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CHINA

Re: GRAS Notice No. GRN 000795

Dear Liu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000795. We received Steviana Bioscience (Suzhou) Inc.'s (Steviana) notice on June 29, 2018, and filed it on July 24, 2018.

The subject of the notice is purified steviol glycosides (SGs) for use as a general purpose sweetener in foods, excluding infant formulas and USDA regulated products, at levels determined by good manufacturing practices, as well as use as a table top sweetener. The notice informs us of Steviana's view that this use of SGs is GRAS, through scientific procedures.

The SGs that is the subject of GRN 000795 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 and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "steviol glycosides," "SGs," "rebaudioside A," "rebaudioside D," "rebaudioside C," or "stevioside," 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 "SGs."

Steviana provides information about the identity and composition of SGs. SGs contains  $\geq 95\%$  total steviol glycosides, a group of structurally-related sweet compounds that are

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constituents of the stevia leaf. Steviol glycosides consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose. Steviana describes five SGs preparations in which the principal components are rebaudioside A, rebaudioside D, rebaudioside C, stevioside, or rebaudioside A and D in combination, respectively.

Steviana provides information about the manufacturing process for SGs. SGs is obtained from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni (stevia) by extraction in hot water that is subsequently filtered and subjected to an adsorbent resin that is then washed with alcohol. The stevia extract is then concentrated and spray dried. Steviana states their manufacturing process may also start with a stevia extract obtained from other suppliers that is typically > 75% steviol glycosides. The stevia extract is dissolved in alcohol, recrystallized, and centrifuged to obtain rebaudioside A. The remaining stevia extract may be subjected to additional recrystallization or column chromatography to obtain stevioside, rebaudioside D, and rebaudioside C.

Steviana provides specifications for SGs that include the content of total steviol glycosides ( $\geq 95\%$ ), limits for moisture ( $\leq 6\%$ ), ethanol ( $\leq 5000$  mg/kg), methanol ( $\leq 200$  mg/kg), lead ( $\leq 1$  mg/kg), arsenic ( $\leq 1$  mg/kg), and microorganisms. Steviana provides the results of three batch analyses conducted with each of the five preparations to demonstrate that SGs can be made to meet specifications.

Steviana provides estimates of dietary exposure to each of the SGs preparations. Steviana discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1 and the relative sweetness intensities of each of the SGs preparations relative to sucrose, Steviana reports the maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.35 mg/kg body weight/day (bw/d) and in children to be 1.98 mg/kg bw/d. Steviana states that the use of SGs in food is self-limiting due to organoleptic factors and consumer taste considerations.

Steviana summarizes published studies pertaining to the metabolic fate and safety of SGs. Based on the pharmacokinetic studies, Steviana concludes that microbes in the colon hydrolyze steviol glycosides completely to steviol and thus SGs shares a common metabolic fate. Steviana 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 SGs. Steviana includes an update of the literature regarding the safety of SGs through April 2018 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that SGs is GRAS for the intended use, Steviana summarizes the decisions on the safety of steviol glycosides 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. Steviana notes that JECFA has established an acceptable daily intake (ADI) for steviol glycosides 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.

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

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

### **Standards of Identity**

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

### **Conclusions**

Based on the information that Steviana provided, as well as other information available to FDA, we have no questions at this time regarding Steviana's conclusion that SGs is GRAS under its intended conditions of use. This letter is not an affirmation that SGs 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 000795 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Michael A.

Adams -S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A.  
Adams -S

Date: 2018.09.25 13:11:23 -04'00'

## 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.