Dietrich B. Conze, Ph.D.
Spherix Consulting Group, Inc.
751 Rockville Pike
Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001179

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001179. We received Crossway Foods, Ltd. (Crossway)'s notice on April 2, 2024, and filed it on May 6, 2024. Crossway submitted an amendment to the notice on August 9, 2024, that clarified the specifications and batch analyses.

The subject of the notice is liquid whole cow milk for use as an ingredient in cow milk-based, non-exempt infant formula for term infants at a maximum level of 153 g/100 g infant formula powder. The notice informs us of Crossway's view that this use of liquid whole cow milk is GRAS through scientific procedures.

Crossway describes the identity and composition of liquid whole cow milk as defined in 21 CFR 131.110. Crossway describes the average proximate composition of liquid whole cow milk to include moisture (87%), carbohydrates (4.6%), fats (3.8%), proteins (3.6%), and ash (0.8%). Crossway states that the milk is neither adjusted nor homogenized and does not contain any optional ingredients permitted in 21 CFR 131.110. Crossway provides the averages and ranges of three non-consecutive batch analyses to describe the composition of liquid whole cow milk, including levels of fatty acids, amino acids, vitamins, minerals, and phospholipids.

Crossway describes the manufacture of liquid whole cow milk and states that it is produced according to current good manufacturing practices using standard dairy-processing techniques. Crossway states that the starting material, raw whole cow milk, complies with applicable regulations and that the suppliers of the raw milk follow Good Agricultural Practices. Crossway notes that all food contact materials comply with applicable regulations. The raw whole cow milk is filtered, pasteurized in accordance with the conditions specified in the Pasteurized Milk Ordinance, chilled, and stored at ≤10 °C for up to 72 hours prior to its use in the production of infant formula.

Crossway provides specifications for liquid whole cow milk that include content of protein (≥ 2.9%), fat (≥ 3.2%), and total solids (11.5-15.0%). Additional specifications include limits for titratable acidity (12-18 Dornic degrees) and antibiotics (not

detectable). Crossway provides the results of six non-consecutive batches to demonstrate that liquid whole cow milk can be manufactured to meet these specifications. Crossway provides additional specifications that are used for the periodic monitoring of raw whole milk and testing milk from new suppliers. These specifications include limits for cholesterol (≤ 15 mg/100 g), ash (≤ 2%), nitrates (≤ 7 mg/kg), nitrites (≤ 0.4 mg/kg), chromium (≤ 0.3 mg/kg), arsenic (≤0.0125 mg/kg), cadmium (≤ 0.00625 mg/kg), lead (≤ 0.00625 mg/kg), and mercury (≤ 0.00625 mg/kg), as well as limits for vitamins A and D3 and several minerals naturally present in whole milk. Crossway provides the averages and ranges of three non-consecutive batch analyses of liquid whole cow milk to demonstrate that the levels of heavy metals are within the specified limits described in GRNs 000980 and 001041[1] on a solids basis. In addition, Crossway provides specifications for heavy metals in the finished infant formula product that include limits for arsenic (≤0.02 mg/kg), cadmium (≤ 0.01 mg/kg), lead (≤ 0.02 mg/kg), and mercury (≤ 0.02 mg/kg). Crossway also provides the results from three non-consecutive batches of liquid whole cow milk for microorganisms, including *Cronobacter sakazakii* (absent in 10 g), *Salmonella* serovars (absent in 25 g), and *Listeria monocytogenes* (absent in 25 g). Crossway notes that in the production of infant formula, liquid whole cow milk is combined with other ingredients to form an intermediate product that is subjected to a heat-treatment step, evaporation, and spray drying. Crossway provides specifications for the intermediate product that includes limits for *Cronobacter* spp. (absent in 300 g) and *Salmonella* spp. (absent in 250 g). Further, Crossway provides specifications for the final infant formula product that includes limits for *Cronobacter* spp. (absent in 300 g), *Salmonella* spp. (absent in 1500 g), and *Listeria monocytogenes* (absent in 250 g).

Crossway estimates the dietary exposure to liquid whole cow milk based on the intended use and infant formula consumption data from the 2011-2018 National Health and Nutrition Examination Surveys incorporated from GRN 001041. The maximum intended use level is 153 g liquid whole cow milk/100 g of infant formula powder, and Crossway calculates that the maximum intended use level on a solids basis is equivalent to 19.9 g/100 g of infant formula powder and 2.6 g/100 mL (3.8 g/100 kcal) of infant formula as consumed based on a reconstitution rate of 12.9 g formula powder/100 mL and a caloric content of 67 kcal/100 mL for formula as consumed. Crossway estimates the dietary exposure to liquid whole cow milk, on a solids basis, for infants up to one year of age (i.e., 0-2 months, 3-5 months, 6-8 months, and 9-11 months). The reported mean and 90th percentile eaters-only dietary exposures range from 16.9 to 20.9 g/person (p)/d and 26.9 to 32.3 g/p/d, respectively, across the first year of life.[2] Further, Crossway states that the intended use of liquid whole cow milk in infant formula would contribute approximately 55% of the total protein, 21% of the total fat, and 12.7% of the total carbohydrates in the infant formula.

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[1] Dry whole milk was the subject of GRNs 000980 and 001041. We evaluated these notices and responded in letters dated July 13, 2021, and May 10, 2022, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

[2] Crossway determined that infants aged 3-5 months have the highest dietary exposures with mean and 90th percentile estimates of 20.9 and 32.3 g/p/d, respectively, and infants aged 0-2 months have the highest dietary exposures on a body-weight (bw) basis with mean and 90th percentile estimates of 3.7 and 5.7 g/kg bw/d, respectively.

Crossway discusses published data and information to support the safety of liquid whole cow milk. Crossway states that milk and milk products have a long history of use in the U.S. food supply, including consumption by infants and young children in the transition from a diet of exclusive human milk/or infant formula to other foods. Crossway states that milk products have been consumed with no adverse effects attributable to milk other than the well-documented occurrence of allergic reactions in susceptible individuals. Crossway states that the intended use and use level of liquid whole cow milk is not different from the current use of dry whole milk in infant formula, which was previously concluded to be GRAS. As such, Crossway states that safety information discussed in GRNs 000980 and 001041 is incorporated into the notice.

Crossway discusses published clinical studies of infants consuming whole milk to support its safety as a component of the diet. Crossway discusses the literature and potential concerns with consuming liquid whole milk as a sole source of nutrition, including potential nutrient deficiency, renal solute load, and fat malabsorption. Crossway states that the intended use of liquid whole cow milk is as an ingredient in infant formula and provides only a portion of the needed nutrients in the total formula. Therefore, Crossway states that potential safety concerns attributed from directly consuming liquid whole cow milk as a sole source of nutrition is unlikely to be of concern from the intended use as a component of milk-based infant formula. Crossway states that the use of liquid whole cow milk in infant formula will provide a source of constituents typically present in lower concentrations in formula, such as phospholipids and other lipids present in milk fat that are not present in vegetable oils. However, Crossway states that the level of these components from the intended use will result in levels similar to or well below the mean concentrations reported in human milk.

Based on the totality of the data and information, Crossway concludes that liquid whole cow milk is GRAS for its intended use.

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 liquid whole cow milk 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) or a food ingredient that contains protein derived from one of those foods. Liquid whole cow milk requires labeling under the FD&C Act because it contains milk, an allergen.

Intended Use in Infant Formulas

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 Crossway's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing liquid whole cow milk 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 Crossway's notice concluding that liquid whole cow milk 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 liquid whole cow milk. Accordingly, our response should not be construed to be a statement that foods containing liquid whole cow milk, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Crossway provided, as well as other information available to FDA, we have no questions at this time regarding Crossway's conclusion that liquid whole cow milk is GRAS under its intended conditions of use. This letter is not an affirmation that liquid whole cow milk 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 001179 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.09.24 17:27:14 -04'00'

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