James Heimbach, Ph.D.
JHeimbach LLC
923 Water Street
#66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000855

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000855. We received the notice that you submitted on behalf of Lallemand Health Solutions (Lallemand) on April 23, 2019, and filed it on June 25, 2019. Lallemand submitted amendments to the notice on November 12, 2019, November 20, 2019, November 22, 2019, December 4, 2019, December 9, 2019, January 15, 2020, and January 30, 2020 providing additional manufacturing specifications, batch analyses, and clarification on the intended use.

The subject of the notice is *Bifidobacterium animalis* subsp. *lactis* CBS-118529 (*B. animalis* CBS-118529) for use as an ingredient in non-exempt powdered milk-based infant formula for term infants at a level up to 8 x 10^7 colony forming units (CFU)/g infant formula powder. The notice informs us of Lallemand's view that this use of *B. animalis* CBS-118529 is GRAS through scientific procedures.

Lallemand describes *B. animalis* CBS-118529 as an ivory to beige powder. Lallemand states that *B. animalis* CBS-118529 is a Gram-positive, non-motile, non-spore forming, rod or V-shaped bacterium. The strain was obtained from a dairy source and is deposited in the strain collection of the Centraalbureau voor Schimmelcultures, Utretch, Netherlands. Lallemand also states that *B. animalis* CBS-118529 is non-pathogenic and non-toxigenic. Lallemand discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity.

Lallemand describes the manufacture of *B. animalis* CBS-118529 by fermentation of a pure culture under controlled conditions. After fermentation, the bacterial culture is concentrated by centrifugation or ultra-filtration. Following this, cryoprotectants are added to the concentrated bacterial culture, which is then freeze-dried and stored. The cake-like freeze-dried bacterial culture is ground into a powder. Lallemand states that the freeze-dried product may be formulated with excipients such as maltodextrin or potato starch.

The manufacturing process is monitored for contamination at three process control points, including the initial fermentation seed vial, after fermentation is complete and the final product. Lallemand states that *B. animalis* CBS-118529 is manufactured under

current good manufacturing practices and with food-grade materials that comply with FDA regulations for such use. Lallemand states that both milk and soy are used during fermentation, and the product contains traces of milk and soy proteins.

Lallemand provides specifications for *B. animalis* CBS-118529 that include total cell count (> 150 x 10^9 CFU/g) and limits for other microorganisms, including yeast and molds (< 1,000 CFU/g), coliforms (< 10 CFU/g), *Escherichia coli* (< 10 CFU/g), *Staphylococcus aureus* (< 10 CFU/g), *Salmonella* serovars (absent in 25 g), *Cronobacter sakazakii* (absent in 10 g) and heavy metals; lead (3 mg/kg), cadmium (1 mg/kg) and mercury (0.1 mg/kg). Lallemand provides the results from batch analyses of three lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

Lallemand intends to use *B. animalis* CBS-118529 as an ingredient in non-exempt powdered milk-based infant formula for term infants at 5 x 10^7 CFU/g of infant formula. To achieve this level, Lallemand intends to add up to 8 x 10^7 CFU/g of infant formula. Lallemand also assumes a reconstitution rate of 12.5-13.5 g of infant formula/100 mL water. Lallemand relies on published literature on daily energy intake of formula-fed infants to calculate a 90th percentile infant formula intake of 207 mL/kg bw/d. Based on the information available, Lallemand estimates the 90th percentile dietary exposure of *B. animalis* CBS-118529 to be 8 x 10^9 CFU/kg bw/d.[1]

Lallemand states that bifidobacteria are commensals within the digestive tract of humans and describes the history of safe use of *B. animalis* in fermented foods. Lallemand relies on publications that support the safe consumption of *B. animalis* CBS-118529, including peer-reviewed scientific journals, governmental reviews, and product approvals. Additionally, Lallemand describes published clinical trials in which infants, children, and adults were fed *B. animalis* CBS-118529 and states that no significant adverse effects were noted in any of these studies.

Based on the totality of evidence, Lallemand concludes that *B. animalis* CBS-118529 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 *B. animalis* CBS-118529 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 did not consult with

[1] FDA estimates the 90th percentile dietary exposure of *B. animalis* CBS-118529 to be 8 x 10^8 CFU/kg bw/d.

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. *B. animalis* CBS-118529 produced using milk and soy during fermentation requires labeling under the FD&C Act because it contains proteins derived from milk and soy.

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 Lallemand's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. animalis* CBS-118529 to make the submission required by section 412. Infant formulas are the purview of 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 Lallemand's notice concluding that *B. animalis* CBS-118529 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 *B. animalis* CBS-118529. Accordingly, our response should not be construed to be a statement that foods containing *B. animalis* CBS-118529, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Lallemand provided, as well as other information available to FDA, we have no questions at this time regarding Lallemand's conclusion that *B. animalis* CBS-118529 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. animalis* CBS-118529 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 000855 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.02.05 13:20:44 -05'00'

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