is intrinsic to the *Bifidobacterium* genus. Bioflag discusses data showing that *B. lactis* CCTCC M 2014588 is unable to produce biogenic amines.

Based on the totality of the data and information provided in the submission, Bioflag concludes that *B. lactis* CCTCC M 2014588 is GRAS for its intended use.

[1] The subjects of GRNs 000952, 000872, and 000856 are various strains of *B. lactis*. We evaluated these notices and responded in letters dated March 17, 2021, December 9, 2019, and December 9, 2019, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Bioflag states its intention to use *B. lactis* CCTCC M 2014588 in several food categories, including foods 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. lactis* CCTCC M 2014588 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 Nutrition Center of Excellence. The Office of Pre-Market Additive Safety (OPMAS) 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. lactis* CCTCC M 2014588 may require labeling under the FD&C Act because it may contain protein derived from milk and soybean from the fermentation process. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OPMAS. Questions related to food labeling in general 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 Bioflag's notice concluding that *B. lactis* CCTCC M 2014588 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. lactis* CCTCC M 2014588. Accordingly, our response should not be construed to be a statement that foods containing *B. lactis* CCTCC M 2014588, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Bioflag provided, as well as other information available to FDA, we have no questions at this time regarding Bioflag's conclusion that *B. lactis* CCTCC M 2014588 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. lactis* CCTCC M 2014588 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 001235 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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