Elizabeth McCartney
DuPont Nutrition & Biosciences
Danisco USA, Inc.
3329 Agriculture Drive
Madison, WI 53716

Re: GRAS Notice No. GRN 000865

Dear Ms. McCartney:

This letter corrects our letter signed March 10, 2020, sent in response to GRN 000865. The purpose of this revised letter is to correct the strain name listed in the fourth paragraph of our March 10, 2020 letter from *L. acidophilus* 30333 and *L. acidophilus* SD5221 to *L. acidophilus* ATCC SD5221.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000865. We received Danisco USA, Inc.'s (Danisco) notice on May 29, 2019, and filed it on July 30, 2019. Danisco submitted amendments to the notice on January 20, 2020 and February 14, 2020, providing additional manufacturing specifications.

The subject of the notice is *Lactobacillus acidophilus* strain ATCC SD5221 (*L. acidophilus* ATCC SD5221) for use as an ingredient in non-exempt milk or soy-based infant formula for term infants and in formula for children 12 months and older at a level of 10^8 colony forming units (CFU) per gram of product. The notice informs us of Danisco's view that these uses of *L. acidophilus* ATCC SD5221 are GRAS through scientific procedures.

Our use of the term, "*L. acidophilus* ATCC SD5221," 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. The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "*L. acidophilus* ATCC SD5221."

Danisco describes the *L. acidophilus* ATCC SD5221 as a white to cream-colored powder. Danisco states that *L. acidophilus* ATCC SD5221[1] was isolated from the intestinal tract of a healthy human and is deposited in the strain collections of the American Type Culture Collection (ATCC) and the Deutsche Sammlung von Mikroorganismen (DSM).[2] Danisco discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity. *L. acidophilus* has a long history of use in foods. Danisco states that *L. acidophilus* ATCC SD5221 is non-pathogenic and non-toxigenic.

Danisco describes the manufacture of *L. acidophilus* ATCC SD5221 by fermentation of a pure culture under controlled conditions. The bacteria are concentrated by centrifugation, followed by the addition of cryoprotectants (a blend of sugars and inorganic phosphate), and pelletized by immersion of droplets of concentrate into liquid nitrogen. The resulting pellets are lyophilized and milled to a powder. During production, the manufacturing process is monitored for contamination at five process control points, including the master seed culture, the initial fermentation seed vial, during lyophilization, during milling and the final powdered product. Danisco states that *L. acidophilus* ATCC SD5221 is manufactured with food-grade materials that comply with FDA regulations for such use under current good manufacturing practices. Danisco states that no components of the manufacturing process are allergens or are derived from allergenic sources.

Danisco provides specifications for *L. acidophilus* ATCC SD5221 that include viable cell count (> 2.0×10^{11} CFU/g) and limits for microorganisms, including *Enterococci* (≤ 100 CFU/g), non-lactics (≤ 5,000 CFU/g), coliforms (≤ 10 CFU/g), *Escherichia coli* (< 0.3 CFU/g), coagulase-positive *Staphylococcus* spp. (< 10 CFU/ g), *Salmonella* serovars (negative in 40 g), *Listeria* spp. (negative in 25 g), *Cronobacter sakazakii* (negative in 10 g) and heavy metals; lead (< 0.5 mg/kg), arsenic (< 1.0 mg/kg), cadmium (< 0.2 mg/kg), and mercury (< 0.05 mg/kg). Danisco provides the results of the batch analyses for five[3] non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

Danisco intends to use *L. acidophilus* ATCC SD5221 at a level of 10^8 CFU/g in non-exempt milk or soy-based infant formula for term infants, and in formula for children 12 months and older to ensure a minimum concentration of 10^6 CFU/g throughout the 12-18-month shelf life of the infant formula powder. Danisco estimates a maximum daily intake of *L. acidophilus* ATCC SD5221 of 10^{10} CFU per person per day. The estimated daily intake of *L. acidophilus* ATCC SD5221 does not consider use in formula for infants who might have immune problems.

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[1] FDA notes that *L. acidophilus* is a Gram-positive, non-spore forming, rod-shaped bacterium, and is a member of the lactic acid bacteria (LAB) classification, a group characterized by the production of lactic acid as the major metabolic end-product of carbohydrate metabolism and other physiological traits.

[2] Danisco states that *L. acidophilus* ATCC SD5221 is deposited in the strain collections of the ATCC, the safe deposit (SD) of the ATCC, and the DSM, and is designated as ATCC 700396, ATCC SD5221, and DSM 22091, respectively.

[3] Danisco provides three additional batch analyses, including analysis of *C. sakazakii*, in the January 20, 2020 amendment to the notice.

Danisco discusses the long history of safe use of LAB in foods and how *L. acidophilus* has been safely used in fermented foods. Danisco notes that *L. acidophilus* ATCC SD5221 is the subject of GRN 000357[4], for use as an ingredient in ready-to-eat breakfast cereals; bars; cheeses, milk drinks, and milk products; bottled water and teas; fruit juices, fruit nectars, fruit "aids", and fruit drinks; chewing gum and confections, at a level to provide 10^9 CFU/serving. Danisco cites publications that support the safe consumption of *L. acidophilus*, including peer-reviewed scientific journals and governmental reviews. Additionally, Danisco describes published clinical trials in which infants, children and adults were fed *L. acidophilus* ATCC SD5221 and states that no significant adverse effects on participants were noted in any of these studies.

Based on the totality of evidence, Danisco concludes that *L. acidophilus* ATCC SD5221 is GRAS for its intended use.

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 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 *L. acidophilus* ATCC SD5221 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 ONFL. 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.

Intended Use in Infant Formulas

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 Danisco's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *L. acidophilus* ATCC SD5221 to make the submission required by section 412. Infant formulas are the purview of the 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 Danisco's notice concluding that *L.*

[4] *L. acidophilus* ATCC SD5221 was the subject of GRN 000357. We evaluated this notice and responded in a letter dated April 19, 2011, stating that we had no questions at that time regarding Danisco's GRAS conclusion.

acidophilus ATCC SD5221 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. acidophilus* ATCC SD5221. Accordingly, our response should not be construed to be a statement that foods containing *L. acidophilus* ATCC SD5221, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Danisco provided, as well as other information available to FDA, we have no questions at this time regarding Danisco's conclusion that *L. acidophilus* ATCC SD5221 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. acidophilus* ATCC SD5221 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 000865 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.04.01 10:29:10 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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