Alexandra Markle
Intertek Assuris
2233 Argentia Rd, Suite 201 W
Mississauga, ON L5N 2X7
CANADA

Re: GRAS Notice No. GRN 001043

Dear Ms. Markle:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001043. We received the notice that you submitted on behalf of Pharmanutra S.p.A. (Pharmanutra) on November 29, 2021, and filed it on March 14, 2021. Pharmanutra submitted amendments to the notice on June 2, 2022, and June 30, 2022, providing additional information regarding the identity, intended uses, specifications, and the safety narrative.

The subject of the notice is cetylated fatty acids (CFA) for use as a source of dietary fatty acids at levels ranging from 0.13 to 2.5 g per 100 g or 100 mL in ice cream; "energy," protein, and meal replacement bars; flavored milk, milk drinks and mixes; milk-based meal replacement, nutritional and protein beverages; and yogurts (including drinkable yogurts).[1] The notice informs us of Pharmanutra's view that the use of CFA is GRAS through scientific procedures.

Our use of the terms "cetylated fatty acids" or "CFA" in this letter is not our recommendation of these terms as appropriate common or usual names 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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual names for "cetylated fatty acids" or "CFA."

Pharmanutra describes CFA as a beige to light yellow solid (waxy flakes at 25 °C). CFA is a mixture consisting of esters of fatty acids with cetyl alcohol (primarily cetyl myristate and cetyl oleate), and refined olive oil.

[1] Pharmanutra states that CFA is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

Pharmanutra provides a description of the manufacturing method for CFA. Cetyl esters are synthesized by mixing cetyl alcohol (1-hexadecanol) with myristic acid or oleic acid at 60 °C. The mixture is placed under vacuum and a zinc catalyst is added. Cetyl myristate and cetyl oleate are then mixed, heated and reacted in an inert environment. After the reaction is completed, the mixture of cetyl esters is cooled, subjected to decolorization and filtration, and mixed with olive oil (75:25). The resulting mixture is subjected to deodorization and the antioxidant *tert*-butylhydroquinone (TBHQ) is added to yield the final CFA product. Pharmanutra states that CFA is manufactured in accordance with current good manufacturing practices and that all raw materials and processing aids are food grade.

Pharmanutra provides specifications for CFA including ester content (70-80%), primarily cetyl oleate (22-30%) and cetyl myristate (41-56%), limits for acid value (≤5 mg KOH/g), iodine value (30-50 g I_2/100 g), hydroxyl value (≤20 mg KOH/g), saponification value (130-150 mg KOH/g), TBHQ (≤0.02 %), aluminum (≤2 mg/kg), arsenic (<0.1 mg/kg), lead (<0.1 mg/kg), and limits for microorganisms. Pharmanutra provides the results from the analyses of five non-consecutive batches to demonstrate that CFA can be manufactured to meet the specifications. Pharmanutra states that CFA is stable for at least 18 months when stored at 25±2°C and for at least 9 months when stored at 40±2°C.

Pharmanutra estimates the eaters-only dietary exposure for CFAs from the intended uses to be 423 mg/person (p)/day (d) (7 mg/kg body weight (bw)/d) at the mean and 959 mg/p/d (16 mg/kg bw/d) at the 90th percentile, respectively, for the U.S. population aged 2 years and older using food consumption data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES). Further, Pharmanutra estimates the dietary exposure to the primary saturated fatty acids (myristic acid and palmitic acid) in CFA based on the dietary exposure estimates for CFA from the intended food uses and the fatty acid composition of CFA. For the U.S. population 2 years and older, the estimated mean and 90th percentile eaters-only dietary exposures are 173 and 393 mg/p/d for myristic acid, respectively, and 14 and 31 mg/p/d for palmitic acid, respectively. Pharmanutra notes that even the highest estimated 90th percentile dietary exposures to saturated fatty acids from the intended uses of CFA are well below the daily reference value of 20 g/d for saturated fatty acids established by the FDA.[2]

Pharmanutra discusses absorption, distribution, metabolism and excretion of CFA and states that CFA are mostly hydrolyzed to cetyl alcohol and fatty acid moieties, which are metabolized and/or excreted by well-known and characterized pathways. Pharmanutra states that the pivotal data to support the safety of CFA under the intended use are from published product-specific toxicology studies performed under OECD guidelines, including a rat 90-day repeated dose oral toxicity study and *in vitro* genotoxicity studies. Pharmanutra states that these studies demonstrated that their CFA showed no genotoxicity concerns and were generally well tolerated with no toxicologically relevant

[2] FDA has established a daily reference value of 78 g/day for total fat and 20 g/day for saturated fat (21 CFR 101.9).

adverse effects up to the highest dose tested. Pharmanutra also discusses safety evaluations of fatty acids and cetyl alcohol by a number of regulatory and authoritative bodies which support their GRAS conclusion. Pharmanutra states that their search through publicly available databases found no information that would be considered counter to their GRAS conclusion.

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

Based on the totality of the data and information, Pharmanutra concludes that CFA is GRAS for its intended use.

Standards of Identity

In the notice, Pharmanutra states its intention to use CFA in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (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 CFA 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 in CFSAN. 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.

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

Conclusions

Based on the information that Pharmanutra provided, as well as other information available to FDA, we have no questions at this time regarding Pharmanutra's conclusion that CFA is GRAS under its intended conditions of use. This letter is not an affirmation that CFA 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 001043 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.10.26 14:03:10 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition