U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Diana Rueda
Atova Regulatory Consulting SLU
Passeig de Gracia, 50, 5
Barcelona, 08019
SPAIN

Re: GRAS Notice No. GRN 001249

Dear Ms. Rueda:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001249. We received the notice that you submitted on behalf of Onego Bio, Inc. (Onego) on December 19, 2024, and filed it on April 10, 2025. Onego submitted amendments to the notice on June 11, 2025, and July 03, 2025, clarifying the identity, manufacturing process, intended uses, dietary exposure, and safety information.

The subject of the notice is ovalbumin preparation produced by *Trichoderma reesei* "TR112" expressing a gene encoding for ovalbumin from *Gallus gallus* (ovalbumin preparation) for use as a source of protein and as a foaming, gelling, and binding agent in a variety of food categories at the maximum use levels as described in Table 1 (excluding use in infant formula and products under the jurisdiction of the United States Department of Agriculture).

Table 1. Food categories and intended use levels

Food Category	Maximum Use Level (%)
Baked goods and baking mixes:	
Breads and rolls, English muffins, cookies, and batter mixes, graham crackers	3
Pastries, pancakes, waffles, biscuits, French toasts, pies and cobblers	5
Cakes	6
Souffles	8
Quiches	12
High-protein breads	25
Beverages and beverage bases, non-alcoholic:	
Smoothies	12
Smoothies with added protein	25
Nutritional beverages	25
Protein and nutritional powders	25[a]
Eggnog and egg white cocktails, alcoholic[b]	4
Breakfast cereals, ready-to-eat	10

Food Category	**Maximum Use Level (%)**
Processed cheeses (breaded, baked, or fried)	6
Marshmallows (candy and topping)	3
Milk substitute beverages	10
Egg products (egg analogs)	12
Salad dressings, vegetable oils, mayonnaise, and spreads	10
Ice cream, frozen yogurt, and sherbet	8
Fruit and water ices (frozen, flavored and sweetened)	8
Gelatins, puddings, and custards	5
Grain products and pasta: Plain pasta and noodles, grain-based cooked products Filled grain-based products (e.g., egg rolls and dumplings)	 10 6
Gravies, sauces, and dips	10
Flavored milk and milk-based beverages	10
Meat analogs	10
Cereal bars, granola bars, and breakfast bars	10
Protein bars	25
Soft candy	3

[a] As consumed
[b] Ovalbumin preparation is used as a functional substitute for egg.

Our use of the term, "ovalbumin produced by *Trichoderma reesei* "TR112" expressing a gene encoding for ovalbumin from *Gallus gallus*" or "ovalbumin preparation" 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 "ovalbumin produced by *Trichoderma reesei* "TR112" expressing a gene encoding for ovalbumin from *Gallus gallus*" or "ovalbumin preparation."

Onego describes ovalbumin preparation as a white to off-white powder containing ≥ 75% protein of which ≥ 80% is ovalbumin, a water-soluble glycoprotein composed of 385 amino acids with a molecular weight of approximately 42.75 kDa. Onego states that ovalbumin from *T. reesei* "TR112" fermentation, and the mature form of native chicken egg ovalbumin (Gal d 2) are substantially equivalent in their chemical properties.

Onego states that ovalbumin preparation is manufactured through fermentation using a genetically engineered production strain *T. reesei* "TR112" derived from the well-characterized host strain *T. reesei* ATCC 13631. The production strain was developed by incorporating an expression cassette containing a codon-optimized, de novo synthesized ovalbumin gene from *G. gallus*, along with homologous DNA sequences for targeted integration. The production strain construction was validated through qPCR and whole genome sequencing to confirm the absence of antimicrobial resistance genes, verify the strain identity, and validate correct insertion and copy number of the expression cassette. Onego states that ovalbumin expression levels remained consistent over at least 75 generations. Onego provides information that shows *T. reesei* "TR112" is non-pathogenic and non-toxigenic.

After fermentation, the *T. reesei* "TR112" cells are removed, and the resulting culture liquid is clarified through a multi-step filtration process and then concentrated via ultrafiltration and diafiltration. The resulting liquid is filter sterilized and dried to produce the final product. Onego states that ovalbumin preparation 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. regulation, are GRAS for their intended use, or are the subject of an effective food contact notification. Onego states that none of raw materials used in the manufacture of ovalbumin are or are derived from major food allergens.

Onego provides specifications for ovalbumin preparation that include ovalbumin as % of protein (≥ 80%), and limits for protein (≥ 75%), carbohydrate (≤ 20%), fat (≤ 1.5%), moisture (≤ 10%), ash (≤ 5%), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and microorganisms, including *Salmonella* serovars (absent in 25 g). Onego provides results from the analyses of three non-consecutive batches to demonstrate that ovalbumin preparation can be manufactured to meet these specifications.

Based on food consumption data from the 2017-2020 National Health and Examination Survey (NHANES), Onego estimates the eaters-only dietary exposure to ovalbumin preparation from the intended uses for the U.S. population aged 2 year and older to be 18.89 g/person (p)/d (0.32 g/kg body weight (bw)/d) at the mean and 39.17 g/p/d (0.74 g/kg bw/d) at the 90th percentile. Onego notes that ovalbumin preparation is intended to replace whole eggs (fresh or powdered) and egg white protein powder in the intended food categories and will be substitutional for animal-derived ovalbumin in the diet and therefore, there will be no increase in the cumulative dietary exposure to ovalbumin from the intended uses.

Onego discusses data and information relevant to the safety of ovalbumin preparation. Onego states that as a major component of egg white, ovalbumin, has an extensive history of safe consumption worldwide. Onego also notes that the FDA previously stated that proteins derived from egg whites did not pose toxicity concerns due to the long history of human consumption of egg whites and the lack of toxicity reports (FDA,

1998[1]). Onego discusses studies that demonstrate ovalbumin's lack of toxicity, as well as data and information discussed in several previous GRAS notices for ovalbumin-containing ingredients (GRN 000064, GRN 000967, and GRN 001104[2]). Onego notes that while ovalbumin is considered non-toxic and safe for consumption as part of a regular diet, the primary concern for ovalbumin is related to allergenicity for egg allergic consumers. Onego discusses the allergenicity related to ovalbumin and notes that it is heat-labile and undergoes changes during cooking that reduces its allergenic potential. Onego also notes that besides ovalbumin, no other significant allergens are expected to be present in ovalbumin preparation.

Based on the totality of the data and information, Onego concludes that ovalbumin preparation is GRAS under the conditions of its intended use.

Standards of Identity

In the notice, Onego states its intention to use ovalbumin preparation 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 ovalbumin preparation 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 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. Ovalbumin

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[1] Federal Register/Vol. 63, No. 49, March 13. (1998). 21 CFR Part 184. Direct Food Substances Affirmed as Generally Recognized As Safe; Egg White Lysozyme.

[2] The subjects of GRNs 000064, 000976, and 001104 are egg white lysozyme, soluble egg-white protein produced by *Komagataella phaffii* strain GSD-1209, and egg-white protein produced by *K. phaffii* ATCC GSD-1235, respectively. FDA evaluated these notices and responded in letters dated April 2, 2001, September 9, 2021, and October 17, 2023, respectively, stating that we had no questions at that time regarding each notifier's GRAS conclusion.

preparation requires labeling under the FD&C Act because it contains protein derived from egg.

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 Onego's notice concluding that ovalbumin preparation 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 ovalbumin. Accordingly, our response should not be construed to be a statement that foods containing ovalbumin preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Onego provided, as well as other information available to FDA, we have no questions at this time regarding Onego's conclusion that ovalbumin preparation is GRAS under its intended conditions of use. This letter is not an affirmation that ovalbumin preparation 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 001249 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

cc: **GRN 001249**
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NAME	ELECTRONIC SIGN-OFF	ACTING?
Denis Wafula Biologist Office of Pre-Market Additive Safety	Denis Wafula -S Digitally signed by Denis Wafula -S Date: 2025.09.10 09:40:44 -04'00'	☐
Mical Honigfort Chief, Regulatory Management Branch Division of Food Ingredients	MICAL E. HONIGFORT -S Digitally signed by MICAL E. HONIGFORT -S Date: 2025.09.10 13:12:47 -04'00'	☐
Susan J. Carlson Director, Division of Food Ingredients	Susan J. Carlson -S Digitally signed by Susan J. Carlson -S Date: 2025.09.16 09:47:48 -04'00'	☐