Varuzhan H. Abelyan, Sc.D.
Chief of Science & Technology
Haigen-BGG Natural Ingredients Limited
11038, 11/F, Tower A
Gateway Square No. 18
Xiaguangli, North Road East Third Ring
Chaoyang District, Beijing
CHINA

Re: GRAS Notice No. GRN 000821

Dear Dr. Abelyan:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000821. We received Haigen-BGG Natural Ingredients Limited (HBNI)'s notice on November 19, 2018, and filed it on January 29, 2019. HBNI submitted an amendment to the notice on March 7, 2019, that specified the date of the updated literature review and clarified information provided in a table of the notice.

The subject of the notice is enzyme modified steviol glycosides (EMSG) obtained by enzyme treatment of steviol glycosides (SGs) purified from the leaves of stevia (*Stevia rebaudiana* (Bertoni) Bertoni) for use as a general purpose sweetener in foods, excluding infant formula and meat and poultry products, at levels determined by current good manufacturing practices, as well as use as a table top sweetener. The notice informs us of HBNI's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000821 is made from a highly purified component of the leaves of the stevia plant. As such, FDA notes that a GRAS notice for the use of a specific purified component of stevia, such as EMSG, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of "EMSG," "steviol glycosides," or "SGs" in this letter is not our recommendation of these terms 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 "EMSG".

HBNI provides information about the identity and composition of EMSG. HBNI describes EMSG as a white to off-white powder that contains ≥ 95% total SGs that include glucosylated SGs and unreacted SGs. The glucosylated SGs are generated by the treatment of a SGs extract preparation that contains a minimum of 95% total SGs with a source of glucose and food-grade cyclomaltodextrin glucanotransferase and food-grade α -amylase. [1] The reaction results in the formation of glucosylated forms of the starting SGs. HBNI describes five formulations of EMSG that result from the use of SGs extract preparations with different initial compositions (i.e., ≥ 95% rebaudioside D, > 90% stevioside, ≥ 95% rebaudioside A, ≥ 50% rebaudioside A, or < 30% rebaudioside A).

HBNI describes the method of manufacture of EMSG. *S. rebaudiana* leaves are extracted in hot water, and the extract is then filtered, treated with calcium hydroxide, and filtered to remove precipitates. The filtrate is deionized and subjected to an adsorption resin that retains SGs. The SGs are eluted from the resin with ethanol. The resulting solution is decolorized with activated carbon, filtered, and spray dried. The dried product is recrystallized, and the crystals are collected and dried. HBNI states that the crystallized product contains a minimum of 95% SGs. This product is reacted with tapioca starch that is treated with cyclomaltodextrin glucanotransferase and α-amylase.[1] After the reaction is complete, the enzymes are inactivated by heat treatment. The reaction mixture is treated with activated carbon, filtered, and subjected to an adsorption resin. The resin is washed with deionized water, and the SGs are eluted with ethanol. The resulting solution is treated with activated carbon, filtered, concentrated, and then spray dried to obtain the final EMSG product. HBNI states that all materials, processing aids, and equipment used in the manufacture of EMSG are food-grade.

HBNI provides specifications for EMSG that include a minimum of 95% total SGs and 80% glucosylated SGs. Specifications also include limits for moisture (≤ 6%), ash (< 1%), lead (< 1 mg/kg), arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), mercury (< 1 mg/kg), methanol (< 0.02%), ethanol (< 0.3%), as well as limits for microorganisms. HBNI provides results of three, non-consecutive batch analyses for each of the five formulations to demonstrate that EMSG can be produced in accordance with these specifications.

HBNI provides estimates of dietary exposure to EMSG. HBNI discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1 and a relative sweetness intensity as low as 120 times that of sucrose, HBNI estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.61 mg/kg body weight (bw)/day (d) and in children to be 1.78 mg/kg bw/d. HBNI states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

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[1] HBNI states that cyclomaltodextrin glucanotransferase and α-amylase are derived from nontoxigenic/nonpathogenic strains of *Bacillus licheniformis* and *Bacillus subtilis*, respectively.

HBNI summarizes published studies pertaining to the metabolic fate and safety of SGs. HBNI concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. HBNI discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies; published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A as well as in vitro and in vivo mutagenicity/genotoxicity studies for the safety conclusion of EMSG. HBNI includes an update of the literature regarding the safety of SGs through November 2018 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that EMSG is GRAS for the intended use, HBNI summarizes the decisions on the safety of SGs by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. HBNI notes that JECFA has established an acceptable daily intake (ADI) for SGs of 0-4 mg/kg bw/d (expressed as steviol equivalents). This ADI was based on a no observed adverse effect level of 970 mg/kg bw/d (383 mg/kg bw/d, as steviol equivalents) from a two-year rat study, and the application of a safety factor of 100 to account for intra- and inter-species differences.

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

Based on all the available scientific information, HBNI concludes that EMSG is GRAS for its intended use in foods.

Standards of Identity

In the notice, HBNI states its intention to use EMSG 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.

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 its review of HBNI's notice that EMSG is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing EMSG. Accordingly, this response should not be construed to be a statement that foods that contain EMSG, if introduced or delivered for introduction

into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that HBNI provided, as well as other information available to FDA, we have no questions at this time regarding HBNI's conclusion that EMSG is GRAS under its intended conditions of use. This letter is not an affirmation that EMSG 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 000821 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2019.05.07 13:41:56 -04'00'

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

Reference

1. Renwick, A.G. 2008. The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A. Food and Chemical Toxicology 46:S61–S69.