



Kevin Gillies
Kevin O. Gillies Consulting Services, LLC
1759 Grape St.,
Denver, CO 80220

Re: GRAS Notice No. GRN 001204

Dear Mr. Gillies:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001204. We received Beijing Scitop Bio-Tech Co., Ltd. (Scitop Bio)'s notice on June 24, 2024 and filed it on September 19, 2024. Scitop Bio submitted amendments to the notice on November 11, 2024, December 10, 2024, January 2, 2025, and January 8, 2025, that clarified the manufacturing process, specifications, intended uses, dietary exposure, and safety information.

The subject of the notice is *Lacticaseibacillus casei* Zhang (*L. casei* Zhang) for use as an ingredient at a level up to 6×10^{10} colony forming units (CFU)/serving in conventional foods.¹ The notice informs us of Scitop Bio's view that this use of *L. casei* Zhang is GRAS through scientific procedures.

Scitop Bio describes *L. casei* Zhang as a white to yellow powder and states that *L. casei* Zhang is a non-pathogenic, non-toxigenic, Gram-positive, rod-shaped, non-motile, non-spore-forming bacterium. Scitop Bio notes that the strain was isolated from the fermented dairy product koumiss, a fermented mare's milk, and has been deposited in the China General Microbiological Culture Collection Center (CGMCC) with the depository number CGMCC 1697. Scitop Bio describes the taxonomic analysis for the identity of the strain. Scitop Bio also discusses the results of genomic analyses to confirm the strain identity and states that the strain is not genetically engineered. Scitop Bio discusses the results of phenotypic and genotypic characterization performed on *L. casei* Zhang. Scitop Bio states that the genome of *L. casei* Zhang is absent of virulence factors and/or toxins associated with pathogenicity and antimicrobial resistance genes, and the strain does not produce concerning biogenic amines, such as putrescine, cadaverine, histamine and tyramine.

Scitop Bio describes the manufacture of *L. casei* Zhang by fermentation of a pure culture under controlled conditions. After fermentation, the bacteria biomass is subjected to

¹ Scitop Bio states that *L. casei* Zhang is not intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture, alcoholic beverages, or in any food for which standards of identity would preclude its use.

centrifugation, lyophilization, grinding, mixing, and packaged to yield the final product. Scitop Bio states that *L. casei* Zhang is manufactured in accordance with current good manufacturing practices using food-grade raw materials. Scitop Bio states that all processing aids used in the manufacture of *L. casei* Zhang are approved food additives, are GRAS for their intended use, or are the subject of an effective food contact notification. Scitop Bio states that the drying process stabilizer may contain milk powder.

Scitop Bio provides specifications for *L. casei* Zhang that include viable cell count $\geq 5 \times 10^{11}$ CFU/g, water activity ≤ 0.2 , moisture ($\leq 6\%$), limits for heavy metals, including lead (≤ 0.1 mg/kg), and microorganisms, including *Escherichia coli* (< 3 most probable number in 1 g), *Salmonella* serovars (not detectable in 25 g), *Listeria monocytogenes* (not detectable in 25 g), *Staphylococcus aureus* (not detectable in 25 g), *Cronobacter sakazakii* (not detectable in 100 g), and *Bacillus cereus* (< 100 CFU/g). Scitop Bio provides the results from the analyses of three non-consecutive batches to demonstrate that *L. casei* Zhang can be manufactured to meet these specifications.

Scitop Bio estimates that the dietary exposure to *L. casei* Zhang from its intended uses is 6×10^{11} CFU/person (p)/day (d) based on the average individual consumes 20 servings of food/p/d in the U.S., and the assumption that 10 servings of food would contain *L. casei* Zhang at the maximum use level of 6×10^{10} CFU/serving. Scitop Bio states that the intended uses of *L. casei* Zhang are substitutional to the uses of other *L. casei* strains and therefore, there is not expected to be an increase in the dietary exposure to *L. casei*.

Scitop Bio discusses the publicly available safety data and information used to support the safety of *L. casei* Zhang, including a history of safe use of the *L. casei* species in fermented foods and commercial starter culture. Scitop Bio incorporates into their notice and provides summaries of the information pertaining to the safety of live *Lactobacillus* in food discussed in GRNs 000231, 000429, 000736, 000840, 001085, and 001093.² Scitop Bio discusses the safety of *L. casei* species and *L. casei* Zhang from a comprehensive literature search, and states that no adverse effects were reported in clinical trials with *L. casei* strains at a level of close to 10^{12} CFU/kg body weight (bw)/d. Scitop Bio provides a corroborative toxicology study of *L. casei* Zhang in a rat model confirming that the strain causes no adverse effects at the test dose of 2.2×10^{11} CFU/kg bw/d.

Based on the totality of the data and information, Scitop Bio concludes that *L. casei* Zhang is GRAS for its intended use.

² *Lactobacillus casei* subsp. *rahmnosus* GG, *L. casei* Shirota, *L. casei* subsp. *paracasei* Lpc-37, *L. paracasei* ssp. *paracasei* F19, *L. casei* KCTC 12398BP, and *L. rhamnosus* IDCC 3201 were the subjects of GRNs 000231, 000429, 000736, 000840, 001085, and 001093, respectively. We evaluated these notices and responded in letters dated May 29, 2008, December 10, 2012, April 11, 2018, August 27, 2019, October 27, 2023 and June 9, 2023, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Scitop Bio states its intention to use *L. casei* Zhang 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 *L. casei* Zhang 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. *L. casei* Zhang may require labeling under the FD&C Act because it may contain milk. 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 Scitop Bio’s notice concluding that *L. casei* Zhang 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. casei* Zhang. Accordingly, our response should not be construed to be a statement that foods containing *L. casei* Zhang, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Scitop Bio provided, as well as other information available to FDA, we have no questions at this time regarding Scitop Bio's conclusion that *L. casei* Zhang is GRAS under its intended conditions of use. This letter is not an affirmation that *L. casei* Zhang 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 001204 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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