James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street
P.O. Box 66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000840

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000840. We received the notice you submitted on behalf of Arla Foods Ingredients Group P/S (Arla) on January 29, 2019, and filed it on April 5, 2019. Arla submitted amendments to the notice on June 7, 2019, and June 12, 2019, that clarified information on dietary exposure, allergenic source monitoring, and the updated literature search date.

The subject of the notice is *Lactobacillus paracasei* ssp. *paracasei* strain F-19 (*L. paracasei* F-19) for use as an ingredient in dairy products (fluid milk and milk drinks, milk-based desserts and meal replacements, dry and powdered milk, yogurt, and cheese); ready-to-eat cereals; fruit juices, nectars, ades, and drinks; confections; chewing gum; and other food categories at levels intended to provide a daily intake of 10^9 colony forming units (CFU)/serving. The notice informs us of Arla's view that this use of *L. paracasei* F-19 is GRAS through scientific procedures.

Arla describes the identity of *L. paracasei* F-19 as a Gram-positive, non-spore-forming, rod-shaped, lactic acid bacterium. Arla states that *L. paracasei* F-19 was isolated from the colons of adults and deposited in the Belgian Coordinated Collections of Microorganisms, Microbiology Laboratory under deposit number LMG-P-17806. Arla states that *L. paracasei* F-19 is non-pathogenic and non-toxigenic.

Arla describes the manufacture of *L. paracasei* F-19. Arla states that *L. paracasei* F-19 is produced by fermentation of a pure culture, under controlled conditions, in media containing milk powder and yeast extract. After fermentation, the bacterial cells are harvested and concentrated by centrifugation. Cryoprotectants (sucrose, maltodextrin and sodium ascorbate) are added to the harvested bacterial cells, which are frozen into pellets, then lyophilized, ground into powder and sieved. Excipients are added to the concentrate, which is then packaged and frozen. Arla states that all raw materials and components used in the production process are food-grade and the production of *L. paracasei* F-19 is conducted in accordance with current good manufacturing practices.

Arla provides specifications for *L. paracasei* F-19. These include color (white to light-

beige), cell count (≥ 3 x 10^{10} CFU/g), water activity (≤ 0.15), and limits for microorganisms, including total yeasts and molds (≤ 100 CFU/g), *Bacillus cereus* (<100 CFU/g), *Cronobacter sakazakii* (absent in 10 g samples), *Salmonella* spp. (absent in 10 g samples), *Staphylococcus aureus* (<10 CFU/g), and total aerobic bacteria (≤ 2000 CFU/g). Arla provides the results of five non-consecutive batch analyses to demonstrate that the *L. paracasei* F-19 can be produced to meet the specifications. Additionally, Arla provides data to demonstrate that *L. paracasei* F-19 is stable for up to two years when stored at temperatures of -20°C and 5°C.

Arla estimates the dietary exposure to *L. paracasei* F-19. Arla intends to use *L. paracasei* F-19 as an ingredient in specified conventional foods at 10^9 CFU/serving. Based on an estimated consumption of 10 servings/day of foods containing *L. paracasei* F-19, Arla estimates that the maximum dietary exposure to *L. paracasei* F-19 to be 10^{11} CFU/day.

Arla discusses the results of analysis of whole-genome sequencing of *L. paracasei* F-19 to support its safety. Arla states that no known antibiotic resistance or virulence genes were identified in the genome. Additionally, Arla states that no production of biogenic amines by *L. paracasei* F-19 was detected.

Arla discusses published information on *L. paracasei* F-19 and other *L. paracasei* strains (same studies as in GRN 000810[1]) to support the safety of *L. paracasei* F-19. Arla states that an updated literature search was also conducted through December 2018 that did not reveal any new relevant data or information. Arla discusses the results of several clinical studies including studies conducted in healthy term infants, children, and adults. Arla states that the results of all these studies demonstrated no adverse events were observed and that *L. paracasei* F-19 is well-tolerated.

Arla also discusses published toxicity studies on *L. paracasei* ssp. *paracasei* strains including *in vitro* and *in vivo* genotoxicity studies (reverse mutation, micronucleus, and mammalian chromosomal aberration tests), and oral toxicity studies (acute, short term, and subchronic) in mice and rats. No evidence of mutagenicity or adverse effects in rats and mice were reported.

Arla notes that the European Food Safety Authority concluded *L. paracasei* met Qualified Presumption of Safety status in 2007 and has maintained this status. Arla also states that the Danish Veterinary and Food Administration approved food uses of *L. paracasei* F-19.

Arla includes the statement of a panel of individuals (Arla's GRAS panel). Based on its review, Arla's GRAS panel concluded that *L. paracasei* F-19 is safe under the conditions of its intended use.

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[1] GRN 000810 describes the use of *L. paracasei* F-19 as an ingredient in non-exempt infant formulas for term infants. FDA evaluated this notice and responded in a letter dated April 5, 2019, stating that we had no questions at that time regarding Arla's GRAS conclusion.

Based on the data and information presented in the notice, Arla concludes that *L. paracasei* F-19 is GRAS for its intended use in conventional foods.

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). The notice raises a potential issue under these labeling provisions. Arla describes *L. paracasei* F-19 as having certain health benefits. If products containing *L. paracasei* F-19 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 the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (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 eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. *L. paracasei* F-19 may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL.

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 *L. paracasei* F-19 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 *L. paracasei* F-19. Accordingly, our response should not be construed to be a statement that foods containing *L. paracasei* F-19, 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 *L. paracasei* F-19 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. paracasei* F-19 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 000840 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.08.27 10:52:53 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition