William J. Rowe
President
GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134

Re: GRAS Notice No. GRN 000838

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000838. We received the notice that you submitted on behalf of Jiang Su Svetia Biotechnology Co., Ltd. (Svetia) on January 29, 2019, and filed it on March 20, 2019.

The subject of the notice is enzyme-modified steviol glycosides (EMSG) 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. The notice informs us of Svetia's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000838 is made from highly purified components of the leaves of the stevia plant. We note that a GRAS notice for the use of specific purified components of stevia, such as EMSG, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "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."

Svetia provides information about the identity and composition of EMSG. Svetia describes EMSG as a white powder that contains ≥ 95% (on a dried weight basis) total SGs. SGs are a group of structurally-related sweet compounds that are constituents of

Stevia rebaudiana (stevia) leaves and consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose. EMSG is produced by the treatment of a stevia extract preparation that contains a minimum of 95% total SGs with a source of glucose and food-grade glucosyltransferase.[1] The reaction results in the formation of glucosylated forms of the starting SGs. The principal SGs in the resulting EMSG product include rebaudiosides A, D, and M, and stevioside.

Svetia describes the method of manufacture of EMSG. The starting material used in the production of EMSG is a stevia leaf extract, containing ≥95% SGs, that is the subject of GRN 000367[2] and is prepared by extraction of stevia leaves with water and multiple purification steps. Svetia states that the recombinant *B. subtilis* strain expressing a glucosyltransferase enzyme is grown in culture and the enzyme is secreted into the culture supernatant. The supernatant is filtered to remove *B. subtilis* cells and water-insoluble components, and then subjected to ultrafiltration to remove small molecules, such as salts, sugars, amino acids, and peptides. The resulting enzyme preparation is fed into a tank containing the stevia extract and a glucose source (i.e., maltodextrin), and the reaction is allowed to proceed. The reaction is inactivated by heat treatment and the supernatant is then separated from the mixture. The supernatant is filtered through diatomaceous earth and activated carbon, and then subjected to ultrafiltration. The filtrate is concentrated by evaporation under vacuum to precipitate SG crystals. The SG crystals are dissolved in ethanol, recrystallized, separated, and dried to obtain the final EMSG product. Svetia notes that all materials, processing aids, and ingredients used to manufacture EMSG are food-grade and meet applicable U.S. regulations or are GRAS for their respective uses.

Svetia provides specifications for EMSG that include the content of total SGs (≥ 95%).[3] Specifications also include limits for moisture (≤ 5%), ash (≤ 1%), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), methanol (≤ 0.02%), ethanol (≤ 0.5%), as well as limits for microorganisms. Svetia provides results from five, non-consecutive batch analyses to demonstrate that EMSG can be produced to meet these specifications.

Svetia provides estimates of dietary exposure to EMSG. Svetia 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 of 200 times that of sucrose, Svetia estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.28 mg/kg body weight (bw)/day (d) and in children to be 1.41 mg/kg bw/d. Svetia states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

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[1] Svetia states that the glucosyltransferase is obtained from a gram-positive, nonpathogenic, and nontoxigenic strain of *Bacillus subtilis* engineered to overexpress uridine 5′-diphospho-glucosyltransferase.

[2] FDA evaluated GRN 000367 and responded to this notice in a letter dated July 8, 2011, stating that the agency had no questions at that time regarding the notifier's GRAS conclusion.

[3] Svetia specifies that the composition of the total SGs in EMSG include rebaudiosides A, B, C, D, E, F, M, and U, stevioside, steviolbioside, and dulcoside A.

Svetia summarizes published studies pertaining to the metabolic fate and safety of SGs. Svetia concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. Svetia discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies, published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A, and *in vitro* and *in vivo* mutagenicity/genotoxicity studies. Svetia 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, Svetia 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. Svetia 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.

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

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

Standards of Identity

In the notice, Svetia 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 Svetia'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 Svetia provided, as well as other information available to FDA, we have no questions at this time regarding Svetia'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 000838 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.07.12 16:37:36 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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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.