U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Marie-Eve Boyte
NutraPharma Consulting Services, Inc.
32 Therese
Sainte-Anne-des-Plaines, Quebec J5N 4B3
CANADA

Re: GRAS Notice No. GRN 001175

Dear Ms. Boyte:

The Food and Drug Administration (FDA, we) received the GRAS notice dated November 24, 2023, that you submitted on behalf of NORDWISE BioTech OÜ (NORDWISE). We received this notice on November 28, 2023, and filed it on May 10, 2024. NORDWISE submitted amendments to the notice on August 27, 2024, and September 19, 2024, clarifying the taxonomy of *Lactiplantibacillus plantarum*[1] DSM 23881, manufacturing process, specifications, batch analyses, and dietary exposure.

The subject of the notice is *L. plantarum* DSM 23881 for use as an ingredient in conventional foods at a level of $1x10^{10}$ colony forming units (CFU) per serving.[2] The notice informs us of NORDWISE's view that these uses of *L. plantarum* DSM 23881 are GRAS through scientific procedures.

NORDWISE states that *L. plantarum* DSM 23881 is a non-pathogenic, non-toxigenic, non-motile, non-spore forming, rod-shaped, anaerobic, Gram-positive bacterium. NORDWISE notes that the strain was isolated from a one-year-old healthy child in 1995 and has been deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH. NORDWISE describes the taxonomic and genomic analyses to confirm the strain identity. NORDWISE discusses the results of phenotypic and genotypic characterization performed on *L. plantarum* DSM 23881.

NORDWISE describes the manufacture of *L. plantarum* DSM 23881 by fermentation of a pure culture under controlled conditions. After fermentation, the cells are separated from the fermentation medium and concentrated by nozzle centrifugation, lyophilized after the addition of cryoprotectants, then milled and sieved to yield the final product, which is stored at 4 ^{0}C. The milled powder is blended with excipients to achieve the desired viable cell count. NORDWISE states that *L. plantarum* DSM 23881 is manufactured under current good manufacturing practices using food-grade raw

[1] FDA notes that recent taxonomic changes to the genus *Lactobacillus* includes the nomenclature of this organism from *Lactobacillus plantarum* to *Lactiplantibacillus plantarum* (Zheng et al., 2020).
[2] NORDWISE states that *L. plantarum* DSM 23881 is not intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture, and foods in which a standard of identity precludes its use.

materials. NORDWISE confirms that all materials used in the manufacture of *L. plantarum* DSM 23881 are permitted for their respective uses under a current U.S. regulation, are the subject of an effective food contact notification, or are GRAS for their intended use. NORDWISE states that *L. plantarum* DSM 23881 does not contain any major allergens.

NORDWISE provides specifications for *L. plantarum* DSM 23881 that include total cell count (≥4 x 10^{11} CFU/g), and limits for microorganisms, including *Listeria monocytogenes* (not detected in 25 g), *Salmonella* serovars. (not detected in 25 g), and heavy metals, including lead (<0.1 mg/kg). NORDWISE provides the results from the analyses of three non-consecutive batches to demonstrate that *L. plantarum* DSM 23881 can be manufactured to meet these specifications.

NORDWISE estimates the dietary exposure to *L. plantarum* DSM 23881 from the intended uses to be 2 x 10^{11} CFU/d based on the assumption that an individual consumes 20 servings of food per day, and that all these servings would contain *L. plantarum* DSM 23881 at the maximum use level of 1 x 10^{10} CFU/serving.

NORDWISE discusses data and information used to support the safety of *L. plantarum* DSM 23881, including a history of safe use of the *Lactobacillus* spp. and the safe use of lactic acid bacteria in fermented foods. NORDWISE notes that we have reviewed and evaluated *L. plantarum* strains in GRNs 000685, 000722, 000847, 000946, 000953, and 001113.[3] NORDWISE discusses opportunistic infection caused by certain *Lactobacilli* species and states that the infection occurs at very low rates, and generally occurs in immunocompromised patients or in hospitals during medical procedures. NORDWISE summarizes an unpublished toxicology study in mice using *L. plantarum* DSM 23881 and published studies in humans using *L. plantarum* DSM 23881 (fermented foods) and other *L. plantarum* species (both fermented foods and bacterium alone) and reported no adverse events or indications of safety concerns.

Based on the totality of the data and information, NORDWISE concludes that *L. plantarum* DSM 23881 is GRAS for its intended use.

Standards of Identity

In the notice, NORDWISE states its intention to use *L. plantarum* DSM 23881 in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to

[3] Various *Lactobacillus* strains were the subjects of GRNs 000685, 000722, 000847, 000946, 000953, and 001113. We evaluated these notices and responded in letters dated October 31, 2017, February 16, 2018, September 30, 2019, February 5, 2021, February 5, 2021, and July 20, 2023, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

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, & 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). If products containing *L. plantarum* DSM 23881 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 Nutrition Center of Excellence. The Office of Pre-Market 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(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 NORDWISE's notice concluding that *L. plantarum* DSM 23881 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. plantarum* DSM 23881. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* DSM 23881, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that NORDWISE provided, as well as other information available to FDA, we have no questions at this time regarding NORDWISE's conclusion that *L. plantarum* DSM 23881 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* DSM 23881 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 001175 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E. Honigfort -S

Digitally signed by Mical E. Honigfort -S
Date: 2024.10.22 09:53:58 -04'00'

for Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program