



Stella Si
Anchor Center for Certification
No. 1295 Chuan Qiao Road, Building 2, Suite 302
Pudong, Shanghai, 201206
CHINA

Re: GRAS Notice No. GRN 001247

Dear Ms. Si:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001247. We received Shanghai Changing Biotechnology Co., Ltd. (Changing Bio)'s notice on October 31, 2024, and filed it on April 11, 2025. Changing Bio submitted an amendment to the notice on June 12, 2025, that clarified the manufacturing process, specifications, and aspects of the safety narrative.

The subject of the notice is β -lactoglobulin produced by *Kluyveromyces lactis* expressing a gene encoding bovine β -lactoglobulin (β -lactoglobulin) for use as a source of protein at levels up to 35% in a variety of foods as shown in Table 1 (excluding use in infant formula and foods under the jurisdiction of the United States Department of Agriculture). The notice informs us of Changing Bio's view that these uses of β -lactoglobulin are GRAS through scientific procedures.

Table 1. Proposed uses and use levels for β -lactoglobulin

Food Category	Food Uses	Maximum Use Level (%)
Nutritional products	Meal replacements and supplements	15
	Powdered nutritional beverages	25
	Electrolyte-sports drinks	6
	Performance nutritional beverages, high protein	25
	Nutritional bars	35
Dairy and dairy-based products	Milk, powdered milk, flavored milk, milk-based drinks, milk substitutes	6
	Cream, half and half, cream cheese, whipped cream	15
	Spreads, dips	10
	Cream substitutes	15
	Yogurt and fermented milk products	8
	Ice cream, frozen yogurt	8
	Cheese used as ingredient	15

	Semi-hard cheese	25
	Mousses and desserts	5
Sugar-based products	Confections (including chocolate)	10
	Coatings and fillings	10
Baked goods	Cookies, brownies	5
	Doughnuts, toaster pastries, muffins	10
	French toast, crepes, pancakes, bagels, scones, biscuits, croissants	10
	Bread, rolls, English muffins, pizza crust	10
	Crackers, popcorn, tortilla chips, potato chips, hard pretzels, snack mix	5
Dressings	Creamy salad dressings	5
	Minor entrée sauces (e.g., Alfredo sauce)	6
Egg products	Egg substitutes	10

Our use of the term, “ β -lactoglobulin,” in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA’s labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Nutrition Center of Excellence (NCE). The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for “ β -lactoglobulin.”

Changing Bio provides information about the identity and composition of β -lactoglobulin and describes it as a white to off-white powder containing at least 85% protein of which more than 90% of the total protein is β -lactoglobulin. Whey protein accounts for 20% of cow’s milk total protein, from which approximately 60% is β -lactoglobulin. Changing Bio states that β -lactoglobulin has a molecular weight of 18.4 kDa, a CAS registry number of 9066-45-9 and is 100% identical to β -lactoglobulin with UniProt sequence accession number P02754, natural variant B.

Changing Bio states that β -lactoglobulin is produced by *K. lactis* “CJ-B1-P11.” Changing Bio states that the production strain was developed from the host strain *K. lactis* CCTCC M20241460 through transformation with a plasmid vector containing a gene encoding for β -lactoglobulin from domestic cow (*Bos taurus*), and regulatory elements from *Kluyveromyces marxianus* and *Saccharomyces cerevisiae*. Changing Bio states the expression of the β -lactoglobulin remained stable for at least 100 generations. Changing Bio states that “CJ-B1-P11” is non-pathogenic and non-toxicogenic. Changing Bio states that the production organism does not contain any antibiotic resistance genes.

Changing Bio states that the β -lactoglobulin is manufactured by controlled fermentation of *K. lactis* “CJ-B1-P11.” β -lactoglobulin is secreted into the fermentation medium and then separated from the biomass by centrifugation, concentrated by ultrafiltration and

then further purified by ion-exchange chromatography. The eluate containing β -lactoglobulin is further concentrated by nanofiltration followed by drying and packaging. Changing Bio states that none of the materials used during the manufacturing process are derived from major allergens. Changing Bio states that β -lactoglobulin is manufactured in accordance with current good manufacturing practices and that all raw materials and processing aids are food grade and approved for their respective uses in accordance with an applicable U.S. regulation, are GRAS for their intended use, or are the subject of an effective food contact notification.

Changing Bio provides specifications for β -lactoglobulin that include protein content ($\geq 85\%$ w/w), β -lactoglobulin as % of the total protein content ($\geq 90\%$ w/w), moisture ($\leq 5\%$ w/w), ash ($\leq 4\%$ w/w), fat ($\leq 2\%$ w/w), total carbohydrates ($\leq 10\%$ w/w), lactose ($\leq 1\%$), pH (6.0 – 8.0), total arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), lead (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and limits for microorganisms. Changing Bio provides the results from the analyses of five non-consecutive batches to demonstrate that β -lactoglobulin can be manufactured to meet the specifications. Changing Bio states that β -lactoglobulin is stable for 12 months at ambient conditions.

Changing Bio states that the uses and use levels for β -lactoglobulin are the same as prior notified uses of β -lactoglobulin produced by microbial fermentation and notes that the dietary exposure estimate presented in GRN 001056¹ is applicable to β -lactoglobulin produced by *K. lactis*. Changing Bio presents the dietary exposure from GRN 001056 and states that the eaters-only dietary exposure to β -lactoglobulin from the proposed uses is 31 g/person (p)/d at the mean and 56 g/p/d at the 90th percentile for the U.S. population aged 2 years and older. Changing Bio states that the intended uses of β -lactoglobulin are substitutional for added dietary protein ingredients, and therefore, the intake of dietary protein is not expected to increase.

Changing Bio conducted a literature search through September 2024 and discusses data and information relevant to the safety of β -lactoglobulin. Changing Bio states that the safety of β -lactoglobulin produced by *K. lactis* “CJ-B1-P11,” which is compositionally identical to native bovine β -lactoglobulin, is supported by the long history of safe consumption of bovine milk and milk-derived proteins, as β -lactoglobulin is a component of milk. Changing Bio also notes that β -lactoglobulin is qualitatively similar to the β -lactoglobulin preparations described in GRN 001056 and GRN 000863², and that the intended uses are identical to those of GRN 001056. Further, Changing Bio states that the β -lactoglobulin component of the notified substance is identical to the whey-derived β -lactoglobulin present in bovine milk at the amino acid level. Therefore, Changing Bio discusses a published 90-day repeated-dose oral toxicity study in Wistar rats conducted on whey-derived β -lactoglobulin, and notes that this study is used to

¹ The subject of GRN 001056 is β -lactoglobulin produced by *Komagataella phaffii* “yRMK-66.” We evaluated this notice and responded in a letter dated February 15, 2023, stating that we had no questions at that time regarding the notifier’s GRAS conclusion.

² The subject of GRN000863 is β -lactoglobulin produced by *Trichoderma reesei*. We evaluated this notice and responded in a letter dated March 25, 2020, stating that we had no questions at that time regarding the notifier’s GRAS conclusion.

support the safety of Changing Bio's β -lactoglobulin. Changing Bio notes that the study was conducted using oral doses of 100, 300, and 1,000 mg/kg body weight/day and that the no observed adverse effect level was the highest dose tested. Changing Bio also states that β -lactoglobulin is not mutagenic in the Ames test, nor does it induce chromosomal damage in human lymphocytes. Changing Bio concludes that β -lactoglobulin is not genotoxic. Changing Bio discusses the potential allergenicity of β -lactoglobulin and notes that β -lactoglobulin may produce a milk protein allergic response when consumed by milk allergic consumers.

Based on the totality of the data and information, Changing Bio concludes that β -lactoglobulin is GRAS for its intended use.

Standards of Identity

In the notice, Changing Bio states its intention to use β -lactoglobulin 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, & 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 β -lactoglobulin 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 ONFL in the NCE. 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. β -lactoglobulin requires labeling under the FD&C Act because it contains proteins derived from milk.

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(l)(1)-(4) applies. In our evaluation of Changing Bio's notice concluding that β -lactoglobulin is GRAS under its intended conditions of use, we did not consider whether section 301(l) or any of its exemptions apply to foods containing β -lactoglobulin. Accordingly, our response should not be construed to be a statement that foods containing β -lactoglobulin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

Conclusions

Based on the information that Changing Bio provided, as well as other information available to FDA, we have no questions at this time regarding Changing Bio's conclusion that β -lactoglobulin is GRAS under its intended conditions of use. This letter is not an affirmation that β -lactoglobulin 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 001247 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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