



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

Re: GRAS Notice No. GRN 000661

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000661. We received the notice, dated August 1, 2016, that you submitted on behalf of Marina Pty. Ltd., Australia (Marinova), 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) on August 8, 2016, and filed it on August 19, 2016. We received an amendment containing clarifying information on October 27, 2016.

FDA published the GRAS final rule on August 17, 2016 (81 FR 54960), with an effective date of October 17, 2016. As GRN 000661 was pending on the effective date of the GRAS final rule, we requested some additional information consistent with the format and requirements of the final rule. We received an amendment responding to this request on October 28, 2016.

The subject of the notice is fucoidan concentrate (fucoidan) from *Fucus vesiculosus*. The notice informs FDA of the view of Marina that fucoidan from *F. vesiculosus* is GRAS, through scientific procedures, for use as an ingredient in food categories such as baked goods, soups, snack foods, imitation dairy products, and seasons and flavorings at levels up to 30 milligrams (mg) per serving.¹

Marinova provides information on the identity and composition of fucoidan. Marina describes fucoidan (CAS registry numbers: 9072-19-9 and 84696-13-9) as an L-fucose polysaccharide containing sulfate ester groups. Fucoidan is an off-white to brown powder.

Marinova describes the manufacturing process for fucoidan. Marina extracts fucoidan from wild-grown brown seaweed. During harvest, the seaweed is inspected and foreign body contamination, including arthropods and mollusks, is removed. The seaweed is then dried, milled, and suspended in slightly acidic water. The suspension is agitated and subjected to membrane filtration to remove the solids. The pH of the filtrate is adjusted to approximately 5 and then filtered through a membrane again to remove salts. The secondary filtrate is dried and milled to produce powdered fucoidan. Marina states that food-grade processing aids are used throughout the manufacturing process.

Marinova provides specifications for fucoidan. These specifications include fucoidan content ($\geq 70\%$) and limits on inorganic arsenic (≤ 1 mg/kilogram (kg)), total arsenic (≤ 10 mg/kg), cadmium (≤ 3 mg/kg), lead (≤ 1 mg/kg), mercury (≤ 1 mg/kg), and microbial contaminants. The remaining product consists of alginate, polyphloroglucinol, mannitol, and other carbohydrates

¹ Marina states that the intended uses of fucoidan exclude infant formulas, foods formulated for infants and toddlers, and meat and poultry products.

naturally present in kelp. Marinova demonstrates conformance with these specifications by analyzing five non-consecutive batches of fucoidan.

Marinova estimates the dietary exposure to fucoidan using the data from the U.S. Department of Agriculture's (USDA) Continuing Survey of Food Intake by Individuals (CSFII) database. The estimated dietary exposure per capita is 135 mg/day at the mean and 250 mg/day (4.17 mg/kg bodyweight (bw)/day for a 60 kg person) at the 90th percentile. Marinova states that the intended uses of fucoidan from *F. vesiculosus* are substitutional to those of fucoidan from *Undaria pinnatifida* as described in GRN 000565 and will not lead to an overall increase in exposure.²

Marinova discusses published, publicly available information through May 2016 supporting the safety of fucoidan. Marinova states that many seaweed species have a long history of safe consumption in Asia. Marinova discusses information from studies for fucoidan from *F. vesiculosus* and studies of fucoidan from other sources.

Marinova discusses one 6-month, one 3-month, and two 28-day oral repeat dose toxicity studies conducted in rats using fucoidan from sources other than *F. vesiculosus* in support of its safety determination. Marinova reports that in the 6-month study of fucoidan from *Laminaria japonica*, no significant toxicological changes were observed at a level of 300 mg/kg bw/day. In studies of fucoidan from *U. pinnatifida*, no significant toxicological changes were observed in the 3-month study at 600 mg/kg bw/day or in the 28-day studies at 1,350 mg/kg bw/day and 1,000 mg/kg bw/day.

Human clinical studies showed no toxicity of fucoidan from a mixture of *F. vesiculosus* (85%), *Macrocystis pyrifera* (10%), and *L. japonica* (5%) at a level of 1 gram (g)/day for up to 3 months or of fucoidan from *U. pinnatifida* at a level of 3 g/day for 12 days. In addition, Marinova concludes from published reports that fucoidan is not genotoxic based on negative Ames, *in vitro* chromosomal aberration, and *in vivo* micronucleus assays.

Marinova discusses a potential safety issue arising from the anticoagulant activity of fucoidan from *F. vesiculosus*, as well as *U. pinnatifida*, *L. japonica*, *Cladosiphon okamuranus*, and *Lessonia vadosa*, and its relevance to Marinova's food safety assessment. First, Marinova states that the lowest oral dose that induced prolongation of clotting time in rats is more than 200-fold greater than the dietary exposure. Second, Marinova describes a study in humans showing that less than 1% of ingested fucoidan is absorbed into the bloodstream. Marinova concludes that considering the totality of the evidence, the reports of anticoagulant activity are not a concern for their intended food uses.

Based on the history of safe consumption of seaweed and seaweed products, the studies discussed above, and the reported minimal digestibility and absorption of fucoidan, Marinova concludes that the intended use of fucoidan from *F. vesiculosus* is GRAS.

Marinova includes the statement of a panel of individuals (Marinova's GRAS panel). Based on its review, Marinova's GRAS panel concludes that fucoidan from *F. vesiculosus* is safe under the conditions of its intended use.

² GRN 000565 describes the uses of fucoidan from *U. pinnatifida* as an ingredient in baked goods, soups, snack foods, imitation dairy products, and seasonings/flavors at levels up to 30 mg/erving, excluding use in infant formula and products under U.S.D.A. jurisdiction. We evaluated this notice and responded in a letter on July 2, 2015 stating that we had no questions at that time regarding Marinova's GRAS determination.

Standards of Identity

In the notice, Marinova states its intention to use fucoidan from *F. vesiculosus* in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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 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, Marinova cites human studies that were conducted to demonstrate beneficial effects of fucoidans from various seaweed species for various indications. If products containing fucoidan from *F. vesiculosus* 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Marinova describes fucoidan from *F. vesiculosus* as off-white to brown. As such, the use of fucoidan from *F. vesiculosus* 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 000661 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.

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 Marinova's notice concluding that fucoidan from *F. vesiculosus* 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 fucoidan from *F. vesiculosus*. Accordingly, our response should not be construed to be a statement that foods containing fucoidan from *F. vesiculosus*, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Marinova provided, as well as other information available to FDA, we have no questions at this time regarding Marinova's conclusion that fucoidan from *F. vesiculosus* is GRAS under its intended conditions of use. This letter is not an affirmation that fucoidan from *F. vesiculosus* 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 GRN000661 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

Digitally signed by Michael A. Adams -S
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