Frederick Stearns
Keller and Heckman LLP
1001 G Street NW, Suite 500 West
Washington, DC 20001

Re: GRAS Notice No. GRN 001100

Dear Mr. Stearns:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001100. We received the notice that Arla Foods Ingredients Group P/S (Arla) submitted on June 29, 2022, and filed it on March 8, 2023. Arla submitted amendments to the notice on March 3, 2023, July 19, 2023, August 15, 2023, September 28, 2023, and October 12, 2023, that provided additional information on the intended use, method of manufacture, specifications, and safety studies.

The subject of the notice is fractionated whey protein concentrate containing 41% alpha-lactalbumin (fractionated WPC (41% ALA)) for use as a source of protein in the food categories and at the maximum levels shown in Table 1.[1,2] The notice informs us of Arla's view that this use of fractionated WPC (41% ALA) is GRAS through scientific procedures.

Our use of the term, "fractionated whey protein concentrate containing 41% alpha-lactalbumin" or "fractionated WPC (41% ALA)" 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 Code of Federal Regulations (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 Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "fractionated whey protein concentrate containing 41% alpha-lactalbumin" or "fractionated WPC (41% ALA)."

[1] Arla states that the intended uses do not include meat and poultry products regulated under the jurisdiction of the U.S. Department of Agriculture.
[2] Arla notes that the ingredient described in GRN 001100 is the same ingredient as that described in GRN 000809. The subject of GRN 000809 was fractionated whey protein concentrate containing 41% alpha-lactalbumin for use as an ingredient at levels up to 2.5 g/L ALA in milk-based, non-exempt infant formula for term infants. We evaluated GRN 000809 and responded in a letter dated May 6, 2019, that we had no questions at that time regarding the notifier's GRAS conclusion.

Table 1: Maximum use level of fractionated WPC (41% ALA) in specified food categories.

Food category	**Maximum use level (g/100 g)**
Nutrition bars including meal replacement and "protein" bars	30
Crackers primarily used as snacks	30
Cookies	30
Dairy-based beverages, ready-to-drink (RTD) or prepared from powder, including the following: flavored and/or fermented milks, buttermilk, nutritional beverages (e.g., meal replacements, meal supplements), milk shakes and other dairy drinks, and smoothies	5
Sports drinks, RTD or prepared from powder	5
Enhanced or fortified waters, RTD or prepared from powder	5
Fruit juice drinks and smoothies, RTD or prepared from powder	5
Yogurt (dairy and non-dairy)	5

Arla provides information about the identity and composition of fractionated WPC (41% ALA). The main protein component is ALA, which consists of a single polypeptide chain of 123 amino acids with a molecular weight of 14.2 kDa. Arla notes that the fractionated WPC (41% ALA) contains higher levels of ALA and lower levels of β-lactoglobulin than whey protein concentrate. In addition to ALA (≥41% of protein) and β-lactoglobulin (~19% of protein), other proteins present in fractionated WPC (41% ALA) include casein glycomacropeptide (~28% of protein) and minor amounts of β-casein-derived peptides. Lactose and ash comprise up to 10% and 5% (weight basis), respectively, of fractionated WPC (41% ALA).

Arla describes the method of manufacture for fractionated WPC (41% ALA) as identical to that described in GRN 000809. Arla describes the sweet whey starting material, produced from pasteurized fluid milk, as a byproduct of cheesemaking. Sweet whey is food-grade and obtained from milk produced in accordance with good agricultural practices, the requirements of the Grade "A" Pasteurized Milk Ordinance (PMO, 2019), and 21 CFR 1240.61. The sweet whey starting material is clarified, pasteurized, and then separated into three fractions, one of which contains a concentrated level of the ALA. This fraction undergoes a two-stage ultrafiltration process to increase the ratio of ALA to β-lactoglobulin and reduce water and other non-protein components. Fractionated WPC (41% ALA) may be standardized with food-grade lactose or pH-adjusting agents (NaOH or HCl) prior to spray drying. Arla states that fractionated WPC (41% ALA) is produced in accordance with current good manufacturing practices, and all membrane materials are safe and suitable for their intended use and are used in accordance with applicable

U.S. regulations, are GRAS for their intended use, or are the subject of an effective food contact notification.

Arla provides specifications for fractionated WPC (41% ALA), including levels of protein (81-87%), a minimum for ALA as a percent of protein (≥41%), and limits for ash (≤5%), moisture (≤5.5%), lactose (≤10%), fat (≤2%), lead (<0.05 mg/kg), arsenic (<0.1 mg/kg), cadmium (<0.05 mg/kg), and microorganisms, including *Salmonella* serovars (absent/25 g), *Bacillus cereus* (<50 colony forming unit (CFU)/g), and *Staphylococcus aureus* (absent/g). Arla provides the results of the analyses of five non-consecutive batches to demonstrate that fractionated WPC (41% ALA) can be manufactured to meet these specifications. Arla states that fractionated WPC (41% ALA) is stable for two years at room temperature.

Arla estimates the eaters-only dietary exposure to fractionated WPC (41% ALA) for ages 4 years and older to be 11.2 g/person(p)/d (0.18 g/kg body weight (bw)/d) at the mean and 31.7 g/p/d (0.403 g/kg bw/d) at the 90th percentile based on food consumption data from the 2013-2016 National Health and Nutrition Examination Survey (NHANES). For toddlers aged 1-3 years, Arla estimates the eaters-only mean and 90th percentile dietary exposure to be 7.5 g/p/d (0.56 g/kg bw/d) and 15.8 g/p/d (1.09 g/kg bw/d), respectively. Arla notes that milk, milk-based foods, and milk-derived ingredients (e.g., whey) also contribute to dietary exposure to milk proteins including alpha-lactalbumin. Arla states that fractionated WPC (41% ALA) is intended to be used as a source of protein that will be substitutional for other dairy protein sources and there will be no increase in the total dietary exposure to protein in the U.S. diet. Citing published data for the mean dietary exposure to protein for adults aged 19 years and older[3] based on 2011-2014 NHANES data[4], Arla notes that two-thirds of the total protein, equal to 56 g/p/d, is from animal foods. Using this value as an upper bound estimate of dietary exposure to dairy proteins, Arla states that, if it is assumed that fractionated WPC (41% ALA) replaces all dairy proteins and contains a mean level of 53.1% ALA, then upper bound estimates of the mean and 90th percentile ALA dietary exposure would be 30 and 59 g/p/d[5], respectively.

Arla describes the absorption, distribution, metabolism, and excretion (ADME) of ALA and WPC, and states that ALA is rapidly digested and leads to the subsequent absorption of amino acids. Arla discusses several published oral toxicology studies in rodents and monkeys, including a 90-day (sub-chronic) rat study, that administered milk proteins supplemented with ALA. No treatment-related adverse effects were observed even at the highest dose in the sub-chronic study. Arla also conducts a

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[3] Pikosky et al. (2022) Association of dietary protein intake and grip strength among adults aged 19+ years: NHANES 2011-2014 analysis. Front. Nutr. 9:873512. doi.org/10.3378.fnut.2022.873512.
[4] FDA notes similar estimates were published with more recent NHANES data. Reference: Hoy MK, Clemens JC, Moshfegh A. 2021. Protein Intake of Adults. What We Eat in America, NHANES 2015-2016. Food Surveys Research Group. Dietary Data Brief No. 29. January 2021. www.ars.usda.gov/nea/bhnrc/fsrg.
[5] Arla estimates the pseudo 90th percentile dietary exposure by multiplying the dietary exposure at the mean by a factor of 2.

literature search through July 2023 and summarizes several published studies performed in human infants and adults orally administered ALA or WPC enriched with ALA. No adverse events were reported in these studies.

Based on the totality of evidence, Arla concludes that fractionated WPC (41% ALA) is GRAS for its intended use.

Standards of Identity

In the notice, Arla states its intention to use fractionated WPC (41% ALA) 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 fractionated WPC (41% ALA) 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 Section 301(ll) of the FD&C Act food ingredient that contains protein derived from one of those foods. Fractionated WPC (41% ALA) requires labeling under the FD&C Act 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 Arla's notice concluding that fractionated WPC (41% ALA) 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

fractionated WPC (41% ALA). Accordingly, our response should not be construed to be a statement that foods containing fractionated WPC (41% ALA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Arla provided, as well as other information available to FDA, we have no questions at this time regarding Arla's conclusion that fractionated WPC (41% ALA) is GRAS under its intended conditions of use. This letter is not an affirmation that fractionated WPC (41% ALA) 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 001100 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.10.27 18:19:42 -04'00'

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Director
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