Steven Overgaard
GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134

Re: GRAS Notice No. GRN 000790

Dear Mr. Overgaard:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000790. We received the notice that you submitted on behalf of GLG Life Tech Corporation (GLG) on June 22, 2018 and filed it on July 26, 2018. We received amendments on October 4, 2018 and October 31, 2018, containing information regarding the intended use; and an amendment on December 21, 2018, containing a clarification regarding the information that GLG initially designated confidential[1].

The subject of the notice is steviol glycosides (SGs) with rebaudioside A and stevioside as the principal components (SG-RS) for use as a sweetener in meat and poultry jerky at up to 2500 mg/kg. The notice informs us of GLG's view that this use of SG-RS is GRAS through scientific procedures.

The SG-RS that is the subject of GRN 000790 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 SG-RS, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "steviol glycosides with rebaudioside A and stevioside as the principal components," "SG-RS," "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

[1] GRN 000790 included information in Part 7 (i.e., Appendix 1 and Appendix 2) that GLG initially designated confidential. In the December 21, 2018 amendment, GLG withdrew its designation of confidentially for Appendix 1 and Appendix 2.

(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 "SG-RS."

GLG provides information about the identity and composition of SG-RS. GLG states that the identity and composition of SG-RS is the same as described in GRN 000493.[2] In GRN 000493, GLG described SG-RS as a white to off-white, hygroscopic crystal, granule or powder composed of ≥ 95% (on a dried weight basis) steviol glycosides, a group of structurally-related sweet compounds that are natural constituents of the leaves of stevia (*Stevia rebaudiana* (Bertoni) Bertoni). GLG described four SG-RS preparations that contain differing proportions of steviol glycosides and the percentages of rebaudioside A (CAS No. 58543-16-1) to be 50, 60, 80, and 85%, respectively.

GLG provides information about the manufacturing process for SG-RS. GLG states that the method of manufacture for SG-RS is the same as described in GRN 000493. In GRN 000493, GLG stated that SG-RS is obtained from the leaves of *S. rebaudiana* through extraction and multiple purification steps. The leaves are extracted in water, which is then re-extracted with ethanol and/or methanol. The steviol glycosides are crystallized, and then concentrated using filtration. The concentrate is dissolved in purified water, subjected to additional filtration, decolorization, and concentration steps prior to sterilization and spray drying.

GLG notes that specifications for SG-RS are the same as described in GRN 000493. These include the minimum content of total SGs (≥ 95%), limits for moisture (≤ 4% w/w), lead (< 1 mg/kg), arsenic (< 1 mg/kg), methanol (< 200 mg/kg), and ethanol (< 5000 mg/kg), as well as limits on microorganisms.

GLG provided an estimate of dietary exposure to SG-RS in GRN 000493 and states that the additional intended use of SG-RS in meat and poultry jerky is not expected to significantly increase dietary exposure. In GRN 000493, GLG discussed a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref.1 and relative sweetness intensities of 280, 320, 360, and 380 times that of sucrose, GLG reported the maximum dietary exposure in adults (expressed as steviol equivalents) to be 0.83 to 1.24 mg/kg body weight (bw)/day and in children to be 0.92 to 1.37 mg/kg bw/day. GLG provides an estimate of dietary exposure to SG-RS based on use in meat and poultry jerky at up to 2500 mg/kg and consumption data from National Health and Nutrition Examination Survey United States (2013-2014). GLG reports that the 90th percentile exposure, on a steviol equivalents basis, for users 2 years and older is 2.33 mg/kg bw/day. GLG states that the use of SG-RS in food is self-limiting due to organoleptic factors and consumer taste considerations.

GLG summarizes published studies pertaining to the metabolic fate and safety of SG-RS. Based on the pharmacokinetic studies, GLG concludes that microorganisms in the colon

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[2] GRN 000493 was submitted on behalf of GLG for SG-RS for use as a general-purpose sweetener in foods, excluding meat and poultry products, at levels determined by good manufacturing practices, as well as use as a table top sweetener. We evaluated this notice and responded in a letter on May 30, 2014, stating that we had no questions at that time regarding GLG's GRAS conclusion.

hydrolyze SGs completely to steviol and thus SG-RS shares a common metabolic fate. GLG 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 its safety conclusion of SG-RS. GLG includes an update of the literature regarding the safety of SGs through March 2018 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that SG-RS is GRAS for the intended use, GLG summarizes the decisions on the safety of SGs by JECFA, the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. GLG 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.

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

Based on all the available scientific information, GLG concludes that SG-RS is GRAS for its intended use in foods.

Use in Products Under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000790, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

FSIS has advised the following with respect to the statutes it administers. FSIS would not object to the use of SG-RS as a sweetener in meat and poultry jerky at a maximum use level of 2500 mg/kg. Regarding labeling, any establishment which uses this product is required to label the ingredient in one of the following ways: "steviol glycosides (≥ 95%)," "highly refined steviol glycosides at a purity ≥ 95%," or "high purity steviol glycosides (≥ 95%)." FSIS requested that we advise you to seek regulatory guidance from its Risk, Innovations, and Management Staff (RIMS) about the use of SG-RS in meat, poultry, and egg products. You should direct such an inquiry to Ms. Melanie Abley, Acting Director, RIMS, Office of Policy and Program Development, FSIS by email at Melanie.Abley@fsis.usda.gov.

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 GLG's notice that SG-RS is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing SG-RS. Accordingly, this response should not be construed to be a statement that foods that contain SG-RS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that GLG provided, as well as other information available to FDA, we have no questions at this time regarding GLG's conclusion that SG-RS is GRAS under its intended conditions of use. This letter is not an affirmation that SG-RS 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 000790 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2019.02.26 13:28:56 -05'00'

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

cc: Ms. Melanie Abley,
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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.