Steven B. Steinborn
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, DC 20004

Re: GRAS Notice No. GRN 000898

Dear Mr. Steinborn:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000898. We received Hogan Lovells US LLP (Hogan Lovells)'s notice on January 9, 2020[1] and filed it on February 5, 2020. Hogan Lovells submitted amendments to the notice on May 1, 2020, June 15, 2020, July 17, 2020, August 13, 2020, and October 21, 2020, that provided additional information and clarifications on the intended conditions of use, manufacturing process, specifications, analytical methods, estimated dietary exposure, compliance with tolerances specified in other United States regulations, and safety information.

The subject of the notice is anhydrous milk fat (AMF) for use as a source of fat in cow milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants[2] at a maximum level of 7.0% by weight of the fat blend in formulas containing up to 50% of kilocalories (kcal) as fat. The notice informs us of Hogan Lovells' view that this use of AMF is GRAS through scientific procedures.

Our use of the term "anhydrous milk fat" or "AMF" in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for

[1] Hogan Lovells submitted Appendices A-C with confidential markings. In an email dated January 9, 2020, Hogan Lovells provided unredacted versions of Appendices A-C showing that only supplier contact information had been redacted and not information related to safety.
[2] In the amendments dated May 1, 2020 and October 21, 2020, Hogan Lovells specifies the infant populations intended to consume infant formula containing AMF. Hogan Lovells states that AMF is intended for term infants (i.e., birth to 12 months of age) with increased energy requirements and/or fluid restrictions and will be used under medical supervision.

U.S. Food and Drug Administration
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nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient 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 regarding the appropriate common or usual name for "anhydrous milk fat" or "AMF."

Hogan Lovells discusses the source, identity, and composition of AMF. Hogan Lovells states that AMF is derived from cow's milk and contains at least 99.8% milk fat and a maximum of 0.1% water. Hogan Lovells further states that the milk used in the manufacture of AMF is pasteurized under conditions equivalent to the applicable provisions of the Pasteurized Milk Ordinance. Hogan Lovells provides representative levels of fatty acids in AMF, as well as concentrations of fat-soluble vitamins. Palmitic, oleic, myristic, and stearic acids account for the largest proportions of fatty acids in AMF. Hogan Lovells states that AMF is also a source of cholesterol and fat-soluble vitamins, including vitamins A, E, and K.

Hogan Lovells describes the manufacturing process for AMF starting with pasteurized cream (40% fat). Hogan Lovells states that the process begins by using physical processes to extract water and non-fat dry matter. The cream is first heated and concentrated to a high-fat cream by separation of water. This step is followed by phase inversion from an oil-in-water emulsion to a water-in-oil emulsion, further concentration, vacuum drying to remove residual moisture, and sieving. The final product is then blanketed with nitrogen. Hogan Lovells states that AMF is manufactured in accordance with current good manufacturing practices. Hogan Lovells also states that the fluid milk, used to produce the cream, is produced in accordance with good agricultural practices.

Hogan Lovells provides specifications for AMF. These include fat content (≥ 99.8% (as solids)), moisture (≤ 0.1%), free fatty acid (as oleic acid, ≤ 0.3%), peroxide value (≤ 0.3 meq O_2/kg fat), aflatoxin M1 (<0.1 µg/kg), mercury (<20 µg/kg), lead (<50 µg/kg), cadmium (<10 µg/kg), total arsenic (<100 µg/kg), iron (≤0.2 mg/kg), copper (≤0.05 mg/kg), as well as limits for microorganisms, including *Salmonella* (absent in 250 g).[3] Hogan Lovells provides results of analyses for five nonconsecutive batches of AMF to demonstrate conformance with the stated specifications.

Hogan Lovells provides estimates of dietary exposure to AMF based on the intended use as a component of the fat blend to contribute fatty acids in exempt infant formula for term infants that require calorically dense formula at a maximum level of 7.0% by weight of the fat blend. Based on the assumptions that infants consume 120 kcal/kg body weight (bw)/day (d)[4] of formula and that 50% of the calories are fat, Hogan Lovells

[3] Hogan Lovells states that the use of AMF in liquid infant formulas requires a retort step and therefore, a specification for *Cronobacter sakazakii* is not needed.

[4] Hogan Lovells notes that this value is consistent with reference energy needs for catch-up growth outlined by the Institute of Medicine (2005) in Dietary Reference Intakes for Energy, Carbohydrate, Fat, Fatty acids, Cholesterol, Protein, and Amino acids. Washington, DC: The National Academies Press.

estimates that infants would typically consume ~6.7 g fat/kg bw/d. If AMF is 7% of the fat blend, the dietary exposure to AMF would be 0.47 g/kg bw/d. Hogan Lovells states that calorically dense infant formula is intended for infants weighing up to 9 kg. Assuming a body weight of 9 kg, this results in a dietary exposure to AMF of 4.2 g/p/d. Hogan Lovells also cites a maximum intake level of formula to be 175 kcal/kg bw/d from the reports in published studies; at this level, a 9 kg infant would consume 6.1 g/p/d of AMF.

Hogan Lovells discusses data and information pertinent to supporting the safety of AMF, including its consumption in the intended infant population.[5] Hogan Lovells states that milk and milk products such as AMF have a long history of use in the U.S. food supply that includes consumption by toddlers and use to produce milk-derived ingredients for infant formula.[6] Hogan Lovells discusses comparison of individual constituents of vegetable oils used in vegetable oil blends, fats in human milk, and AMF. Specifically, Hogan Lovells discusses information on components of AMF not found in typical vegetable oil blends used in infant formula. These included butyric acid, *trans* fatty acids, conjugated linoleic acid, odd-chain fatty acids, branched-chain fatty acids, and cholesterol. For these constituents, Hogan Lovells states that their safety assessment approach is based on evaluating data and information to compare constituents in AMF to those present in human milk. Based on the mean concentrations found in AMF, as well as proposed use and maximum use levels, Hogan Lovells concludes that levels of these components from the intended use are within levels found in human milk, and thus safe. In addition, Hogan Lovells states that the naturally occurring levels of vitamins A, E, and K in AMF are low relative to required levels of these vitamins in infant formula and thus not a safety concern. Hogan Lovells also discusses published and unpublished clinical studies of infants consuming milk fat as supportive evidence that milk fat as a component of the fat blend in infant formula supports growth and is well tolerated by infants.

Based on the totality of data and information available, Hogan Lovells concludes that AMF 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). If products containing AMF

[5] In amendments dated May 1, 2020, June 15, 2020, and October 21, 2020, Hogan Lovells discusses the infant populations intended to consume AMF, as well as data and information supporting safety of this intended use.

[6] Hogan Lovells states that regulations and guidance by the FDA, the Life Sciences Research Office Expert Panel, and other international organizations do not specify suitable fats and oils for use in infant formula and thus, do not prohibit the use of AMF in infant formula.

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 ONFL. 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.

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 Hogan Lovells' GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing AMF to make the submission required by section 412. Infant formulas are the purview of 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. AMF derived from milk requires labeling under the FD&C Act because it contains milk.

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 Hogan Lovells' notice concluding that AMF 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 AMF. Accordingly, our response should not be construed to be a statement that foods containing AMF, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hogan Lovells provided, as well as other information available to FDA, we have no questions at this time regarding Hogan Lovells' conclusion that AMF is GRAS under its intended conditions of use. This letter is not an affirmation that AMF 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 000898 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.10.28 16:10:45 -04'00'

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