U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Stella Si
Anchor Center for Certification
No. 1295 Chuan Qiao Road, Building 2, Suite 302
Pudong, Shanghai
CHINA

Re: GRAS Notice No. GRN 001307

Dear Ms. Si:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001307. We received the notice that you submitted on behalf of Shanghai Shenghe Zhizao Biotechnology Co., Ltd (Shanghai Shenghe) on November 18, 2025, and filed it on March 5, 2026. Shanghai Shenghe submitted an amendment to the notice on May 6, 2026, that provided additional information about potential allergens, the identity and source of the starting material, production strain, fermentation process, and an updated literature search.

The subject of the notice is rebaudioside M produced by enzymatic treatment of rebaudioside A purified from the leaves *of Stevia rebaudiana* (Bertoni) Bertoni (rebaudioside M) for use as a general-purpose sweetener in foods excluding infant formula and products under the U.S. Department of Agriculture's jurisdiction, at levels determined by current good manufacturing practice. The notice informs us of Shanghai Shenghe's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 001307 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," "steviol glycosides," or "SGs" in this letter is not our recommendation of these terms as appropriate common or usual names 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 Nutrition Center of Excellence. The Office of Pre-Market

Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual names for "rebaudioside M," "steviol glycosides," and "SGs."

Shanghai Shenghe provides information about the identity and composition of rebaudioside M. Shanghai Shenghe states that the subject of the notice is ≥95% rebaudioside M with minor amounts of rebaudiosides A, B, and D. Rebaudioside M (CAS No. 1220616-44-3) is a glycoside of steviol and is one of a group of known steviol glycosides (SGs), which differ from each other by the number of glycoside moieties and bonding order.

Shanghai Shenghe describes the method of manufacture for rebaudioside M. Shanghai Shenghe states that rebaudioside M is obtained through the enzymatic conversion of rebaudioside A.[1] The enzymes utilized include two uridine diphosphate (UDP)-glucosyltransferases and sucrose synthase that are obtained from the fermentation of non-pathogenic and non-toxicogenic *Escherichia coli* strain M20251069. This production strain is derived from *E. coli* BL21(DE3). Shanghai Shenghe describes the construction of the production strain that includes insertion of three synthesized genes.

The production microorganism is grown in a culture medium and after the fermentation step is complete, the fermentation broth is centrifuged to obtain the bacterial biomass. The biomass is then incubated in a buffered solution containing rebaudioside A. The enzymatic reaction results in the production of rebaudioside M. The resulting mixture is acidified with citric acid and then subjected to heat treatment. Diatomite and cellulose are added and the mixture filtered, followed by ultrafiltration. The permeate then undergoes crystallization, and the resulting crystals are removed by filtration and dissolved in ethanol. Activated carbon is added to the solution and filtered. The filtrate is cooled to induce crystallization, and the crystals are dried under vacuum to obtain the final rebaudioside M product. Shanghai Shenghe states that rebaudioside M is produced under current good manufacturing practices and that all materials and processing aids used to manufacture rebaudioside M are food-grade and used in accordance with U.S. regulations.

Shanghai Shenghe provides specifications for rebaudioside M that include the content of total SGs (≥ 98%, dry matter basis (DM)), rebaudioside M (≥ 95% DM), limits for ash (≤ 1%), loss on drying (≤ 6%), ethanol (≤ 2000 mg/kg), methanol (≤ 100 mg/kg), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and limits on microorganisms. Shanghai Shenghe provides results from the analyses of three non-consecutive batches to demonstrate that rebaudioside M can be produced in accordance with the stated specifications. Shanghai Shenghe provides the results of an accelerated stability study and an ongoing long-term stability study conducted with rebaudioside M and concludes that the results demonstrate that the product is stable under the conditions tested.

[1] Shanghai Shenghe states that the rebaudioside A is obtained from the leaves of *S. rebaudiana* and meets the specifications established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for SGs.

Shanghai Shenghe provides estimates of dietary exposure to rebaudioside M. Shanghai Shenghe 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 200 to 350 times that of sucrose, Shanghai Shenghe estimates the maximum dietary exposure in adults (expressed as steviol equivalents) to be up to 1.12 mg/kg body weight (bw)/day (d) and in children to be 1.24 mg/kg bw/d. Shanghai Shenghe states that the use of rebaudioside M in food is self-limiting due to organoleptic factors and consumer taste considerations.

Shanghai Shenghe summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on the pharmacokinetic studies, Shanghai Shenghe concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. Shanghai Shenghe discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies, published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A, and *in vitro* and *in vivo* mutagenicity/ genotoxicity studies for the safety conclusion for rebaudioside M. Shanghai Shenghe includes an update of the literature regarding the safety of SGs through May 2026, 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, Shanghai Shenghe summarizes the decisions on the safety of SGs by the JECFA, the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. Shanghai Shenghe 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.

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

Standards of Identity

In the notice, Shanghai Shenghe 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 CFR. 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a “major food allergen” declare the allergen’s presence (section 403(w)). The FD&C Act defines a “major food allergen” as one of nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. The

manufacturing process for rebaudioside M includes the use of milk-derived lactose as a component of the fermentation media. Rebaudioside M may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OPMAS. Questions related to food labeling in general should be directed to the ONFL.

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 Shanghai Shenghe's notice concluding that rebaudioside M 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 rebaudioside M. Accordingly, our response should not be construed to be a statement that foods containing rebaudioside M, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Shanghai Shenghe provided, as well as other information available to FDA, we have no questions at this time regarding Shanghai Shenghe'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 001307 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

Digitally signed by SUSAN J. CARLSON -S
Date: 2026.06.04 16:52:30 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program

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. https://doi.org/10.1016/j.fct.2008.05.009