



James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
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P.O. Box 66
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Re: GRAS Notice No. GRN 000810

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000810. We received the notice you submitted on behalf of Arla Foods Ingredients Group P/S (Arla) on August 22, 2018, and filed it on September 27, 2018.

The subject of the notice is *Lactobacillus paracasei* ssp. *paracasei* strain F-19 (*L. paracasei* F-19) for use as an ingredient in non-exempt powdered infant formulas for term infants at levels of 10^9 colony-forming units (CFU)/800 mL of reconstituted formula. 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, homofermentative, lactic acid bacterium. Arla states that *L. paracasei* F-19 was isolated from the colon of healthy 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-toxicogenic.

Arla describes the method of production for *L. paracasei* F-19. Arla states that *L. paracasei* F-19 is produced by a fermentation process, under controlled conditions, using medium based on milk powder and yeast extract. The medium is first sterilized by ultra-heat treatment, then inoculated with the production strain and incubated. After fermentation, the bacterial cells are harvested and concentrated by centrifugation. Cryoprotectants are added to the harvested bacteria 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 ($\geq 3 \times 10^{10}$ CFU/gram (g)), water activity (≤ 0.15), and limits for microorganisms, including yeasts and molds (≤ 100 CFU/g), *Bacillus cereus* (<100

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CFU/g), *Enterobacteriaceae* (absent in 10 g), *Cronobacter sakazakii* (absent in 10 g), *Salmonella* spp. (absent in 10 g), *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 at temperatures of -20°C and 5°C .

Arla intends to use *L. paracasei* F-19 as an ingredient in non-exempt powdered infant formula for term infants at levels of 10^9 CFU/ 800 mL of reconstituted formula. Based on published estimates of daily energy intake by formula-fed infants, the assumption that most term infant formulas contain 67.6 kcal/100 mL formula, and the intended use levels, Arla estimates the 90th percentile dietary exposure for *L. paracasei* F-19 to be 10^9 CFU/kg body weight (bw)/d.

Arla discusses whole-genome sequencing of *L. paracasei* F-19 to support its safety. Arla states that a complete genome sequencing of the strain revealed a circular chromosome, a linear plasmid, and three circular plasmids. The genome of *L. paracasei* F-19 was analyzed for the presence of antibiotic resistance and virulence genes. Arla states that no known antibiotic resistance or virulence genes were identified, and no production of biogenic amines was detected.

Arla discusses published information on *L. paracasei* F-19 and other related strains to support the safety of *L. paracasei* F-19. Arla discusses several human studies including studies conducted in healthy term infants, children, and adults. Arla discusses a randomized, double-blind, placebo-controlled study in which four-month-old term infants were fed cereal supplemented with 10^8 CFU *L. paracasei* F-19 daily until age 13 months, with follow-up studies up to age 8-9 years. Arla also discusses two prospective, randomized, double-blind multi-center studies. In one study, healthy term infants (age 28 days) consumed 10^9 CFU *L. paracasei* F-19 daily up to age 6 months. In the second study, children (age 1-1.5 years) consumed gelatin capsules providing 2×10^{10} CFU/d *L. paracasei* F-19 for 3 weeks with no adverse effects. Additionally, Arla discusses a double-blind, placebo-controlled study on healthy children (average age 13 years) that consumed gelatin capsules providing 10^{10} CFU/d *L. paracasei* F-19 daily for 3 weeks with no adverse effects reported. Arla also discusses several studies in adults given *L. paracasei* F-19 with no significant adverse effects reported. Arla states that the results of all these studies demonstrated no significant differences between the treated and placebo groups 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 assay, and mammalian chromosomal aberration test), 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 also notes that the European Food Safety Authority's Scientific Committee lists *L. paracasei* and other species of *Lactobacillus* as suitable for "Qualified Presumption of Safety" status. Arla also states that the Danish Veterinary and Food Administration

expanded its approval of food uses of *L. paracasei* F-19 to include use in infant formula in 2009.

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.

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

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 produced using milk-based medium requires labeling under the FD&C Act because it may contain protein derived from milk.

Intended Use in Infant Formula

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Arla's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *L. paracasei* F-19 to make the submission required by section 412. Infant formulas are the purview of the ONFL.

Section 301(l) 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 000810 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S Digitally signed by
Michael A. Adams -S
Date: 2019.04.05
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Dennis M. Keefe, Ph.D.
Director
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