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

Re: GRAS Notice No. GRN 000735

Dear Dr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement to GRN 000735 that you submitted on behalf of FrieslandCampina Domo B. V. (FrieslandCampina). We received the supplement on February 20, 2020. The supplement addresses changes in the method of manufacture and specifications for the subject of GRN 000735.

We previously responded to GRN 000735 on April 6, 2018. We stated that we had no questions at that time regarding Glycosyn and FrieslandCampina's conclusion that 2′-fucosyllactose (2′-FL) is GRAS for the intended use as an ingredient in milk and soy-based, non-exempt infant formulas for term infants and in toddler formulas at a maximum level of 2.4 g/L of formula as consumed; infant and toddler foods at levels of 0.24-1.2 g/serving; and in the following food categories at levels of 0.28-1.2 g/serving: beverages and beverage bases; breakfast cereals; dairy product analogs; frozen dairy desserts and mixes; gelatins, puddings, and fillings; grain products and pastas; jams and jellies; milk and milk products; processed fruits and fruit juices; and sweet sauces, toppings, and syrups.[1] In the supplement dated February 12, 2020, FrieslandCampina informs us of its view that 2′-FL is GRAS, through scientific procedures, for the same uses described in GRN 000735.

In GRN 000735, Glycosyn and FrieslandCampina state that 2′-FL is enzymatically produced from lactose and glucose using a modified strain of *Escherichia coli* K-12 GI724 (E997), secreted into the fermentation medium, and obtained through a series of purification steps resulting in a spray-dried powder. In this supplement, FrieslandCampina states that no changes were made to the production organism, the fermentation process, or the purification steps; however, FrieslandCampina describes three changes to the components of the fermentation medium from GRN 000735. These changes include the use of glucose syrup in place of dextrose monohydrate, cobalt

[1] Glycosyn and FrieslandCampina stated that 2′-FL is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

sulfate heptahydrate in place of cobalt chloride hexahydrate, and manganese sulfate monohydrate in place of manganese chloride tetrahydrate. Additionally, FrieslandCampina discusses changes to the specifications from GRN 000735. These changes include a lower minimum content of 2′-FL in the finished product from ≥90% to ≥88% (on a dry matter basis), an increase in the maximum water content from ≤5% to ≤9%, and a lower limit for aflatoxin M1 from ≤0.2 µg/kg to ≤0.025 µg/kg. FrieslandCampina provides the results of five non-consecutive batch analyses to demonstrate that 2′-FL can be produced to meet these specifications.

FrieslandCampina states that it did not conduct a stability study with 2′-FL produced as described in this supplement. Rather, the supplement describes the results of stability studies that were reported in GRN 000735 and provides the more recent results of an on-going shelf-stability study showing that 2′-FL is stable for at least 24 months. The amount of moisture after 24 months exceeds the previously specified limit of 5% in GRN 000735, leading to the change in the specification described above.

FrieslandCampina conducted an updated literature search through October 2019 and discusses new published studies surrounding the safety of the production organism, as well as toxicological and human clinical studies with 2′-FL in support of safety. FrieslandCampina did not identify any data or information that would contradict its safety conclusion from GRN 000735.

FrieslandCampina includes the report of a panel of individuals (FrieslandCampina's GRAS panel). Based on its review, FrieslandCampina's GRAS panel concluded that 2′-FL is safe under the conditions of its intended use.

Based on the totality of the data and information described above, FrieslandCampina concludes that 2′-FL is GRAS for its intended use in food.

Standards of Identity

In the supplement, FrieslandCampina states its intention to use 2′-FL 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, & 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 2′-FL 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 (OFAS) 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 eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. 2′-FL derived from lactose may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to the ONFL.

Intended Use in Infant Formula

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to FrieslandCampina's supplement does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 2′-FL to make the submission required by section 412. Infant formulas are the purview of 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 FrieslandCampina's supplement concluding that 2′-FL 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 2′-FL. Accordingly, our response should not be construed to be a statement that foods containing 2′-FL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that FrieslandCampina provided, as well as other information available to FDA, we have no questions at this time regarding FrieslandCampina's conclusion that 2′-FL is GRAS under its intended conditions of use. This letter is not an affirmation that 2′-FL 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 the supplement to GRN 000735 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.04.30 14:49:59 -04'00'

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