



James T. Heimbach, Ph.D., F.A.C.N.
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Re: GRAS Notice No. GRN 000758

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000758. We received the notice that you submitted on behalf of Lallemand Health Solutions (Lallemand) on January 25, 2018, and filed it on March 6, 2018. We received amendments to the notice clarifying the intended use, specifications, safety, and exposure levels on April 24, 2018, and May 4, 2018. We received an amendment to the notice clarifying the components of the fermentation medium on August 1, 2018.

The subjects of the notice are *Lactobacillus helveticus* R0052, *Bifidobacterium longum* ssp. *infantis* R0033, and *Bifidobacterium bifidum* R0071, for use individually (individual bacterial culture), or in combination at a 80:10:10 ratio of *L. helveticus* R0052, *B. longum* ssp. *infantis* R0033, and *B. bifidum* R0071, respectively (combined bacterial culture), as an ingredient in non-exempt powdered infant formulas for term infants. Each individual bacterial culture is intended for use at a maximum level of 3×10^9 colony forming units (CFU)/800 mL of reconstituted formula. The combined bacterial culture is intended for use at a maximum level of 5×10^9 CFU/800 mL of reconstituted formula. The notice informs us of Lallemand's view that the use of each individual bacterial culture and that the use of the combined bacterial culture are GRAS through scientific procedures.

Lallemand describes the identities of the individual bacterial strains. Lallemand describes *L. helveticus* R0052 as a Gram-positive, non-spore forming, rod-shaped bacterium that was isolated from a North American dairy starter culture. Lallemand describes *B. longum* ssp. *infantis* R0033 and *B. bifidum* R0071 as Gram-positive, non-spore forming, irregular rod-shaped bacteria that were isolated from the intestines of healthy adults. Lallemand provides the results of phenotypic and genotypic analyses of each strain, including 16S rDNA and whole genome sequencing, to confirm the strain identities. All three bacterial strains are registered in the Collection Nationale de Cultures de Microorganismes at the Pasteur Institute. Lallemand provides a discussion on potential for toxicity and pathogenicity for each strain and concludes that there is no evidence for either trait in any of the strains.

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Lallemand describes the production of each bacterial culture, which is initiated by fermentation of a pure culture of each individual bacterial strain. Lallemand states that fermentation occurs under controlled conditions.¹ After fermentation, the bacterial cell mass is concentrated by centrifugation. Cryoprotectants are added to the bacterial cell concentrate which is then lyophilized, ground into powder, packaged, and frozen. To produce the combined bacterial culture, the individual bacterial cultures are blended. Lallemand states that all components used in the manufacturing process are food grade, pharmacopeial or of equivalent standards, and the production is conducted in accordance with current good manufacturing practices.

Lallemand provides specifications for each individual bacterial culture. These include cell counts (*L. helveticus* R0052, 4×10^9 CFU/g; *B. longum* ssp. *infantis* R0033, 5×10^8 CFU/g; *B. bifidum* R0071, 5×10^8 CFU/g), and limits for microorganisms, including yeast and molds (<1000 CFU/g), *Salmonella* serovars (absent in 25 g samples), and *Cronobacter sakazakii* (absent in 10 g samples). Lallemand provides the total cell count specification for the combined bacterial culture as 5×10^9 CFU/g. Lallemand provides certificates of analyses for the individual and combined bacterial cultures to demonstrate that the cultures can be manufactured to meet specifications. Lallemand provides data to demonstrate stability of each bacterial culture for 24 months.

Lallemand provides estimates of the dietary exposure to each individual bacterial culture when used in the combined bacterial culture in target populations of infants. Based on the daily energy intake by formula-fed infants and the assumption that infant formulas contain 67.6 kcal/100 mL formula, Lallemand states that the estimated dietary exposures are 6.4×10^8 CFU/kg body weight (bw)/day for *L. helveticus* R00052, 8×10^7 CFU/kg bw/day for *B. longum* ssp. *infantis* R0033, and 8×10^7 CFU/kg bw/day for *B. bifidum* R0071.²

Lallemand discusses whole-genome sequencing and bioinformatic analyses of the three bacterial strains to support their safety. Lallemand states that none of the three strains encode any putative virulence factors that are considered harmful to humans. Lallemand also states that their analyses show that the three strains either lack genes related to the production of, or do not produce, detectable levels of biogenic amines, and that the strains lack genes involved in the biosynthesis of lipopeptides, enterotoxins, or hemolysins that could be potentially harmful to humans. Lallemand states that the three bacterial strains do not carry genes conferring antibiotic resistance.

Lallemand also discusses published information to support the safety of each bacterial culture. The safety of *L. helveticus* R0052, *B. longum* ssp. *infantis* R0033, and *B. bifidum* R0071 for use in non-exempt infant formulas for term infants was based on information derived from studies conducted in infants. Lallemand summarizes a

¹ Lallemand states that there are no allergens in the fermentation medium used to produce the bacterial cultures, nor are there allergens in the final products.

² FDA notes that the estimated dietary exposure for each individual bacterial culture when used in the combined bacterial culture is higher than the estimated dietary exposure for the use of each individual bacterial culture. FDA notes that the lower dietary exposures for the individual cultures are addressed by considering the higher exposures to the combined bacterial culture.

published, 12-week placebo-controlled study in infants 3 to 12 months of age. The infants were divided into four study groups: one group consumed one of the three bacterial strains, and the fourth group consumed a placebo. Lallemand states that the results demonstrated no statistically significant differences between the treated and placebo groups and that the daily consumption of 3×10^9 CFU of each of the individual bacterial cultures was well tolerated and did not adversely affect infants. Lallemand also summarizes published studies showing that the daily consumption of 3×10^9 CFU or 5×10^9 CFU of the combined bacterial culture by children 0 to 5 years did not result in adverse effects.

Lallemand states that *L. helveticus* R0052, *B. longum* ssp. *infantis* R0033, and *B. bifidum* R0071 have been granted Qualified Presumption of Safety status by the European Food Safety Authority. Lallemand also states that the Food Directorate of Health Canada assessed the characterization profile of *L. helveticus* R0052 and issued a letter of non-objection for its use in food. Additionally, Lallemand states that the Food Directorate of Health Canada recognizes the use of *B. longum* ssp. *infantis* R0033 and *B. bifidum* R0071 in foods without pre-market authorization.

Lallemand includes the statement of a panel of individuals (Lallemand's GRAS panel). Based on its review, Lallemand's GRAS panel concluded that the individual bacterial cultures and the combined bacterial culture are safe under the conditions of their intended use.

Based on the data and information described above, Lallemand concludes that the individual bacterial cultures and the combined bacterial culture are GRAS for their intended use in infant formula.

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). The notice raises a potential issue under these labeling provisions. In the notice, Lallemand cites studies that describe the individual bacterial cultures and the combined bacterial culture as having health benefits. If products containing the individual bacterial cultures or the combined bacterial culture 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 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 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 Lallemand's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing the individual bacterial cultures or the combined bacterial culture to make the submission required by section 412. Infant formulas are the purview of ONFL.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Lallemand's notice concluding that the individual bacterial cultures and the combined bacterial culture are GRAS under their intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing the individual bacterial cultures or the combined bacterial culture. Accordingly, our response should not be construed to be a statement that foods containing the individual bacterial cultures or the combined bacterial culture, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

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 the individual bacterial cultures and the combined bacterial culture are GRAS under their intended conditions of use. This letter is not an affirmation that the individual bacterial cultures and the combined bacterial culture are 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 000758 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M.

Keefe -S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Dennis M. Keefe -S
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