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

Re: GRAS Notice No. GRN 000899

Dear Mr. Steinborn:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000899. We received Hogan Lovells US LLP's (Hogan Lovells) notice on November 12, 2019[1] and filed it on February 21, 2020. Hogan Lovells submitted amendments to the notice on May 1, 2020 and June 11, 2020,[2] and October 21, 2020, that provided clarifications and additional information on the intended use, method of manufacture, specifications, dietary exposure, and safety of the subject of the notice.

The subject of the notice is citric acid esters of mono- and diglycerides (CITREM) for use as an emulsifier in cow milk-based, calorically dense, ready-to-feed, and exempt infant formula for term infants[3] at a maximum level of 233 mg per 100 mL. The notice informs us of Hogan Lovells' view that this use of CITREM is GRAS through scientific procedures.

Our use of the term, "CITREM" 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 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 did not consult with ONFL regarding the appropriate common or usual name for "CITREM."

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[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] Hogan Lovells submitted the June 11, 2020, amendment with confidential markings and redacted supplier contact information not related to safety.
[3] In the amendments dated May 1, 2020 and October 21, 2020, Hogan Lovells specifies the infant populations intended to consume infant formula containing CITREM. Hogan Lovells states that CITREM 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.

Hogan Lovells discusses the identity and composition of CITREM. The notifier describes CITREM as a white to ivory-colored substance with an oily to waxy consistency. CITREM is composed of citric acid esters of mono- and diglycerides of edible fatty acids. The mono- and diglycerides in CITREM may include either one or two fatty acids with chain lengths ranging from C12 to C22. Hogan Lovells states that CITREM is produced by the reaction of citric acid with mono- and diglycerides that are produced with glycerol and fatty acids from fully hydrogenated palm oil.[4] The notifier states that the product is partially neutralized with sodium acetate and is spray dried to form a coarse powder. The notifier states that all materials used in the production of CITREM are food-grade and it is produced in accordance with current good manufacturing practices.

Hogan Lovells provides specifications for CITREM that includes total citric acid (13 to 50%), total glycerol (8 to 33%), and total free fatty acids (37 to 81%, as oleic acid). Specifications also include limits on free glycerol (≤ 2%), acids other than citric and fatty acids (< 1%), sulfated ash (≤ 10%), lead (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), mercury (≤ 1 mg/kg), as well as limits on microorganisms[5] including *Salmonella* (not detected in a 1 g sample). Hogan Lovells describes limits for 3-monochloropropane-1,2-diol esters (3-MCPDE) of 1.25 mg/kg and for glycidyl esters (GE) of 1 mg/kg. Hogan Lovells provides the results of the analyses of three nonconsecutive batches to demonstrate that CITREM can be manufactured to meet specifications.

Hogan Lovells provides estimates of dietary exposure to CITREM based on the intended use in calorically dense, exempt infant formula. The notifier discusses data on consumption by term infants administered calorically dense infant formula as reported in published clinical trials and in a study of infants in the pediatric intensive care unit. Hogan Lovells reports that the average and highest caloric intakes to be 120 and 175 kcal/kg body weight (bw)/day, respectively, from calorically dense infant formula and notes that such formulas provide 100 kcal/100 mL. Based on the intended maximum use level of 233 mg of CITREM/100 mL, Hogan Lovells estimates the average and high dietary exposure to CITREM to be 280 and 408 mg/kg bw/day, respectively.

In the amendment dated June 11, 2020, Hogan Lovells provides additional discussion of the estimated dietary exposure to CITREM and infant energy requirements. The notifier compares published estimates of recommended energy intakes for infants with elevated nutrient requirements and estimates of energy needs based on a predictive model (i.e., Schofield equation). This model incorporates adjustment factors to energy intakes for infants with health conditions who would likely consume calorically dense infant formulas necessary for catch-up growth. Based on these stress factors, Hogan Lovells calculates the highest energy requirements at the midpoint for catch-up growth to be 116 kcal/kg bw/day for infants aged 1 to 6 months and 110 kcal/kg bw/day for

[4] Hogan Lovells states that the fatty acids obtained from hydrogenated palm oil are primarily palmitic and stearic acids.

[5] In an amendment dated June 11, 2020, the notifier states that CITREM is intended for use in liquid calorically dense infant formula that undergo processes, including heat treatment, to ensure elimination of microbial contaminants and therefore a specification for *Cronobacter sakazakii* in CITREM is not needed.

infants ages 6 to 12 months, respectively. The notifier states that the caloric consumption estimate for infants aged 1 to 6 months based on this method is similar to the typical energy intake reported in clinical studies and discussed above (120 kcal/kg bw/day). Hogan Lovells estimates the 90th percentile energy intakes to be 144 kcal/kg bw/day for infants aged 1 to 6 months, and 132 kcal/kg bw/day for infants 6-12 months respectively, based on a factor of 1.2 times the estimated mean energy intake. Hogan Lovells calculates the mean and 90th percentile dietary exposures to CITREM to be 280 and 336 mg/kg bw/day for infants aged 0 to 6 months and 256 and 308 mg/kg bw/day for infants aged 6 to 12 months, respectively, based on the estimates of energy intake and the maximum intended use level of CITREM.

Hogan Lovells discusses the data and information supporting the safety of CITREM including published and unpublished studies and states that the toxicity of CITREM is intrinsically low. Based on *in vivo* and *in vitro* digestibility studies, CITREM is expected to be substantially hydrolyzed into its components including citric acid, glycerol, and free fatty acids that are common components of the infant diet and Hogan Lovells concludes any remaining partially hydrolyzed products do not present a safety concern. Hogan Lovells states that the intended infant population[6] consuming the energy dense formula would reasonably digest and metabolize CITREM as would other term infants, and thus, the biochemical aspects of CITREM are applicable to the current safety assessment. Hogan Lovells performed an updated literature search through January 2019 and states that no new information relevant for the safety assessment was identified. Hogan Lovells notes that the safe use of CITREM has been previously reviewed by authoritative bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Union's Scientific Committee on Food and Health Canada. JECFA has concluded that levels of CITREM up to 900 mg/100 mL of infant formula are safe. Additionally, CITREM was the subject of GRN 000511[7] for use in exempt amino acid-based and extensively hydrolyzed infant formulas at an identical use level as in the current notice. The proposed maximum intake of CITREM is below that in GRN 000511 and below an intake for which JECFA concluded to present no toxicological concerns.

Based on the totality of data and information discussed above, Hogan Lovells concludes that CITREM is GRAS for its intended use.

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 CITREM to make the submission required by section 412.

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[6] In an amendment dated May 1, 2020, Hogan Lovells discusses the infant populations intended to consume CITREM, as well as data and information supporting the safety of this intended use.
[7] CITREM was the subject of GRN 000511. We evaluated this notice and responded in a letter dated November 10, 2014, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Infant formulas are the purview of the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 CITREM 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 CITREM. Accordingly, our response should not be construed to be a statement that foods containing CITREM, 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 CITREM is GRAS under its intended conditions of use. This letter is not an affirmation that CITREM 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 000899 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.10.30 09:47:09 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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