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

Re: GRAS Notice No. GRN 000878

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000878. We received the notice that you submitted on behalf of Daepyung Co., Ltd (Daepyung) on July 30, 2019 and filed it on August 28, 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 Daepyung's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000878 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," and "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."

Daepyung provides information about the identity and composition of EMSG. Daepyung describes two formulations of EMSG that are white powders containing either 80-90% or 85-95% (on a dried weight basis) total steviol glycosides (SGs) and up to 20%

maltodextrin. 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 leaf extract preparation that contains a minimum of 95% total SGs with a source of glucose (i.e. maltodextrin) and food-grade cyclomaltodextrin glucanotransferase (CGTase).[1] The reaction results in the formation of glucosylated forms of the starting SGs. Daepyung states that the two EMSG formulations contain ≥65 or ≥70% glucosylated SGs.

Daepyung describes the method of manufacture of EMSG. The starting material used in the production of EMSG is a stevia leaf extract, containing ≥95% total SGs and ≥85% rebaudioside A, that is prepared by extraction of stevia leaves and multiple purification steps. The stevia extract is combined with maltodextrin and CGTase and the reaction allowed to proceed. The reaction mixture is heated to deactivate the enzyme and then subjected to an adsorption resin to retain SGs. The SGs are eluted from the resin with ethanol, and the resulting solution is concentrated, filtered through diatomaceous earth, sterilized by ultra-high temperature treatment, and then spray dried to obtain the final EMSG product. Daepyung 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.

Daepyung provides specifications for two formulations of EMSG that include the content of total SGs (80-90% or 85-95%) and content of glycosylated SGs (≥ 65% or ≥ 70%). Specifications for both formulations also include limits for moisture (≤ 6%), ash (≤ 1%), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), methanol (≤ 200 mg/kg), ethanol (≤ 5000 mg/kg), as well as limits for microorganisms. Daepyung provides results of five, non-consecutive batch analyses for each formulation to demonstrate that EMSG can be produced to meet these specifications.

Daepyung provides estimates of dietary exposure to EMSG. Daepyung 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 100 to 110 times that of sucrose, Daepyung estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 3.46 mg/kg body weight (bw)/day (d) and in children to be 3.82 mg/kg bw/d. Daepyung states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

Daepyung summarizes published studies pertaining to the metabolic fate and safety of SGs. Daepyung concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. Daepyung 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

[1] Daepyung states that the CGTase used in the manufacture of EMSG is a food grade enzyme produced by submerged fermentation of a genetically engineered stain of *Bacillus licheniformis*.

studies for the safety conclusion of EMSG. Daepyung includes an update of the literature regarding the safety of SGs through May 2019 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, Daepyung 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. Daepyung 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.

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

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

Standards of Identity

In the notice, Daepyung state 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 Daepyung'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 Daepyung provided, as well as other information available to FDA, we have no questions at this time regarding Daepyung'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 000878 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.12.09 14:59:00 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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.