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

Re: GRAS Notice No. GRN 000858

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000858. We received the notice that you submitted on behalf of Qufu Shengren Pharmaceutical Co., Ltd. (Qufu), Sunwin Stevia International (Sunwin), and NuNaturals, Inc. (NuNaturals) on April 25, 2019, and filed it on June 10, 2019. Qufu, Sunwin, and NuNaturals submitted an amendment to the notice on August 6, 2019 that clarified information listed in the table of specifications and in the certificates of analysis provided in 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 FDA of Qufu, Sunwin, and NuNaturals' view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000858 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."

Qufu, Sunwin, and NuNaturals provide information about the identity and composition of EMSG. Qufu, Sunwin, and NuNaturals describe two preparations of EMSG that are white to off-white powders with ≥ 95% total SGs (on a dried weight basis) and < 1% dextrin or ≥ 80% SGs with up to 20% dextrin. SGs are a group of structurally-related sweet compounds that are constituents of *S. 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 SGs with a source of glucose and food-grade alpha-amylase[1] that results in glucosylated forms of the starting SGs.

Qufu, Sunwin, and NuNaturals describe the method of manufacture of EMSG. The starting material used in the production of EMSG is a stevia leaf extract, containing ≥ 95% total SGs (≥ 80% stevioside), that is prepared by extraction of stevia leaves with water and multiple purification steps. The stevia extract is combined with water, food-grade maltodextrin, and alpha-amylase and the reaction allowed to proceed. The enzyme is then deactivated by heat treatment and the mixture treated with an adsorption resin. The resin is eluted with food grade ethanol and the eluate is then concentrated and spray-dried to obtain an EMSG product that contains glucosylated SGs, unreacted SGs, and residual maltodextrin (≤ 20%). This product may then be treated to an additional resin purification step to remove residual maltodextrin with up to 1% remaining in the final EMSG product.

Qufu, Sunwin, and NuNaturals provide specifications for the two EMSG preparations that include a minimum of either 95% or 80% total SGs and a limit on residual dextrin of ≤ 1% or ≤ 20%, respectively. Specifications for both preparations 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. Qufu, Sunwin, and NuNaturals provide results of five, non-consecutive batch analyses for both EMSG preparations to demonstrate that EMSG can be produced to meet these specifications.

Qufu, Sunwin, and NuNaturals provide estimates of dietary exposure to EMSG. The notifier discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1 and a relative sweetness intensities of 100 and 260 times that of sucrose, the notifier estimates maximum dietary exposures in adults (expressed as steviol equivalents) to be 3.32 mg/kg body weight (bw)/day (d) and in children to be 3.66 mg/kg bw/d. Qufu, Sunwin, and NuNaturals state that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

Qufu, Sunwin, and NuNaturals summarize published studies pertaining to the metabolic fate and safety of SGs. The notifier concludes that microbes in the colon hydrolyze SGs

[1] The notifier states that alpha-amylase from *Geobacillus stearothermophilius* is GRAS for use as an enzyme (21 CFR 184.1012).

completely to steviol and thus EMSG shares a common metabolic fate. Qufu, Sunwin, and NuNaturals discuss 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 to support the safety conclusion for EMSG. Qufu, Sunwin, and NuNaturals include an update of the literature regarding the safety of SGs through March 2019 and report that no studies relevant to toxicology were found that would alter the safety conclusion. To further support the view that EMSG is GRAS for the intended use, Qufu, Sunwin, and NuNaturals summarize 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. Qufu, Sunwin, and NuNaturals note 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.

Qufu, Sunwin, and NuNaturals include the statement of a panel of individuals (Qufu, Sunwin, and NuNaturals' GRAS panel). Based on its review, Qufu, Sunwin, and NuNaturals' GRAS panel concluded that EMSG is safe under the conditions of its intended use. Based on all the available scientific information, Qufu, Sunwin, and NuNaturals conclude that EMSG is GRAS for its intended use in foods.

Standards of Identity

In the notice, Qufu, Sunwin, and NuNaturals 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 our evaluation of Qufu, Sunwin, and NuNaturals' notice 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, 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 Qufu, Sunwin, and NuNaturals provided, as well as other information available to FDA, we have no questions at this time regarding Qufu, Sunwin, and NuNaturals' 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 000858 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.10.04 17:03:57 -04'00'

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.