William J. Rowe
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 001063

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001063. We received OraPharm, Inc's (OPI) notice on March 24, 2022 and filed it on June 24, 2022. OPI submitted amendments to the notice on October 31, 2022, March 31, 2023, and April 4, 2023 that discussed manufacturing, specifications, dietary exposure, analytical methods, data about the phenotypic characteristics, and the literature search.

The subject of the notice is *Weissella cibaria* CMU (*W. cibaria* CMU) for use as an ingredient at levels up to 8 x 10^9 colony forming units (CFU)/serving in yogurt; frozen dairy desserts; ices, sorbets, and sherbet; and hard candy, mints, and chewing gum. The notice informs us of OPI's view that these uses of *W. cibaria* CMU are GRAS through scientific procedures.

OPI describes *W. cibaria* CMU as a yellowish-white powder. OPI states that *W. cibaria* CMU is a non-pathogenic, nontoxigenic bacterium that can be described as a short, rod-shaped, Gram-positive, non-spore-forming, nonmotile, heterofermentative, catalase-negative lactic acid bacterium. The strain was isolated from saliva samples from 460 kindergarten children aged 4 to 7 residing in Gwangju, South Korea and was deposited in the Korean Collection for Type Cultures on June 04, 2004, with the accession number KCTC 10650BP. OPI discusses the results of phenotypic and genotypic characterization used to confirm the strain identity and states that the complete genome for *W. cibaria* CMU has been sequenced and deposited in the NCBI GenBank under the accession number CP013936. OPI states that the *W. cibaria* CMU genome contains no antimicrobial resistance genes or any genes for virulence factors, and that the strain does not produce secondary amines.

OPI describes the manufacture of *W. cibaria* CMU by fermentation of a pure culture under controlled conditions. Upon completion of fermentation, the culture is cooled, concentrated by centrifugation, the live microbial pellet is mixed with a cryoprotectant, then freeze-dried and ground. OPI states that *W. cibaria* CMU is manufactured under current good manufacturing practices using food-grade materials and that all raw

materials and processing aids are used in accordance with existing U.S. regulations or are GRAS for their intended use.

OPI provides specifications for *W. cibaria* CMU that include viable cell count (≥1 x 10^{11} CFU/g), moisture (≤5%), ash (≤2%) and limits for heavy metals, including lead (≤0.1 mg/kg) and for microorganisms, including *Salmonella* serovars (absent in 25 g), *Listeria monocytogenes* (absent in 25 g), and *Staphylococcus aureus* (absent in 1 g). OPI provides the results from the analyses of five non-consecutive batches to demonstrate that *W. cibaria* CMU is manufactured to conform with the provided specifications. OPI states that *W. cibaria* CMU is stable for up to 48 weeks at 4 °C and 25 °C.

OPI estimates dietary exposure to *W. cibaria* CMU based on the maximum intended use level for each food category and food consumption data in the 2017-2020 National Health and Nutrition Examination Survey (NHANES). OPI estimates the eaters-0nly dietary exposure to *W. cibaria* CMU for the U.S. population all ages to be 3.9 x 10^{9} CFU/person (p)/d at the mean and 1 x 10^{10} CFU/p/d at the 90th percentile.

OPI discusses the history of safe consumption of *W. cibaria* in human food, which mainly consists of fermented foods. OPI performed a literature search and summarizes the published literature that supports the safety of *W. cibaria* CMU, including genetic toxicity studies, a single dose oral toxicity study, a 14-day dose range finding study, and a 90-day sub-chronic oral toxicity study. OPI notes that no test-article related adverse events or genotoxicity was observed. OPI also summarizes six published clinical studies in healthy subjects that consumed *W. cibaria* CMU as additional support for its safety conclusion.

Based on the data and information, OPI concludes that *W. cibaria* CMU is GRAS for its intended use.

Allergen Labeling

The Federal Food, Drug, and Cosmetic (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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. *W. cibaria* CMU requires labeling under the FD&C Act because it contains protein derived from milk.

Standards of Identity

In the notice, OPI states its intention to use *W. cibaria* CMU in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations (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 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 *W. cibaria* CMU 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(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 OPI's notice concluding that *W. cibaria* CMU 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 *W. cibaria* CMU. Accordingly, our response should not be construed to be a statement that foods containing *W. cibaria* CMU, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that OPI provided, as well as other information available to FDA, we have no questions at this time regarding OPI's conclusion that *W. cibaria* CMU is GRAS under its intended conditions of use. This letter is not an affirmation that *W. cibaria* CMU 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 001063 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.04.14 16:52:43 -04'00'

Susan J. Carlson, Ph.D.
Director
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