Mizue Naito
Dose Biosystems Inc.
661 University Ave, Suite 1300
Toronto, Ontario
CANADA
M5G 0B7

Re: GRAS Notice No. GRN 001022

Dear Dr. Naito,

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001022. We received Dose Biosystems Inc.'s (Dose Biosystems) notice on June 24, 2021 and filed it on September 30, 2021. Dose Biosystems submitted amendments to the notice on February 15, May 22, June 15, and August 2, 2022, providing additional information about the microorganism, specifications, intended uses, and estimated dietary exposure.

The subject of the notice is *Streptococcus salivarius* DB-B5 for use as an ingredient at a maximum level of 10^{10} colony forming units (CFU)/ serving in cookies; meal replacement powders and bars; sports and "energy" drinks; flavored waters; breakfast cereals; cheeses; chewing gum; dairy product analogs; frozen dairy desserts and mixes; gelatins, puddings, and fillings; snack bars (granola, protein); hard candy; milk drinks and milk products; peanut butter; fruit juices and drinks (ready to drink and powder); soft candy; and toppings (flavored sprinkles).[1] The notice informs us of Dose Biosystems' view that this use of *S. salivarius* DB-B5 is GRAS through scientific procedures.

Dose Biosystems describes *S. salivarius* DB-B5 as a white to off-white powder. Dose Biosystems states that *S. salivarius* DB-B5 is a gram-positive, non-pathogenic, non-toxigenic bacterium. The strain was isolated from the mouth of an adult donor and is deposited in the International Depository Authority of Canada under accession number 160720-01. Dose Biosystems discusses the results of phenotypic and genotypic characterization used to confirm the strain identity and cites a published study describing the whole genome sequencing of *S. salivarius* DB-B5.

Dose Biosystems describes the manufacture of *S. salivarius* DB-B5 by fermentation of a pure culture under controlled conditions. Dose Biosystems states that *S. salivarius* DB-B5 is manufactured under current good manufacturing practices with food-grade raw materials suitable for such use. After fermentation, the *S. salivarius* DB-B5 cells are

[1] Dose Biosystems states that *S. salivarius* DB-B5 is not intended for use in infant formula, infant and toddler foods, or in foods that fall under the purview of the U.S. Department of Agriculture.

harvested from the fermentation medium by centrifugation and filtration. Dose Biosystems states that food-grade cryoprotectants are added to the concentrated cell mixture that is then frozen and lyophilized. Dose Biosystems notes that the fermentation medium contains soy peptone and the final product contains protein from soy.

Dose Biosystems provides specifications for *S. salivarius* DB-B5 that include limits for *S. salivarius* DB-B5 ($\geq 10^{10}$ CFU/g); heavy metals, including lead (< 0.3 mg/kg); and other microorganisms, including yeast and mold (≤ 50 CFU/g), *Escherichia coli* (negative in 10 g), and *Salmonella* serovars (negative in 10 g). Dose Biosystems provides the results from the analyses of three non-consecutive lots to demonstrate that their ingredient meets these specifications.

Dose Biosystems intends to use *S. salivarius* DB-B5 at levels up to 10^{10} CFU/serving in conventional foods to achieve target levels, as consumed, of 10^{9} CFU/serving. Dose Biosystems estimates dietary exposure to *S. salivarius* DB-B5 to be up to 2×10^{11} CFU/person/day; this is based on published estimated consumption of 20 servings of food per person per day in the U.S. and the assumption that all 20 servings of food would contain *S. salivarius* DB-B5 at levels up to 10^{10} CFU/serving.

Dose Biosystems discusses publicly available data and information used to support the safety of *S. salivarius* DB-B5, including the presence of *S. salivarius* as a commensal microorganism in the oral cavity and the history of consumption of *S. salivarius* in foods. Dose Biosystems states that *S. salivarius* DB-B5 is closely related to *S. salivarius* K12 and *S. salivarius* M18, two microorganisms that were the subjects of GRNs 000591[2] and 000807[3], respectively, with intended uses as ingredients in multiple food categories. Dose Biosystems incorporates summaries of clinical studies from GRN 000591 and 000807 showing no adverse effects from the consumption of strains of *S. salivarius*. Dose Biosystems also discusses two clinical studies with *S. salivarius* DB-B5 conducted in healthy adults and states that no serious adverse events were observed. Dose Biosystems discusses newly published reports of adverse events associated with consuming *S. salivarius* strains and incorporates into the notice previous adverse case reports reviewed in GRNs 000591 and 000807. Dose Biosystems concludes that adverse events are rare and have occurred only in subjects with an underlying disease or health condition. Dose Biosystems also conducted *in silico* analysis to demonstrate the absence of functional and transferrable antibiotic resistance genes.

Based on the data and information summarized above, Dose Biosystems concludes that *S. salivarius* DB-B5 is GRAS for its intended use.

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[2] *S. salivarius* K12 was the subject of GRN 000591. We evaluated this notice and responded in a letter dated January 25, 2016 (correction letter issued June 5, 2019) stating that we had no questions at the time regarding the notifier's GRAS conclusion.

[3] *S. salivarius* M18 was the subject of GRN 000807. We evaluated this notice and responded in a letter dated June 6, 2019 stating that we had no questions at the time regarding the notifier's GRAS conclusion.

Standards of Identity

In the notice, Dose Biosystems states its intention to use *S. salivarius* DB-B5 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 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 *S. salivarius* DB-B5 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.

Allergen Labeling

The 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 (effective January 1, 2023)) or a food ingredient that contains protein derived from one of those foods. *S. salivarius* DB-B5 requires labeling under the FD&C Act because it contains proteins derived from soy.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Dose Biosystems' notice concluding that *S. salivarius* DB-B5 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 *S. salivarius* DB-B5. Accordingly, our response should not be construed to be a statement that foods containing *S. salivarius* DB-B5, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Dose Biosystems provided, as well as other information available to FDA, we have no questions at this time regarding Dose Biosystems' conclusion that *S. salivarius* DB-B5 is GRAS under its intended conditions of use. This letter is not an affirmation that *S. salivarius* DB-B5 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 001022 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.08.22 17:55:26 -04'00'

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