



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

Re: GRAS Notice No. GRN 000967

Dear Mr. Gillies:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000967. We received the notice that you submitted on behalf of Clara Foods Co. (Clara) on September 14, 2020 and filed it on December 14, 2020. Clara submitted an amendment to the notice on April 4, 2021, providing information about the production organism, a discussion of the physical and chemical properties of the ingredient, and clarifying information regarding the manufacturing process, specifications, and the dietary exposure estimate.

The subject of the notice is soluble egg-white protein produced by *Komagataella phaffii* strain GSD-1209¹ (*K. phaffii* GSD-1209) for use as a substitute for egg-white protein in foods containing eggs; and as a source of protein in nutritional powders and drinks; bars; and certain snack foods at levels in accordance with current good manufacturing practices.² The notice informs us of Clara's view that this use of soluble egg-white protein is GRAS through scientific procedures.

Our use of the term, "soluble egg-white protein," 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 Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "soluble egg-white protein."

Clara describes soluble egg-white protein as a glycoprotein containing predominantly recombinant ovomucoid. Soluble egg-white protein is a white to off-white amorphous powder. Clara states that the physical characteristics of the recombinant ovomucoid in

¹ Clara states that *Pichia pastoris* was reclassified as *K. phaffii* as reported in Kurtzman (Ref. 1).

² Clara states that soluble egg-white protein produced by *K. phaffii* GSD-1209 is not intended for use in infant formula, or in any products under the jurisdiction of the United States Department of Agriculture.

soluble egg-white protein and deglycosylated native hen egg white ovomucoid are equivalent in molecular weight, isoelectric point, and glycosylation sites.

Clara describes the production organism used in the manufacture of soluble egg-white protein. Clara states that *K. phaffii* GSD-1209 is non-pathogenic and non-toxicogenic, and is deposited in the strain collection of the American Type Culture Collection (ATCC) in Manassas, VA with the deposit designation GSD-1209. *K. phaffii* GSD-1209 is genetically engineered from the commercially-available base strain, *K. phaffii* strain “BG10”. Clara states that the production organism was constructed through transformation and chromosomal-integration of an expression cassette carrying a gene sequence that encodes hen egg ovomucoid that is identical to the gene sequence from chicken egg (*Gallus gallus*). In addition to the hen egg ovomucoid gene sequence, Clara inserted genes that support the secretion of soluble egg-white protein into the fermentation medium. Clara states that the genome of *K. phaffii* GSD-1209 has been fully sequenced, verifying the sequence of the inserted DNA. Clara explains 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 further confirms that the production organism does not contain any antibiotic resistance genes. Additionally, Clara states that the production organism does not contain vector plasmid sequences and therefore, is not capable of DNA transfer to other organisms.

Clara states that soluble egg-white protein is manufactured through fermentation of the production organism, *K. phaffii* GSD-1209. After fermentation, the *K. phaffii* cells are separated by centrifugation and microfiltration. The resulting lysate is further purified using pH adjustment and ultra-filtration, and then dried to produce the final product. Clara states that the components of the fermentation media are not derived from major food allergens. Clara also states that the raw materials are food grade and GRAS, or certified USP, NF or ACS grade, and that soluble egg-white protein is manufactured in accordance with current good manufacturing practice.

Clara provides specifications for soluble egg-white protein that include protein (> 75%), carbohydrate (\leq 20%), fat (< 0.1%), moisture (\leq 10%), ash (\leq 2%); heavy metals, including lead (< 1 mg/kg); and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Clara provides results from the analyses of three non-consecutive batches of soluble egg-white protein to demonstrate compliance with the stated specifications.

Clara indicates that soluble egg-white protein will be used as a substitute for egg-white protein ovomucoid in foods containing eggs, and as a source of protein in select food categories. Clara provides an estimate of the dietary exposure to soluble egg-white protein from the substitutional uses in foods containing eggs to be 0.4 g/person (p)/d at the mean, and 0.8 g/p/d at the pseudo 90th percentile based on per capita U.S. egg consumption data collected from the 2013-2016 What We Eat in America survey.

For the intended uses as a source of protein in select food categories, Clara provides an eaters-only mean and 90th percentile dietary exposure for the U.S. population 2 years

and older to be 21.1 g/p/d and 47.1 g/p/d, respectively, based on food consumption data from the 2015-2018 National Health and Examination Survey. In addition, Clara estimates a cumulative dietary exposure from the substitutional uses in foods and the use as a source of protein in the select food categories to be 21.5 g/p/d at the mean and 47.9 g/p/d at the 90th percentile for the U.S. population aged 2 years and older. Clara notes that they do not anticipate that soluble egg-white protein will substitute for all egg white proteins, and that the use as a source of protein in the select food categories would be a subset of the current uses of egg white protein. Therefore, Clara concludes that there would be no increase in the cumulative dietary exposure to ovomucoid-related protein.

Clara states that soluble egg-white protein and the native hen egg ovomucoid sequences are identical except for the fact that the majority of soluble egg-white protein contains four extra amino acids (EAEA) and a minor fraction contains a larger extension (EEGVSLEKREAEA) at the N-terminal end. Clara notes that these extra amino acid sequences are unlikely to pose any risk to consumers because they are from *Saccharomyces cerevisiae*, which has a safe history of use in food. Clara also states that *K. phaffii* GSD-1209 is safe for use as a production organism. The residual *K. phaffii* GSD-1209 proteins in the soluble egg-white protein do not raise any safety concerns. In this context, Clara notes that FDA previously reviewed the safety of proteins produced by *K. phaffii* and had no questions concerning the safe use of *K. phaffii* as a production organism.³ Clara notes that hen egg ovomucoid is a known allergenic protein in egg, and products containing soluble egg-white protein will be labeled as “contains egg.”

Clara includes the report of a panel of individuals (Clara’s GRAS panel). Based on its review, Clara’s GRAS panel concluded that soluble egg-white protein is safe under the conditions of its intended use.

Based on the evidence, Clara concludes that soluble egg-white protein is GRAS for its intended use.

Standards of Identity

In the notice, Clara states its intention to use soluble egg-white protein 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

³ Clara references GRNs 000204 and 000737. Phospholipase C enzyme preparation from *K. phaffii* expressing a heterologous phospholipase C gene, and soy leghemoglobin preparation produced by a strain of *K. phaffii*, are the subjects of GRNs 000204 and 000737, respectively. We evaluated these notices and responded in letters respectively dated December 5, 2006 and July 23, 2018, stating that we had no questions at that time regarding the notifiers’ GRAS conclusions.

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 soluble 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 (effective January 1, 2023)) or a food ingredient that contains protein derived from one of those foods. Soluble egg-white protein produced by *K. phaffii* GSD-1209 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 soluble 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 soluble egg-white protein. Accordingly, our response should not be construed to be a statement that foods containing soluble 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 soluble egg-white protein is GRAS under its intended conditions of use. This letter is not an affirmation that soluble 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 000967 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Digitally signed by Susan J.
Carlson -S
Date: 2021.09.09 16:56:58
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Susan 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/ijms.0.63491-0