



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

Re: GRAS Notice No. GRN 000846

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000846. We received the notice that you submitted on behalf of GLG Life Tech Corporation (GLG) on February 27, 2019, and filed it on May 2, 2019.

The subject of the notice is rebaudioside M obtained by enzyme treatment of steviol glycosides (SGs) purified from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni (rebaudioside M) for use as a general-purpose sweetener in foods, excluding infant formula and meat and poultry products, at levels determined by good manufacturing practices. The notice informs us of GLG's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 000846 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 rebaudioside M, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "rebaudioside M," 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 "rebaudioside M."

GLG provides information about the identity and composition of rebaudioside M. Rebaudioside M (CAS No. 1220616-44-3), a glycoside of steviol, is identified as 13-[(2-

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O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oic acid, 2-O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D-glucopyranosyl ester. Rebaudioside M is one of a group of known SGs, which differ from each other by the number of glycoside moieties and bonding order.

GLG provides information about the method of manufacture of rebaudioside M and states that all reagents, solvents, and processing aids used are food grade and meet applicable regulations. The manufacturing process starts with a purified extract of *S. rebaudiana* (Bertoni) Bertoni leaves (stevia extract) that is $\geq 97\%$ rebaudioside A. GLG describes the production strains used in the manufacture of rebaudioside M that are non-pathogenic and non-toxicogenic strains of either *Escherichia coli* K-12 and *E. coli* B or *Bacillus brevis* and *B. licheniformis*. The production strains express two uridine diphosphate (UDP)-glucosyltransferase enzymes and a sucrose synthase enzyme that are used to produce rebaudioside M. The production strains are grown in culture media and the UDP-glucosyltransferases and sucrose synthase are secreted into the culture supernatant. After fermentation, the culture is heat-treated, and the enzymes separated by modular membrane filtration. The stevia extract, sucrose, and enzymes are combined, and the reaction allowed to proceed. After the reaction is complete, the solution is centrifuged, and the supernatant separated and subjected to an adsorption resin. The SGs are eluted from the resin with food grade ethanol and the resulting solution is then spray dried. The dried product is dissolved in ethanol, crystallized, filtered, and dried under vacuum to obtain the final rebaudioside M product.

GLG provides specifications for rebaudioside M that include the content of total SGs ($\geq 95\%$) and rebaudioside M ($\geq 95\%$). Specifications also include limits for total ash ($\leq 1\%$), loss on drying ($\leq 6\%$), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), mercury (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), methanol (≤ 200 mg/kg), ethanol ($\leq 5,000$ mg/kg), as well as limits on microorganisms. GLG provides results from five, non-consecutive batch analyses to demonstrate that rebaudioside M can be produced to meet specifications.

GLG provides an estimate of dietary exposure to rebaudioside M. GLG 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 that is 200 times that of sucrose, GLG estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.1 mg/kg body weight (bw)/day (d) and in children to be 1.22 mg/kg bw/d. GLG states that the use of rebaudioside M 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 rebaudioside M. Based on the pharmacokinetic studies, GLG concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M 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 the safety conclusion of rebaudioside M. GLG includes an update of the literature regarding the safety of SGs through December 2018 and reports that no studies relevant to toxicology were found

that would alter its safety conclusion.

To further support its view that rebaudioside M is GRAS for the intended use, GLG 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. 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 rebaudioside M is safe under the conditions of its intended use.

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

Standards of Identity

In the notice, GLG states its intention to use rebaudioside M 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 GLG's notice that rebaudioside M is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing rebaudioside M. Accordingly, this response should not be construed to be a statement that foods that contain rebaudioside M, 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 rebaudioside M is GRAS under its intended conditions of use. This letter is not an affirmation that rebaudioside M 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 000846 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Digitally signed by Susan J.
Carlson -S
Date: 2019.08.23 15:06:21
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Susan Carlson, Ph.D.
Director
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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.