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

Re: GRAS Notice No. GRN 000452

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement to GRN 000452 that you submitted on behalf of Daepyung Co., Ltd. (Daepyung). We received the supplement on October 4, 2018. The supplement includes updated information on the production of enzyme-modified steviol glycosides (EMSG).

We previously responded to GRN 000452 on July 1, 2013. We stated that we had no questions at that time regarding Daepyung's conclusion that EMSG is GRAS for use as a general purpose sweetener in foods, excluding meat and poultry products and infant formulas, at levels determined by good manufacturing practices, as well as use as a table top sweetener. Daepyung states that the intended use of the EMSG described in the supplement is the same as described in GRN 000452.

Our use of the terms "enzyme-modified steviol glycosides" or "EMSG" 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 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."

In the supplement, Daepyung states that the manufacturing process for EMSG is the same as described in GRN 000452 with the exception in starting material composition. The starting material is an extract of the leaves of *Stevia rebaudiana* (Bertoni) Bertoni (stevia) that is > 95% total steviol glycosides, however, the starting material described in GRN 000452 is > 80% rebaudioside A and that described in the supplement is either > 90% or > 95% rebaudioside A. The change in the composition of the starting material

results in EMSG with differences in the composition of individual steviol glycosides. As described in GRN 000452, EMSG is produced by the treatment of stevia extract and maltodextrin with food-grade cyclomaltodextrin glucanotransferase from a genetically engineered strain of *Bacillus licheniformis*.

Daepyung provides specifications for EMSG that are similar to those described in GRN 000452. Specifications for EMSG include total steviol glycosides (≥ 95%) and limits for unreacted steviol glycoside (≤ 15%), ash (≤ 1%), loss on drying (≤ 6%), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), ethanol (≤ 5000 mg/kg), methanol (≤ 200 mg/kg), as well as limits on microorganisms. Daepyung provides the results of ten non-consecutive batches to demonstrate that EMSG can be produced to meet these specifications.

In GRN 000452, Daepyung provides estimates of dietary exposure to EMSG based on the methodology described in Ref. 1 and a relative sweetness intensity of 150 times that of sucrose. In the supplement, Daepyung states that the intended use of EMSG is the same as described in GRN 000452, however, due to the increase in relative sweetness (180 to 240 times that of sucrose), a revised estimate of dietary exposure is provided. Daepyung reports the highest estimated upper percentile (≥ 90$^{th}$ percentile) dietary exposure in adults (expressed as steviol equivalents) to be 1.33 mg/kg body weight per day (bw/d) and in children to be 1.47 mg/kg bw/d. Daepyung states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

In GRN 000452, Daepyung discusses published and unpublished studies pertaining to the metabolic fate and safety evaluation of EMSG. In the supplement, Daepyung provides an updated review of studies related to the safety of steviol glycosides and published through September 2018. Daepyung reports that no studies were found that would alter its conclusion that EMSG is GRAS for its intended use in foods.

To further support its view that EMSG is GRAS for the intended use, Daepyung summarizes decisions by JECFA, the Food Standards Australia New Zealand (FSANZ), Health Canada, the European Food Safety Authority (EFSA), and other governmental bodies on the safety of SGs for use in food as a sweetener. Daepyung notes that JECFA established an acceptable daily intake (ADI) for SGs of 0–4 mg/kg bw/d (expressed as steviol equivalents) and FSANZ and EFSA established an ADI for SGs of 4 mg/kg bw/d (expressed as steviol equivalents).

Daepyung includes a report of a panel of individuals (Daepyung's GRAS panel). Based on its review of the data and information in the supplement, 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 supplement, Daepyung 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 our evaluation of Daepyung's supplement concluding that EMSG 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 EMSG. Accordingly, our response should not be construed to be a statement that foods containing 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 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 the supplement to GRN 000452 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2018.12.10 16:52:46 -05'00'

Susan Carlson, Ph.D.
Director
Division of Biotechnology
and GRAS Notice Review
Office of Food Additive Safety
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References

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.