



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

Re: GRAS Notice No. GRN 000953

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000953. We received the notice that you submitted on behalf of Kaneka Americas Holding, Inc. (Kaneka) and AB-Biotics on June 3, 2020 and filed it on October 23, 2020. Kaneka and AB-Biotics submitted amendments to the notice on December 16, 2020, December 23, 2020, and January 11, 2021, providing information about the microorganisms, additional manufacturing specifications, clarifying information regarding stability, intended uses, a description of the dietary exposure assessment, and an updated literature search.

The subject of the notice is *Lactiplantibacillus plantarum* strain CECT 7527, *L. plantarum* strain CECT 7528 and *L. plantarum* strain CECT 7529<sup>1</sup> (*L. plantarum* CECT 7527, CECT 7528 and CECT 7529), individually or in combination, for use as an ingredient in conventional foods at a maximum level of  $4 \times 10^9$  colony forming units (CFU)/serving, when used individually and at a maximum level of  $1.2 \times 10^{10}$  CFU/serving, when used in combination.<sup>2</sup> The notice informs us of Kaneka and AB-Biotics' view that this use of *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 is GRAS through scientific procedures.

Kaneka and AB-Biotics describe *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 as ivory-white powders. Kaneka and AB-Biotics state that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 are Gram-positive, non-pathogenic, non-toxigenic, non-motile, non-spore forming, rod-shaped bacteria. The strains were isolated from the feces of healthy South American infants and are deposited in the strain collection of the Colección Española de Cultivos Tipo (CECT) in Valencia, Spain. Kaneka and AB-Biotics discuss the results of the phenotypic and genotypic characterization used to confirm the strains' identity.

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<sup>1</sup> We note that *Lactobacillus plantarum* was reclassified as *Lactiplantibacillus plantarum* as reported in Zheng, et al. (Ref. 1).

<sup>2</sup> Kaneka and AB-Biotics state that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 are not intended for use in infant formula, foods formulated for infants, or any products under the jurisdiction of the United States Department of Agriculture.

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Kaneka and AB-Biotics describe the manufacture of *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 by fermentation of a pure culture under controlled conditions. Kaneka and AB-Biotics state that all strains are fermented independently and later combined at the appropriate ratio when they are to be used in combination. After fermentation, the fermentation media is centrifuged to remove excess water. Following this, food-grade cryoprotectants are added to the concentrate to protect the bacteria during lyophilization. The concentrate is lyophilized and the resulting powder is milled, passed through a 1 mm sieve, and blended with food-grade excipients (such as maltodextrin, microcrystalline cellulose or corn starch) to achieve the necessary product concentration. If the intended use is in combination, the three separate strains are blended, resulting in a uniform bulk powder. Kaneka and AB-Biotics state that all ingredients, processing aids and excipients used during manufacturing are free from allergens. Kaneka and AB-Biotics state that the manufacturing process is monitored for contamination, and that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 are manufactured under current good manufacturing practices using food-grade materials that are approved for their respective use.

Kaneka and AB-Biotics provide specifications for *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 that include limits for microorganisms, including bacterial count ( $> 1.2 \times 10^{11}$  CFU/g), yeast and mold ( $< 10$  CFU/g), *Enterobacteriaceae* ( $< 10$  CFU/g), *Escherichia coli* ( $< 1$  CFU/g), coagulase-positive *Staphylococcus* spp. ( $< 10$  CFU/g), *Bacillus cereus* ( $< 100$  CFU/g), *Listeria monocytogenes* (absent in 25 g), and *Salmonella* serovars (absent in 25 g); and heavy metals, including lead ( $\leq 0.2$  mg/kg). Kaneka and AB-Biotics provide the results from the analysis of three non-consecutive lots of the 1:1:1 combination powder to demonstrate that the ingredient can be manufactured to conform with the provided specifications. Kaneka and AB-Biotics provide data indicating that the shelf life of the individual strains and a combination of the strains is 18 months when stored at  $-20$  °C.

Kaneka and AB-Biotics state what when used individually at a maximum level of  $4 \times 10^9$  CFU/serving, or in combination at a maximum level of  $1.2 \times 10^{10}$  CFU/serving, the likely maximum exposure to *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 is less than  $10^{11}$  CFU/day. Kaneka and AB-Biotics state that this conservative estimate is based on the mean consumption of 20 food servings/day and allows for ten or more servings of food and drinks to contain *L. plantarum* CECT 7527, CECT 7528 and CECT 7529.

Kaneka and AB-Biotics state that lactic acid bacteria have a long history of safe use in human food, including several fermented foods. Kaneka and AB-Biotics performed a literature search through December 2020 and summarize published scientific journal articles and governmental reviews that support the safe consumption of *L. plantarum* by humans. Kaneka and AB-Biotics discuss published *in vitro*, *in vivo*, and clinical studies pertaining to the safety of milled, lyophilized *L. plantarum* CECT 7527, CECT 7528 and CECT 7529 in a 1:1:1 combination. Kaneka and AB-Biotics state that *in vitro* data show no significant findings for safety-related issues of the strains (i.e., antibiotic resistance, bacterial virulence, biogenic amine production, and D-lactic acid production). Kaneka and AB-Biotics summarize and discuss acute and sub-chronic animal studies in which no toxicologically relevant findings were reported at any doses

examined, as well as clinical studies that indicate no treatment-related adverse effects.

Kaneka and AB-Biotics include the statement of a panel of individuals (Kaneka and AB-Biotics' GRAS panel). Based on its review, Kaneka and AB-Biotics' GRAS panel concluded that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, are safe under the conditions of the intended use.

Based on the totality of evidence, Kaneka and AB-Biotics conclude that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, are GRAS for the intended use.

### **Standards of Identity**

In the notice, Kaneka and AB-Biotics state their intention to use *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

### **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. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, 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.

### **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 Kaneka and AB-Biotics' notice concluding that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, are GRAS under the intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination. Accordingly, our response should not be construed to be a statement that foods containing *L.*

*plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

## Conclusions

Based on the information that Kaneka and AB-Biotics provided, as well as other information available to FDA, we have no questions at this time regarding Kaneka and AB-Biotics' conclusion that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, are GRAS under the intended conditions of use. This letter is not an affirmation that *L. plantarum* CECT 7527, CECT 7528 and CECT 7529, individually or in combination, 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 000953 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

Digitally signed by Susan J.  
Carlson -S  
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Susan Carlson, Ph.D.  
Director  
Division of Food Ingredients  
Office of Food Additive Safety  
Center for Food Safety  
and Applied Nutrition

## Reference

1. Zheng, J., et al. (2020). A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. *International Journal of Systematic and Evolutionary Microbiology*, 70(4), 1-77. doi: 10.1099/ijsem.0.004107