Evangelia Pelonis
Keller and Heckman LLP
1001 G St., NW, Suite 500W
Washington, DC, 20001

Re: GRAS Notice No. GRN 001104

Dear Ms. Pelonis:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001104. We received the notice that you submitted on behalf of Clara Foods Co., doing business as The EVERY Company (Clara), on September 12, 2022, and filed it on March 2, 2023. Clara submitted amendments on June 30, 2023, August 15, 2023, and September 12, 2023, that clarified the identity, manufacturing process, specifications, intended uses, dietary exposure and provided additional safety information.

The subject of the notice is egg-white protein produced by *Komagataella phaffii* ATCC GSD-1235[1] for use as a substitute for hen egg-white protein and whole eggs at levels in accordance with current good manufacturing practices (cGMP) in baked goods and baking mixes; gluten-free bread; plant-based meat alternatives; egg noodles; ready-to-eat cereals; scrambled eggs, egg patties, quiche, and souffles; pancakes and waffles; protein and snack bars; salad dressings; eggnog; egg white cocktails, and powdered shake mixes;[2] and as a fining agent in wine and juice.[3] The notice informs us of Clara's view that these uses of egg-white protein are GRAS through scientific procedures.

Our use of the term, "egg-white protein" or "egg-white protein produced by *Komagataella phaffii* ATCC GSD-1235" 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 non-standardized 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 Center for Food Safety and Applied Nutrition (CFSAN). The Office of

[1] We note that *Pichia pastoris* was reclassified as *K. phaffii* as reported in Kurtzman (Ref. 1).

[2] Clara states that the egg-white protein is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

[3] Clara states that egg-white protein will be removed from the final beverage product due to precipitation during the manufacturing process.

Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "egg-white protein."

Clara describes egg-white protein as a phosphoglycoprotein containing predominantly recombinant ovalbumin. Egg-white protein is a white to off-white amorphous powder. Clara states that the physical characteristics of the recombinant egg-white protein and mature form of native hen egg ovalbumin (Gal d 2) are substantially equivalent in molecular weight, isoelectric point, and glycosylation sites.

Clara describes the production organism used in the manufacture of egg-white protein. Clara states that *K. phaffii* ATCC GSD-1235 is nonpathogenic and non-toxigenic, and is deposited in the American Type Culture Collection (ATCC) in Manassas, VA. *K. phaffii* ATCC GSD-1235 is genetically engineered to produce egg-white protein from the parent strain, *K. phaffii* "DFB-001A". Clara states that the production organism was constructed through the chromosomal integration of an expression cassette carrying a *de novo* synthesized gene sequence that encodes Gal d 2 that is identical to the gene sequence from chicken egg (*Gallus gallus*). Clara states that the genome sequence of the parent strain was published, and the identity and location of the inserted gene sequence for egg-white protein were confirmed via DNA sequencing. Clara states that the inserted DNA is stably integrated into the genome of the production organism and is confirmed to be present after 45 generations of growth on non-selective growth media. Clara states that the production organism, *K. phaffii* ATCC GSD-1235, does not contain any antibiotic resistance genes and does not produce toxic secondary metabolites. Clara states that *K. phaffii* ATCC GSD-1235 is not detected in the final product.

Clara states that egg-white protein is manufactured through a controlled fermentation using the production organism, *K. phaffii* GSD-1235. After fermentation, the *K. phaffii* cells are separated by centrifugation followed by microfiltration. The resulting lysate is further purified using ultrafiltration, chromatography, and pH adjustments, and subsequently dried to produce the final egg-white protein. Clara states that the raw materials are food grade and GRAS, or certified USP, NF or ACS grade, and that egg-white protein is manufactured in accordance with cGMP.

Clara provides specifications for egg-white protein that include protein (> 75%, w/w) and limits for carbohydrate (≤ 10%), fat (< 0.4%), moisture (≤ 10%), ash (≤ 5%); heavy metals, including lead (≤ 0.1 mg/kg); and microorganisms, including *Salmonella* serovars (absent in 25 g). Clara provides results from the analyses of three non-consecutive batches to demonstrate that egg-white protein can be manufactured to meet the stated specifications.

Clara estimates an eaters-only dietary exposure to egg-white protein from the intended uses to be 8.6 g/person (p)/d at the mean and 16.3 g/p/d at the 90th percentile for the U.S. population aged 2 years and older based on food consumption data from the 2017-March 2020 National Health and Nutrition Examination Survey (NHANES). Clara notes that egg-white protein will be added to various foods as a direct substitute for whole eggs (fresh and powdered) and hen egg-white protein powder and therefore, there will be no increase in the dietary exposure to egg-white protein.

Clara discusses publicly available data and information supporting the safety of egg-white protein and its production organism *K. phaffii* ATCC GSD-1235. Clara states that egg-white protein is equivalent to Gal d 2, a major protein component of chicken egg white, with an N-terminal extension of four amino acids (EAEA). Clara states that the safety of egg-white protein is further supported by the widespread consumption of eggs and egg proteins in the human diet. Based on the weight-of-evidence, including results of *in silico* sequence alignment-based approaches, Clara concludes that egg-white protein does not pose an increased allergenic or toxigenic risk to consumers, relative to chicken Gal d 2. Clara states that Gal d 2 is a known allergenic protein and egg-white protein will likely elicit an allergic response in egg-allergic consumers, and therefore, food allergen labeling will be applicable to all products containing egg-white protein.

Clara conducted a comprehensive literature search to identify available safety information relevant to egg-white protein produced by *K. phaffii* ATCC GSD-1235. Clara did not identify any safety concerns or information that would contradict its GRAS conclusion.

Based on the totality of information, Clara concludes that egg-white protein is GRAS for its intended use.

Standards of Identity

In the notice, Clara states its intention to use egg-white protein in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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 egg-white protein 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 CFSAN. OFAS 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. Egg-white protein produced by *K. phaffii* ATCC GSD-1235 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 Clara's notice concluding that egg-white protein 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 egg-white protein. Accordingly, our response should not be construed to be a statement that foods containing egg-white protein, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Clara provided, as well as other information available to FDA, we have no questions at this time regarding Clara's conclusion that egg-white protein is GRAS under its intended conditions of use. This letter is not an affirmation that egg-white protein 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 001104 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.10.17 18:07:36 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
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Reference

1. Kurtzman, C. (2005). Description of *Komagataella phaffii* sp. nov. and the transfer of *Pichia pseudopastoris* to the methylotrophic yeast genus *Komagataella*. International Journal of Systematic and Evolutionary Microbiology, 55, 973-976. doi: 10.1099/ijs.0.63491-0