



Lynley Drummond  
Drummond Food Science Advisory Ltd.  
1137 Drain Road, Killinchy  
RD 2, Leeston 7682  
New Zealand

Re: GRAS Notice No. GRN 000669

Dear Ms. Drummond:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000669. We received the notice, dated September 12, 2016, that you submitted on behalf of Synlait Milk, Ltd. (Synlait) under the format of the agency's final rule (81 FR 54960; August 17, 2016; Substances Generally Recognized as Safe (GRAS)) on September 13, 2016 and filed it on September 27, 2016. We received amendments on November 23, 2016, November 28, 2016, and December 18, 2016 containing additional safety information and an update on the information that Synlait initially designated confidential.<sup>1</sup>

The subject of the notice is cow's milk-derived lactoferrin (cMDLf) for use as an ingredient in cow's milk-based non-exempt infant formula for term infants at a level of 100 mg/100 g formula solids, which corresponds to approximately 13-14 mg/100 mL infant formula (ready-to-feed (RTF) or prepared for consumption from powder or liquid concentrate),<sup>2</sup> and in follow-on formula at a level of 15 mg/100 mL RTF or prepared for consumption from powder. The notice informs us of Synlait's view that these uses of cMDLf are GRAS through scientific procedures.

Synlait provides information on the identity and composition of cMDLf, which is isolated from skimmed cow's milk. Synlait states that the cMDLf ingredient is a pink- to tan-colored powder containing  $\geq 95\%$  protein, of which  $\geq 95\%$  is bovine lactoferrin (bLf). Synlait describes bLf, a member of the transferrin protein family, as an iron-binding glycoprotein existing as a single polypeptide chain of approximately 700 amino acids and 75-80 kilodaltons. bLf's three-dimensional structure is characterized by two homologous lobes, each with an iron-binding site. bLf can exist in both the iron-free and iron-saturated states, the latter being more resistant to proteolysis and thermal denaturation. bLf contains multiple N-linked glycans that were reported and characterized in the published literature.

Synlait describes the manufacturing process for cMDLf.<sup>3</sup> First, raw skim milk is chilled to below 8 °C to minimize microbial growth, and then it is clarified and microfiltered to remove bacteria

<sup>1</sup> GRN 000669 included information in the Appendices in Part 7 that Synlait initially designated confidential dated September 12, 2016. In the November 23, 2016 amendment, Synlait states that with the exception of Appendix 6, which consists of each GRAS panel member's Curriculum Vitae, the rest of Part 7 of the notice is not confidential.

<sup>2</sup> Synlait notes that this use level is identical to that of GRN 000465. GRN 000465 describes the use of cMDLf in cow's milk-based term infant formula at a level of 13 mg/100 mL formula (RTF or prepared for consumption from powder or liquid concentrate). We evaluated GRN 000465 and responded in a letter dated February 18, 2014 stating that we had no questions at that time regarding Morinaga's GRAS determination.

<sup>3</sup> Synlait notes that the method of manufacture is similar to that described in GRN 000465, but differs in the final drying step.

U.S. Food & Drug Administration  
Center for Food Safety & Applied Nutrition  
5001 Campus Drive  
College Park, MD 20740

and remaining insolubles. cMDLf is isolated from the filtrate using ion-exchange chromatography and eluting of bound material with sodium chloride. The isolated cMDLf is then desalted, ultrafiltered, pasteurized,<sup>4</sup> and microfiltered prior to evaporation and spray drying. Synlait reports that cMDLf is stable at 40 °C for up to 36 weeks when stored in multilayer packages resistant to oxygen and water vapor. Synlait states that all processing aids are food grade and its cMDLf ingredient is produced in accordance with current good manufacturing practices using standard methods of skim milk production and subsequent methods of cMDLf isolation. Synlait states that the starting material is produced in accordance with good agricultural practices for dairy farming and is in compliance with U.S. regulations, including applicable regulations for use and maximum tolerances of agricultural pesticides and veterinary drugs, and the standards outlined in the Grade “A” Pasteurized Milk Ordinance (revised 2015).

Synlait provides specifications for cMDLf expressed on a weight percent basis that include a minimum of 95.0% protein (of which  $\geq 95\%$  is bLf), 4.5% moisture, and 1.3% ash. The iron content is  $\leq 200$  mg/kg, and calculated iron saturation is  $\leq 20\%$ . Additional specifications include limits for lead ( $< 0.15$  mg/kg), arsenic ( $< 0.02$  mg/kg), *Cronobacter sakazakii* (not detected/300 g), *Salmonella* (not detected/250 g), melamine ( $< 0.1$  mg/kg), and aflatoxin M1 ( $< 0.5$   $\mu\text{g/kg}$ ). Synlait provides the results of five nonconsecutive batch analyses of cMDLf to demonstrate that it meets specifications.

Synlait estimates dietary exposure for infants consuming formula containing cMDLf based on intended uses of cMDLf in infant and toddler formulas, estimated combined background intake of bLf from consumption of milk-based formula, and food consumption data from the National Health and Nutrition Examination Survey (NHANES, 2007-2012). Synlait states that, in general, infants 0 to 6 months of age would consume 269 mg/d (43.7 mg/kg·body weight (bw)/d) and 395 mg/d (68.8 mg/kg·bw/d) cMDLf at the mean and 90<sup>th</sup> percentile, respectively. Infants 7 to 12 months of age would consume 235 mg/d (26.1 mg/kg·bw/d) and 345 mg/d (38.2 mg/kg·bw/d) cMDLf at the mean and 90<sup>th</sup> percentile, respectively. Toddlers 13 to 36 months of age would consume 235 mg/d (26.1 mg/kg·bw/d) and 345 mg/d (38.2 mg/kg·bw/d) of cMDLf at the mean and 90<sup>th</sup> percentile, respectively. Synlait further explains that infants and toddlers are currently exposed to cMDLf by consuming cow’s milk-based infant formula and that by consuming cMDLf from the intended uses, their average daily exposure will increase approximately two-fold over their background dietary exposure.

Synlait incorporates into the notice and summarizes several published toxicological studies on cMDLf from previous GRAS notices (GRN 000464<sup>5</sup> and 000465<sup>1</sup>). These include an acute, a 4-week, a 13-week, and two chronic oral toxicity studies in rats. Synlait reports that an updated literature search was conducted through July 2016. As part of the safety discussion, Synlait discusses published information on hypersensitivity and allergenicity as it relates to cMDLf, and concludes that cMDLf is unlikely to be a clinically relevant allergen or the primary causative agent of any immunologically driven hypersensitivity. Synlait also discusses several published studies on the digestion, absorption, and excretion of cMDLf in neonatal piglets and in human infants. From the results of these studies, Synlait concludes that cMDLf is partially digested in the infant gut. The undigested cMDLf and its peptide fragments are excreted in the feces, while

---

<sup>4</sup> Synlait states that the conditions exceed the requirements for milk pasteurization as described in FDA’s Grade “A” Pasteurized Milk Ordinance (revised 2015).

<sup>5</sup> GRN 000464 describes the use of cMDLf in cow’s milk-based products [yogurts (100 mg/100 g), powdered milk (400 mg/100 g), and milk-based frozen desserts (200 mg/100 g)] and in chewing gum (30 mg/g). We evaluated GRN 000464 and responded in a letter dated February 18, 2014 stating that we had no questions at that time regarding Morinaga’s GRAS determination.

a small fraction of the consumed cMDLf is absorbed in the intestine. Synlait also discusses a published mutagenicity study. Based on the results of the toxicological studies, Synlait concludes that cMDLf consumption does not produce adverse effects, even at the highest dose tested, and cMDLf is not mutagenic. Synlait summarizes several clinical studies where cMDLf was fed as part of the milk-based formula to pre-term infants with very low/low birth weight and term infants, or fed to toddlers and children. No adverse effects were observed in these studies. Synlait emphasizes that although pre-term infants with very low/low birth weight are not the intended consumers of formula with cMDLf, studies in this group of infants showed no adverse effects with cMDLf.

Synlait notes that the intended cMDLf use levels in this GRAS notice are lower than the cMDLf use levels authorized by the European Commission (22 November 2012) for infant formula and follow-on formula following a review by the European Food Safety Authority.

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

Based on the totality of information discussed above, Synlait concludes that cMDLf is GRAS for its intended use.

### **Potential Labeling Issues**

Under section 403(a) of the Federal Food, Drug, and 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). The notice raises a potential issue under these labeling provisions. In the notice, Synlait cites studies that describe cMDLf as having certain health benefits. If products containing cMDLf 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 includes 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. cMDLf would require labeling under section 403(w) because it is a protein derived from milk. Questions related to food labeling in general should be directed to ONFL.

### **Potential Requirement for a Color Additive Petition**

There is no GRAS provision for color additives. In the notice, Synlait describes cMDLf as a pink to tan powder. As such, the use of cMDLf in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70.

Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000669 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Petition Review in OFAS.

### **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 Synlait's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing cMDLf 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 your notice concluding that cMDLf 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 cMDLf. Accordingly, our response should not be construed to be a statement that foods containing cMDLf, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

### **Conclusions**

Based on the information that Synlait provided, as well as other information available to FDA, we have no questions at this time regarding Synlait's conclusion that cMDLf is GRAS under its intended conditions of use. This letter is not an affirmation that cMDLf 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 000669 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Michael A. Adams

-S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S  
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, o.9.2342.19200300.100.1.1=1300042713,  
cn=Michael A. Adams -S  
Date: 2017.03.09 12:40:24 -0500