



Marcel Wubbolts, PhD
Vivici B.V.
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NETHERLANDS

Re: GRAS Notice No. GRN 001200

Dear Dr. Wubbolts:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001200. We received Vivici B.V.'s (Vivici's) notice on June 18, 2024, and filed it on September 3, 2024. Vivici submitted amendments to the notice on November 12, 2024, and January 5, 2025, providing clarifying information on the intended use, manufacturing process, and safety.

The subject of the notice is β -lactoglobulin produced by *Komagataella phaffii* "VIPLA" for use as a source of protein at levels up to 35% in food. The intended uses and use levels are shown in Table 1.¹ The notice informs us of Vivici'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-type sports drinks	6
	Performance nutritional beverages, high protein	25
	Nutritional bars	35
Dairy and dairy-based products	Milk, powdered milk, flavored milk, 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	10

¹ Vivici states that β -lactoglobulin produced by *K. phaffii* "VIPLA" is not intended for use in infant formula or in products under the jurisdiction of the United States Department of Agriculture.

Food Category	Food Uses	Maximum Use Level (%)
	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
	Doughnut, toaster pastries, muffins	10
	French toast, crepes, pancakes, bagels, scones, biscuits, croissants	10
	Bread, rolls, English muffins, pizza crust	10
	Crackers, popcorn, tortilla chips, hard pretzels, snack mix	5
Dressings and Sauces	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. The Office of Pre-Market Additive Safety did not consult with ONFL regarding the appropriate common or usual name for “ β -lactoglobulin.”

Vivici 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 88% of the total protein is β -lactoglobulin. β -lactoglobulin is a whey protein with a concentration in bovine milk ranging from 2-3 g/L, which represents 7-9% of the total milk protein content. Vivici states that β -lactoglobulin produced by *K. phaffii* has a molecular weight of approximately 18 kDa, a CAS registry number of 50863-92-8 and is 100% identical to β -lactoglobulin with UniProt sequence accession number P02754, natural variant A.

Vivici describes the production organism used in the manufacture of β -lactoglobulin. Vivici states that *K. phaffii* “VIPLA” is non-pathogenic and non-toxicogenic, and that the strain’s identity was confirmed using whole genome sequencing. *K. phaffii* “VIPLA” is genetically engineered to produce β -lactoglobulin from the host strain, *K. phaffii* ATCC 76273. Vivici states that an expression cassette carrying a *de novo* synthesized, codon-optimized β -lactoglobulin variant A gene from *Bos taurus* was stably integrated into the genome of *K. phaffii* ATCC 76273. Vivici states that the correct insertion of the β -lactoglobulin variant A gene was confirmed by whole genome sequence data analysis, and the genetic stability of the

production organism was confirmed through polymerase chain reaction. Vivici states that the production organism does not contain any antibiotic resistance markers or vector sequences.

Vivici states that β -lactoglobulin is manufactured by controlled batch-fed fermentation of a modified *K. phaffii*. β -lactoglobulin is secreted into the medium and then separated from the biomass by a series of centrifugation, filtration, and ultrafiltration steps followed by further purification by cation-exchange chromatography. The eluate containing β -lactoglobulin is again concentrated by ultra and diafiltration followed by drying and packaging. Vivici states that none of the materials used during the manufacturing process are derived from major allergens. Vivici 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 or are GRAS for their intended use.

Vivici provides specifications for β -lactoglobulin that include protein content (≥ 85 % w/w), β -lactoglobulin as % of the total protein content (≥ 88 % w/w), moisture (≤ 6 % w/w), ash (≤ 5 % w/w), fat (≤ 1 % w/w), total carbohydrates (≤ 3 % w/w), 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. Vivici provides the results from the analyses of three non-consecutive batches to demonstrate that β -lactoglobulin can be manufactured to meet the specifications.

Using food consumption data from the 2017-2018 National Health and Examination Survey (NHANES), Vivici estimates the eaters-only dietary exposure to β -lactoglobulin from the proposed uses to be 32 g/p/d at the mean and 60 g/p/d at the 90th percentile for the U.S. population aged 2 years and older. Vivici 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 that the intended uses of β -lactoglobulin will substitute for other protein ingredients. Therefore, there will be no increase in the dietary exposure to protein from the intended uses of β -lactoglobulin.

Vivici states that the safety of β -lactoglobulin produced by *K. phaffii* “VIPLA,” 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.

Vivici discusses publicly available safety data and information on β -lactoglobulin, produced in different microbial strains, that was previously discussed in GRNs 000863² and 001056³ and sourced from an updated search of the scientific literature through November 2024. These data include a battery of published genotoxicity studies that report native bovine β -

² The subject of GRN 000863 is β -lactoglobulin produced by *Trichoderma reesei* “QM6a-PD1.” 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.

³ The subject of GRN 001056 is β -lactoglobulin produced by *K. 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.

lactoglobulin is non-genotoxic and a published 13-week oral toxicity study in rats where the No Observed Adverse Effect Level for native bovine β -lactoglobulin was 1,000 mg/kg body weight/d, the highest dose tested. Regarding digestibility of β -lactoglobulin, Vivici notes that β -lactoglobulin is known to be resistant to simple hydrolysis in the stomach and is instead digested and absorbed in the small intestine. Vivici further states that from their survey of the literature, there were no reports of adverse effects associated with the consumption of β -lactoglobulin generally, except for in certain sensitive populations like milk-allergic and lactose-intolerant individuals. Vivici discusses the allergenic potential of residual *K. phaffii* proteins that remain in the final product following manufacturing, but notes that it is highly unlikely these residual proteins will induce an allergenic response in consumers and incorporates relevant safety data on the production organism *K. phaffii*, which has a long history of safe use in food production.⁴ Additionally, as the intended use and use level of β -lactoglobulin is substitutional to previous GRNs, Vivici does not anticipate an increased instance of consumer allergenic responses to milk products through dietary incorporation of β -lactoglobulin from GRN 001056.³

Based on the available data and information, Vivici concludes that β -lactoglobulin produced by *K. phaffii* “VIPLA” is GRAS for its intended uses.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and 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 Nutrition Center of Excellence. The Office of Pre-Market 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.

Standards of Identity

In the notice, Vivici 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains

⁴ GRNs 000967, 001056, 001104, and 001142. The subjects of these notices are soluble egg white protein produced by “GSD-1209,” β -lactoglobulin produced by strain “yRMK-66,” egg-white protein produced by strain “GSD-1235” and brazzein produced by strain “P-BRZ-013.” We evaluated these notices and responded in letters dated September 9, 2021, February 15, 2023, October 17, 2023, and March 11, 2024, respectively, stating that we had no questions at those times regarding the notifiers’ GRAS conclusions.

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 produced by *K. phaffii* “VIPLA” requires labeling under the FD&C Act because it contains protein 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(ll)(1)-(4) applies. In our evaluation of Vivici’s notice concluding that β -lactoglobulin 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 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(ll).

Conclusions

Based on the information that Vivici provided, as well as other information available to FDA, we have no questions at this time regarding Vivici’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 001200 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary
Supplements, and Innovation
Human Foods Program