Andrey I. Nikiforov, Ph.D.
Toxicology Regulatory Services, Inc.
154 Hansen Road, Suite 201
Charlottesville, VA 22911

Re: GRAS Notice No. GRN 000740

Dear Dr. Nikiforov:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000740. We received the notice you submitted on behalf of IMD Natural Solutions GmbH (IMD) on October 30, 2017, and filed it on November 27, 2017.

The subject of the notice is long-chain glycolipids from *Dacryopinax spathularia* (glycolipids preparation) for use as an antimicrobial agent in select non-alcoholic beverages at use levels ranging from 2 to 100 mg/kg. The notice informs us of IMD's view that this use of glycolipids preparation is GRAS through scientific procedures.

Our use of the term "glycolipids preparation" 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 section 101.4 in Title 21 of the Code of Federal Regulations (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 non-standardized 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 "glycolipids preparation."

IMD provides information about the identity and composition of glycolipids preparation. IMD describes this preparation as a glycolipid mixture that is a white to ivory colored, water-soluble powder. IMD states that glycolipids preparation consists of three structurally-related glycolipid congeners containing a saturated C26 fatty acid and the glucopyranosyl-(1→2)-xylopyranosyl-(1→2)-xylopyranosyl trisaccharide moiety, and provides structure diagrams for the main components. The remaining components are congeners of the major components differing in the acylation pattern.

IMD provides information about the manufacturing process for glycolipids preparation. This preparation is obtained *via* fermentation of glucose by the edible[1] jelly fungus *D.*

[1] IMD cites a 2004 Food and Agriculture Organization publication titled, "Wild edible fungi: A global overview of their use and importance to people" which lists *D. spathularia* as edible.

*spathularia*. IMD states that *D. spathularia* is grown in a batch-fed fermentation process in a medium containing glucose and yeast extract. Fermentation is controlled at constant temperature until a maximum titer of glycolipids is reached. The feed is then stopped and the cells are further cultivated until no free glucose remains in the culture medium. The fungal cells are quantitatively removed by microfiltration, followed by acid precipitation of the glycolipids. The precipitate is washed with water and neutralized using sodium hydroxide and spray- or freeze-dried. IMD confirms that no viable fungal cells remain in the final powder by fungal cell count and microscopic examination. IMD states that all nutrients and solutions for pH adjustment are food-grade. Additionally, IMD states that organic solvents are not used during the production of glycolipids preparation, and the glycolipids are not chemically modified. IMD states that the production process follows current good manufacturing practices, including a Hazard Analysis and Risk-based Preventive Controls plan as demanded by the FDA Food Safety Modernization Act.

IMD provides specifications for glycolipids preparation that include total glycolipids content of ≥ 93% (dry weight basis, calculated as sodium salt). The remaining ≤ 7% of dry weight is comprised of protein, fat, and sodium chloride. Additionally, IMD provides limits for arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), mercury (< 1 mg/kg), nickel (< 2 mg/kg), lead (< 2 mg/kg), and microorganisms. IMD supplies batch analyses for three non-consecutive lots of glycolipids preparation to demonstrate that it can be manufactured to conform to the specifications. IMD presents studies showing that the product is stable for at least three years when stored as a dry powder. IMD states that glycolipids preparation is stable in aqueous solution at room temperature for at least six months.

IMD states that glycolipids preparation is intended for addition to non-alcoholic beverages as an antimicrobial agent used to prevent growth of microorganisms and subsequent spoilage. IMD states that glycolipids preparation has a primary antifungal effect against certain yeasts and molds. IMD notes that glycolipids preparation also has antimicrobial activity against Gram-positive bacteria (including spoilage organisms such as *Bacillus cereus* or *Listeria* spp.) and weak or no antimicrobial activity against Gram-negative bacteria. IMD provides data on glycolipids preparation's antimicrobial efficacy in a variety of beverages. IMD provides Minimum Inhibitory Concentrations (MIC) determined for glycolipids preparation against *Aspergillus niger* in Sabouraud Dextrose Broth (SDB) medium (pH 5.6; 3.1 mg/L) or clear apple juice medium (pH 3.3; 7.8 mg/L) and compared them to MICs of 250 mg/L (in SDB medium) or ≥1000 mg/L (in apple juice medium) for sorbic acid and benzoic acid, respectively.

IMD intends to use glycolipids preparation in the following drink categories: carbonated soft drinks, fruit drinks, sports drinks, energy drinks, enhanced waters, ready-to-drink tea, and juice. IMD states that the estimated dietary exposure of glycolipids preparation was calculated based on maximum use levels ranging from 25 – 100 mg/kg. IMD estimates that total exposure for glycolipids preparation from all intended uses, assuming the maximum intended use level for each beverage category, is 0.5 mg/kg body weight (bw)/day (d) at the mean and 1 mg/kg bw/d at the 90th percentile of intake among users in the total U.S. population (equivalent to 29 mg/d and 59 mg/d,

respectively). Furthermore, IMD states that glycolipids preparation would become self-limiting due to its viscosity and possible effect on organoleptic properties of intended beverage categories at levels higher than those specified in the notice (i.e., 2 – 100 mg/kg).

IMD provides information on the safety of consumption of glycolipids preparation using three published studies: one study on the absorption, distribution, metabolism, and excretion (ADME) in Sprague Dawley (SD) rats, and one 90-day toxicity study each in SD rats and beagle dogs. Based on the published ADME study in rats, IMD concludes that glycolipids preparation and its metabolites, produced in the GI tract, are poorly absorbed by the oral route and are primarily eliminated in the feces. Based on the published 90-day study in rats in which glycolipids preparation was supplied through drinking water, IMD concludes that up to 1,201 and 1,423 mg/kg bw/d of glycolipids preparation, the highest dose tested in male and female rats, respectively, did not produce treatment-related adverse effects. IMD attributed a decrease in drinking water consumption in male and female rats at the high dose groups to the decreased palatability of the drinking water containing high concentration of glycolipids preparation, which has increased viscosity and surfactant qualities. From the published 90-day study in dogs in which glycolipids preparation was supplied through capsules, IMD concludes that up to 1,000 mg/kg bw/d of glycolipids preparation, the highest dose tested, did not produce treatment-related adverse effects. IMD attributed a statistically significant reduction in cumulative body weight gains in a few study week intervals in the high-dose group of female dogs to a reduction in food consumption. A reduction in food consumption in the same group of females, although not statistically significant, was noticed for most weeks of administration. IMD considers that the surfactant nature of the high concentrations of glycolipids preparation released in the stomach from the capsules led to the suppression of appetite.

In the notice, IMD provides details from unpublished studies, which IMD concludes corroborates the safety of glycolipids preparation. These are *in vitro* mutagenicity and genotoxicity studies, and reproductive and developmental toxicity studies.

IMD includes the report of a panel of individuals (IMD's GRAS panel). Based on its review, IMD's GRAS panel concluded that glycolipids preparation is safe under the conditions of its intended use.

Based on all the available scientific information, IMD concludes that glycolipids preparation is GRAS for its intended use in select non-alcoholic beverages.

**Standards of Identity**

In the notice, IMD states its intention to use glycolipids preparation in several food categories, including foods for which standards of identity exist, located in 21 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.

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

**Conclusions**

Based on the information that IMD provided, as well as other information available to FDA, we have no questions at this time regarding IMD's conclusion that glycolipids preparation is GRAS under its intended conditions of use. This letter is not an affirmation that glycolipids preparation 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 000740 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2018.05.17 11:27:15 -04'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition