



Katrina Emmel, Ph.D.
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Re: GRAS Notice No. GRN 000733

Dear Dr. Emmel:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000733. We received the notice that you submitted on behalf of Shangdong Shengxiangyuan Biotechnology Co., Ltd. (Shangdong) on September 18, 2017, and filed it on November 29, 2017. We received an amendment to the notice on December 4, 2017. In the amendment, the notifier clarifies the manufacturing process.

The subject of the notice is steviol glycosides (SGs) with rebaudioside A and stevioside as the principal components (SG-RS). The notice informs FDA of the view of Shangdong that SG-RS is GRAS, through scientific procedures, 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 SG-RS that is the subject of GRN 000733 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 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

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(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.”

Shangdong provides information about the identity and composition of SG-RS. Shangdong describes SG-RS as a white powder composed of $\geq 95\%$ total SGs, a group of structurally-related sweet compounds that are natural constituents of the stevia leaf. Rebaudioside A (CAS Reg. No. 58543-16-1) and stevioside (CAS Reg. No. 57817-89-7) are the principal steviol glycoside components of SG-RS with the remainder composed of related SGs (e.g., rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, dulcoside A, rubusoside, and steviolbioside).

Shangdong provides information about the manufacturing process for SG-RS. SG-RS is obtained from the dried leaves of *S. rebaudiana* that are extracted with water and filtered. Calcium hydroxide and ferrous sulfate are added to the extract and then filtered. The extract is subjected to an adsorption resin and the SGs subsequently eluted with aqueous ethanol. The extract is subjected to ion-exchange chromatography, and then concentrated and dried. The dried product is recrystallized using ethanol and the final crystalline product is obtained by centrifugation and drying. Shangdong states that all materials used in the manufacture of SG-RS are food grade and meet applicable FDA regulations.

Shangdong provides specifications for SG-RS that includes the minimum content of total SGs ($\geq 95\%$) and ranges for rebaudioside A (50 to 70%), rebaudioside B (1 to 3%), rebaudioside C (2 to 5%), rebaudioside D (0.3 to 1.5%), rebaudioside F (0.5 to 1.5%), dulcoside A (0.3 to 1%), rubusoside (2 to 4%), and steviolbioside (0.1 to 1%). Specifications for SG-RS also include limits for moisture ($\leq 4\%$), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), methanol (≤ 200 mg/kg), ethanol (≤ 5000 mg/kg), and limits on microbial contaminants. Shangdong states that SG-RS meets the specifications for SGs established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 73rd meeting in 2010. Shangdong provides the results of five batch analyses to demonstrate that SG-RS can be produced in accordance with specifications.

Shangdong provides an estimate of dietary exposures to SG-RS. Shangdong 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 of 280 times that of sucrose, Shangdong reports the maximum dietary exposure in adults (expressed as steviol equivalents) to be 0.86 mg/kg body weight (bw)/d and in children to be 0.95 mg/kg bw/d. Shangdong states that the use of SG-RS in food is self-limiting due to organoleptic factors and consumer taste considerations.

Shangdong summarizes published studies pertaining to the metabolic fate and safety of SG-RS. Based on the pharmacokinetic studies, Shangdong concludes that microbes in the colon hydrolyze SGs completely to steviol and thus SG-RS shares a common metabolic fate. Shangdong 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 SG-RS. Shangdong includes an update of the literature regarding the safety of SGs through August 2017 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, Shangdong 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. Shangdong 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.

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

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

Standards of Identity

In the notice, Shangdong states its intention to use SG-RS 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(II) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(II) 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(II)(1)-(4) applies. In its review of Shangdong's notice that SG-RS is GRAS for the intended use, FDA did not consider whether section 301(II) 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(II).

Conclusions

Based on the information that Shangdong provided, as well as other information available to FDA, we have no questions at this time regarding Shangdong'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 000733 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams

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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

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ou=People, 0.9.2342.19200300.100.1.1=1300042713,
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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.