



James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal VA 22535

Re: GRAS Notice No. GRN 000980

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000980. We received the notice that you submitted on behalf of ByHeart, Inc. (ByHeart) on November 20, 2020, and filed it on February 9, 2021.¹ ByHeart submitted amendments to the notice on April 16, 2021, and May 25, 2021, that clarified the intended use, use level, identity, manufacturing, specifications, exposure, and safety-related data and information.

The subject of the notice is dry whole milk for use as an ingredient in cow milk-based, non-exempt infant formula for term infants at a maximum level of 16% (w/w) of powdered infant formula. The notice informs us of ByHeart's view that this use of dry whole milk is GRAS through scientific procedures.

ByHeart describes the identity and composition of dry whole milk as defined in 21 CFR 131.147. ByHeart states that dry whole milk contains lactose, proteins, fat, and minerals in the same relative proportions as the milk from which it was produced. Dry whole milk also contains 26%-40% by weight of milk fat on an as is basis and \leq 5% by weight of moisture on a milk solids not fat basis. ByHeart notes that its dry whole milk does not contain added vitamins A and D or other optional ingredients permitted in dry whole milk (21 CFR 131.147).

ByHeart describes the manufacture of dry whole milk, stating that it uses standard dairy processing techniques (i.e., pasteurization and spray-drying) and that no component of the whole milk is concentrated to greater than naturally occurring levels on a dry basis. ByHeart states that the cow milk starting material in the manufacture is Grade "A," produced in accordance with all applicable standards and certification requirements for fluid milk, and pasteurized in accordance with the provisions of the Pasteurized Milk Ordinance (PMO, 2019).

¹ ByHeart clarified information on the intended infant formula protein base in an update on February 9, 2021.

ByHeart discusses the protein and fat components of dry whole milk. Protein in dry whole milk contains the same casein:whey ratio (80:20) as nonfat dry milk commonly used, in combination with whey protein, in non-exempt infant formulas. Milk fat contains predominantly triglycerides, with minor amounts of phospholipids (approximately 0.3% of dry whole milk) and cholesterol. Major fatty acids in milk fat include myristic, palmitic, stearic, and oleic fatty acids.

ByHeart provides specifications for dry whole milk that include content of protein (22-30%) and fat (26-40%). The remaining major macronutrient component is lactose (~38%).² Additional specifications for dry whole milk include limits for moisture ($\leq 5\%$), titratable acidity ($\leq 0.15\%$), peroxide value (≤ 5 meq/kg fat), scorched particles (≤ 15 mg), cholesterol (≤ 150 mg/100 g), and ash ($\leq 7\%$), as well as limits for vitamins A and D and several minerals present in whole milk. ByHeart further provides limits for heavy metals, including arsenic (≤ 0.5 mg/kg), cadmium (≤ 0.05 mg/kg), lead (≤ 0.05 mg/kg), and mercury (≤ 0.05 mg/kg), as well as limits for microorganisms, including *Salmonella* serovars (absent in 25 g), *Bacillus cereus* (≤ 100 CFU/g), and *Cronobacter* sp. (absent in 10 g). ByHeart provides the results of three non-consecutive batch analyses to demonstrate that the dry whole milk can be manufactured to meet these specifications. ByHeart describes stability studies conducted with dry whole milk up to 10 months at 10-30 °C and $< 70\%$ relative humidity, noting that no significant degradation in quality parameters was observed.

ByHeart estimates the dietary exposures to dry whole milk from the intended use. The maximum intended use level is 16 g/100 g formula powder, and ByHeart calculates the use level to be equivalent to 3 g/100 kcal of formula as consumed based on a reconstitution rate of 12.5 g formula powder/100 mL and a caloric content of 67 kcal/100 mL for formula ready to consume. ByHeart cites 90th percentile energy intake values of 141.3 kcal/kg body weight (bw)/d for male and 138.9 kcal/kg bw/d for female infants aged 14-27 days. This age group has the highest reported energy intakes per kg bw for formula-fed infants. Using these published estimates of energy intake, ByHeart estimates the 90th percentile dietary exposure to dry whole milk at the maximum intended use level to be approximately 4 g/kg bw/d. Further, ByHeart notes that based on the intended use level, dry whole milk is expected to contribute a minor fraction of total protein, fat, and carbohydrate (lactose) in infant formula for term infants.

ByHeart discusses published data and information to support the safety of dry whole milk. ByHeart states that whole milk and dry whole milk are widely consumed by infants, children, and adults with no adverse effects other than allergic reactions in susceptible individuals. ByHeart discusses published clinical studies in infants and toddlers fed whole milk or components derived from whole milk, in support of the safety of dry whole milk as a component of the infant diet. ByHeart discusses potential safety concerns with feeding infants whole milk as a sole source of nutrition, including the need to adjust concentrations of iron and other minerals and vitamins, protein, and fat content to meet the nutritional needs of infants. ByHeart states that dry whole milk is

² Based on the U. S. Department of Agriculture (USDA) Nutrient Database for Standard Reference, Legacy Release (USDA, 2020).

not intended for use as a sole source of nutrition and will become part of a complex mixture that includes sources of other nutrients when used in infant formula. Dry whole milk contributes only a portion of the formula's protein (26%), fat (12%), and lactose (8%). As such, ByHeart states that the milk fat and lipid components contributed by the dry whole milk are insignificant in relation to the vegetable oil-based infant formulas on the market, and that the amount of phospholipids in ByHeart's infant formula is similar to the range observed in human milk and other marketed infant formulas in the U.S. Furthermore, ByHeart discusses physico-chemical similarities and differences arising from how unmodified milk, dry whole milk, and dry nonfat milk are processed as they relate to potential physiological consequences. ByHeart asserts that any differences between unmodified milk and/or dry nonfat milk compared to dry whole milk are not expected to impact the overall safety profiles. Finally, ByHeart states that the use of dry whole milk does not differ from current uses of nonfat dry milk and whey powders in infant formula. ByHeart states that the use of dry whole milk as an ingredient in non-exempt infant formula is not intended as the sole source of protein, fat, or other nutrients in the formula, and infant formula containing dry whole milk is expected to meet all nutrient specifications for infant formula listed in 21 CFR 107.100.

ByHeart includes the statement of a panel of individuals (ByHeart's GRAS panel). Based on its review, ByHeart's GRAS panel concluded that dry whole milk is safe under the conditions of its intended use.

Based on the totality of the data and information, ByHeart concludes that dry whole 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 dry whole 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 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. Dry whole milk requires labeling under the FD&C Act because it is a "major food 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 ByHeart's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing dry whole milk to make the submission required by section 412. Infant formulas are the purview of ONFL.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of ByHeart's notice concluding that dry whole milk is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing dry whole milk. Accordingly, our response should not be construed to be a statement that foods containing dry whole milk, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that ByHeart provided, as well as other information available to FDA, we have no questions at this time regarding ByHeart's conclusion that dry whole milk is GRAS under its intended conditions of use. This letter is not an affirmation that dry whole 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 000980 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Susan Carlson, Ph.D.
Director

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

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