Agency Response Letter GRAS Notice No. GRN 000371

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CFSAN/Office of Food Additive Safety

July 22, 2011

Madhu G. Soni, Ph.D
Soni and Associates, Inc.
749 46th Square
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 000371

Dear Dr. Soni:

The Food and Drug Administration (FDA) is responding to the notice, dated December 14, 2010, that you submitted on behalf of Aker Biomarine Antarctic AS (Aker Biomarine) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on December 16, 2010, filed it on February 7, 2011, and designated it as GRAS Notice No. GRN 000371.

The subject of the notice is krill oil.(1) The notice informs FDA of the view of Aker Biomarine that krill oil is GRAS, through scientific procedures, for use as a food ingredient in non-alcoholic beverages, breakfast cereals, cheeses, frozen dairy desserts, whole and skim milk, processed fruit and fruit juices, and medical foods at use levels ranging from 0.05 to 0.5 grams (g) per serving.

As part of its notice, Aker Biomarine includes the report of a panel of individuals (Aker Biomarine's GRAS panel) who evaluated the data and information that are the basis for Aker Biomarine's GRAS determination. Aker Biomarine considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Aker Biomarine's GRAS panel discusses identity, specifications, method of manufacture, dietary exposure and safety, and concluded that krill oil is GRAS under the intended conditions of use.

The notifier states that krill oil is manufactured in accordance with current good manufacturing practices and meets appropriate food grade specifications. The marine organism known as krill (*Euphasia superba*) is first cooked and dried. The oil is extracted from the resultant krill meal using food grade ethanol, and the ethanol-oil solution is concentrated by evaporation and clarified by centrifugation. The ethanol is then evaporated from the oil solution. The major components of krill oil are triglycerides and phospholipids, which include esters of the fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The notifier provides product specifications for krill oil, including levels of fatty acids, total phospholipids, and astaxanthin. Specifications also include limits for lead (< 0.10 mg/kg), mercury (< 0.05 mg/kg), arsenic (< 0.05 mg/kg), residual ethanol (< 3.0 %), and *trans*-fatty acids (< 0.3%).

Aker Biomarine calculates an estimated daily intake (EDI) of krill oil using food consumption data from the 1994-1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII) and intended use levels in their notice. Aker Biomarine states that average EDI calculations were doubled to approximate 90th percentile EDIs. Aker Biomarine reports an average EDI of 4.1 g per person per day (g/p/d) and an approximated 90th percentile EDI of 8.3 g/p/d. Aker Biomarine calculates that, based on the 90th percentile EDI for krill oil, the combined maximum EDI for EPA and DHA would be 1.95 g/p/d. Aker Biomarine states that use of krill oil in medical foods would be meal replacements for patients whose diets would consist solely of these foods for 3 meals per day. Total krill oil consumption in these patients would be 0.90 to 1.50 g/p/d.

Aker Biomarine discusses FDA's recommendations regarding safe levels of exposure to EPA and DHA, noting that krill oil is intended as a substitute for fish oil. Consequently, dietary intake of total EPA and DHA from krill oil will be substitutional and not additive to that ingested from fish oil. Aker Biomarine states that the daily intake of EPA and DHA estimated from krill oil does not exceed 3 g/p/d set for EPA and DHA for menhaden oil in 21 CFR 184.1472.(2)

In its discussion of the safety of krill oil, Aker Biomarine provides a compositional comparison between krill oil and other marine-derived oils in the marketplace, including menhaden oil and tuna oil. Aker Biomarine concludes that the composition of krill oil is similar to other marine oils commonly consumed.

Aker Biomarine summarizes the results of published and unpublished human and rodent data from GRN 000242, in addition to considering more recently published human data which further support the safe use of krill oil under the intended conditions of use. Aker Biomarine also provides a discussion of the evidence supporting the safety of the krill oil components astaxanthin and the *trans*-fatty acid, vaccenic acid, concluding that the presence of these substances does not affect the safety of krill oil at their current concentrations in the final product.

Allergen Labeling

The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to require that the label of a food that is or contains an ingredient that bears or contains a "major food allergen" declare the presence of the allergen (section 403(w)). FALCPA 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. Issues associated with labeling food are the responsibility of the Center for Food Safety and Applied Nutrition's Office of Nutritional Products, Labeling, and Dietary Supplements.

Standards of Identity

In the notice, Aker Biomarine states its intention to use krill oil in several food categories, including foods for which standards of identity exist located in Title 21 of the Code of Federal Regulations (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 Requirement for a Color Additive Petition

In its notice, Aker Biomarine describes krill oil as a dark red-colored viscous oil. As such, the use of krill oil in food products may constitute the use of a color additive under section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food; except that such term does not include any material which the Secretary,(3) by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempt from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Given the construct of section 201(t)(1) of the FFDCA and 21 CFR 70.3(f) and (g), the use of a substance that is capable of imparting color may constitute use as a color additive in addition to use as a food additive or GRAS substance. For example, β-carotene is both approved for use as a color additive (21 CFR 73.95) and affirmed as GRAS for use as a nutrient supplement (21 CFR 184.1245); in some food products, β-carotene is used for both purposes. Importantly, if the use of krill oil constitutes use as a color additive within the meaning of section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR 70.3(f) and (g), section 721(a) of the FFDCA requires premarket review and approval of that use by FDA. Under section 402(c) of the FFDCA, a food product that contains an unapproved color additive would be deemed adulterated.(4)

In its notice, Aker Biomarine states that use of krill oil in foods is not intended to function as a color additive as defined in 21 CRF 70.3(f). Aker Biomarine further states that the addition of its krill oil to the various food products occurs at a level low enough to be consistent with the "non-apparent color" exemption 21 CFR 70.3 (f); the intended use of krill oil as a nutrient would contribute a color in a manner consistent with the "unimportant color" exemption addressed in 21 CFR 70.3 (g); and, the intended use of krill oil does not relate to any use of the ingredient as a color additive (21 CFR 70.3 (f)). In its review of Aker Biomarine's notice that the ingredient krill oil is GRAS for the intended uses, FDA did not consider whether section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR Part 70 apply to the use of krill oil in foods. Accordingly, this response should not be construed to be a statement that the use of krill oil in foods is lawful under section 721(a). If, after receipt of this letter, Aker Biomarine has any further questions about this issue, we recommend that Aker Biomarine contact the Office of Food Additive Safety.

Medical Foods

In its notice, Aker Biomarine informs FDA that one intended use of krill oil is in medical foods. Section 5(b) of the Orphan Drug Act (ODA) defines a medical food as a food that is formulated to be consumed or administered enterally under the supervision of a physician and that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Section 403(q) of the FFDCA lays out the statutory framework for nutrition labeling of food products. Section 403(r) of the FFDCA lays out the statutory framework for health claims and nutrient content claims. Under section 403(q)(5)(A)(iv) of the FFDCA and FDA's implementing regulations in 21 CFR 101.9(j)(8), the requirements for nutrition labeling do not apply to medical foods as defined in section 5(b) of the ODA. Under

section 403(r)(5)(A) of the FFDCA and FDA's implementing regulations in 21 CFR 101.13(q)(4)(ii) and 21 CFR 101.14(f)(2), the requirements for nutrient content claims and health claims, respectively, do not apply to medical foods as defined in section 5(b) of the ODA. For your information, FDA's response to Aker Marine's notice that krill oil is GRAS for use in medical foods does not address the question of whether any particular food product that contains krill oil as an ingredient would be a medical food within the meaning of section 5(b) of the ODA and, thus, would be exempt from the requirements for nutrition labeling, nutrient content claims, and health claims.

Section 301(ll) of the FFDCA

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, 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 its review of Aker Marine's notice that the ingredient krill oil is GRAS for the intended uses, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing krill oil. Accordingly, this response should not be construed to be a statement that foods that contain krill oil if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Aker Biomarine, as well as other information available to FDA, the agency has no questions at this time regarding Acker Biomarine's conclusion that krill oil is safe under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of krill oil. As always, it is the continuing responsibility of Aker Biomarine to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000371, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov/grasnoticeinventory.

Sincerely,

Mitchell A. Cheeseman, Ph.D.
Acting Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

(1)FDA notes that krill oil was the subject of GRN 000242 for the same uses. The primary difference between the subjects of these notices is that the solvents used in manufacturing the oil were acetone and ethanol for GRN 000242 and GRN 000371, respectively.

(2)FDA has affirmed the GRAS status of menhaden oil for use as a direct food ingredient (21 CFR 184.1472) provided that the combined intake of EPA and DHA from consumption of menhaden oil does not exceed 3 g/p/d. FDA had raised concerns about the consumption of high levels of EPA and DHA and possible adverse effects of consumption on bleeding time, glycemic control, and low-density lipoprotein cholesterol levels (62 FR 30751 at 30757; June 5, 1997). FDA subsequently revised the menhaden oil rule to reallocate the uses of menhaden oil in

conventional food, while maintaining the 3 g/p/d limit on EPA and DHA, and to require that menhaden oil not be used as an ingredient in foods in combination with another added oil that is a significant source of EPA and DHA (70 FR 14530; March 23, 2005).

(3)The Secretary of the Department of Health and Human Services.

(4)We note that section 721(b)(4) of the FFDCA provides that a color additive shall be deemed to be safe and suitable for the purpose of listing under section 721(b) of the FFDCA while there is in effect a published finding of the Secretary declaring that the substance is exempt from the definition of "food additive" because of its being generally recognized by qualified experts as safe for its intended use as provided in section 201(s) of the FFDCA. Importantly, FDA's response to GRN 000371 does not constitute a "finding of the Secretary" within the meaning of section 721(b)(4) of the FFDCA.

More in GRAS Notice Inventory (/7993/20171031011218/https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm)