



Arie Carpenter
Chr. Hansen, Inc.
9015 West Maple St.
Milwaukee, WI 53214

Re: GRAS Notice No. GRN 000946

Dear Ms. Carpenter:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000946. We received Chr. Hansen, Inc.'s (Chr. Hansen) notice on June 2, 2020 and filed it on September 18, 2020. Chr. Hansen submitted amendments to the notice on November 20, 2020, December 8, 2020 and December 21, 2020 providing information about the microorganism, manufacturing specifications, results from the analysis of five non-consecutive batches, and an updated literature review.

The subject of the notice is *Lactiplantibacillus plantarum* strain DSM 33452¹ (*L. plantarum* DSM 33452) for use in the production of wine and musts at a level of 10⁷ colony forming units (CFU)/g. The notice informs us of Chr. Hansen's view that this use of *L. plantarum* DSM 33452 is GRAS through scientific procedures.

Chr. Hansen describes *L. plantarum* DSM 33452 as an off-white to slightly brown pellet. Chr. Hansen states that *L. plantarum* DSM 33452 is a Gram-positive, non-pathogenic, non-toxigenic, non-motile, non-spore forming, rod-shaped bacterium. The strain was isolated from South African red wine and is deposited in the strain collection of the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ) in Braunschweig, Germany. Chr. Hansen discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

Chr. Hansen describes the manufacture of *L. plantarum* DSM 33452 by fermentation of a pure culture under controlled conditions. After fermentation, the fermentation media is centrifuged to concentrate the bacterial culture and to remove the fermentation medium. Following this, the concentrated bacterial culture is frozen into pellets. The resulting pellets may also be lyophilized. Chr. Hansen states that no components of the fermentation media are allergens or are derived from allergenic sources. Chr. Hansen states that the manufacturing process is monitored for contamination, and that *L. plantarum* DSM 33452 is manufactured under current good manufacturing practices using food-grade materials that are approved for their respective use under 21 CFR or

¹ Chr. Hansen states that *Lactobacillus plantarum* was reclassified as *Lactiplantibacillus plantarum* as reported in Zheng, et al. (Ref. 1).

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are GRAS for that use.

Chr. Hansen provides specifications for *L. plantarum* DSM 33452 that include limits for microorganisms, including non-lactic acid bacteria (< 500 CFU/g), molds (< 10 CFU/g), yeasts (< 10 CFU/g), *Acetobacter* spp. (< 100 CFU/g), *Enterobacteriaceae* (< 100 CFU/g), *Listeria monocytogenes* (absent in 25 g), *Salmonella* serovars (absent in 25 g), and heavy metals, including lead (< 2 mg/kg)². Chr. Hansen provides the results from the analyses of five non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

Chr. Hansen states that *L. plantarum* DSM 33452 is sensitive to alcohol and is expected to die as the alcohol content rises under the intended conditions of use in the production of wine and musts. Chr. Hansen states that *L. plantarum* DSM 33452 cannot tolerate alcohol contents above 5% and therefore, would not be viable in the finished product and does not contribute to exposure to lactic acid bacteria. Chr. Hansen further notes that if the *L. plantarum* survived the alcoholic fermentation, the adult microbiome is very stable and only shifts with significant dietary changes or extreme weight loss. Chr. Hansen states that *L. plantarum* is commonly found in the human oral cavity and intestinal tract of healthy individuals, and lactic acid bacteria, including *L. plantarum*, are found in most fermented foods that are consumed daily. Therefore, the addition of *L. plantarum* DSM 33452 to wine would not cause a significant increase in lactic acid bacteria in the gut or the diet.

Chr. Hansen cites published literature that documents the history of safe use of *L. plantarum* in human foods, including several fermented foods. Chr. Hansen summarizes published scientific journal articles and governmental reviews that support the safe consumption of *L. plantarum* by humans. Chr. Hansen explains that infection linked to *L. plantarum* is rare and has not been linked to its consumption in food. Chr. Hansen further addresses the safety of *L. plantarum* DSM 33452 by stating that *L. plantarum* DSM 33452 does not carry transferrable antibiotic resistance genes, does not produce toxic biogenic amines and does not produce citrulline, a precursor of ethyl carbamate in wine.

Based on the totality of evidence, Chr. Hansen concludes that *L. plantarum* DSM 33452 is GRAS for its intended use.

Section 301(II) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(II) of the Federal Food, Drug, and Cosmetic Act (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

² Chr. Hansen states that they have not detected heavy metals in batches of *L. plantarum* DSM 33452 and heavy metal contamination is not a potential hazard in their manufacturing process or in the finished ingredient, however, their specification is consistent with international standards set by the Oenological Codex.

product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(l)(1)-(4) applies. In our evaluation of Chr. Hansen's notice concluding that *L. plantarum* DSM 33452 is GRAS under its intended conditions of use, we did not consider whether section 301(l) or any of its exemptions apply to foods containing *L. plantarum* DSM 33452. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* DSM 33452, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).


Conclusions

Based on the information that Chr. Hansen provided, as well as other information available to FDA, we have no questions at this time regarding Chr. Hansen's conclusion that *L. plantarum* DSM 33452 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* DSM 33452 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 000946 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

 Digitally signed by Susan J. Carlson -S
Date: 2021.02.05 12:00:20 -0500

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