U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Wing Yu
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Re: GRAS Notice No. GRN 001310

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001310. We received the notice that you submitted on behalf of Hangzhou Levinthal Biotechnology Co., Ltd. (Levinthal) on December 1, 2025, and filed it on April 2, 2026. Levinthal submitted an amendment to the notice on May 22, 2026, that provided additional information about the safety of enzymes, purity of the microbial inoculum for the 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 Levinthal's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 001310 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."

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

Levinthal describes the method of manufacture for rebaudioside M. Levinthal states that rebaudioside M is obtained through the enzymatic conversion of rebaudioside A.[1] The enzymes utilized include β-1,2-glucosyltransferase, β-1,3-glucosyltransferase, and sucrose synthase that are obtained from fermentation of non-pathogenic and non-toxicogenic *Escherichia coli* "LV2206-3G2P". Levinthal provides information on the parent strain *E. coli* BL21(DE3) and describes the construction of the production organism strain that includes insertion of synthesized enzyme genes into expression plasmids. The production microorganism is grown in a culture medium and Levinthal states that lactose is used to induce the enzyme expression. After the fermentation step is complete, the fermentation broth is centrifuged to obtain the bacterial biomass. The biomass is then incubated with sucrose and rebaudioside A. The resulting enzymatic reaction results in the production of rebaudioside M. After the reaction is complete, the pH is adjusted using citrate buffer and the mixture is heat treated. Activated carbon is added to the mixture and then filtered. The filtrate is cooled to induce crystal formation, and the crystals then obtained by centrifugation and dried under vacuum. The dried crystals are crushed and sieved to obtain the final rebaudioside M product. Levinthal states that rebaudioside M is produced under current good manufacturing practices and that all materials, processing aids, and food contact substances used to manufacture rebaudioside M are food-grade, permitted by U.S. regulations, previously determined to be GRAS for the respective use, or subject of an effective food contact notification.

Levinthal provides specifications for rebaudioside M that include the content of rebaudioside M (≥ 95%, dry matter basis (DM)), limits for ash (≤ 1%), loss on drying (≤ 6%), ethanol (≤ 5000 mg/kg), methanol (≤ 200 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. Levinthal provides results from the analyses of three non-consecutive batches to demonstrate that rebaudioside M can be produced in accordance with the stated specifications.

Levinthal provides estimates of dietary exposure to rebaudioside M. Levinthal 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 times that of sucrose, Levinthal 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. Levinthal states that the use of rebaudioside M in food is self-

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

limiting due to organoleptic factors and consumer taste considerations.

Levinthal summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on the pharmacokinetic studies, Levinthal concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. Levinthal 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. Levinthal 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, Levinthal 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. Levinthal 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, Levinthal concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

In the notice, Levinthal 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 Federal Food, Drug, and Cosmetic Act (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 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 Levinthal'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 Levinthal provided, as well as other information available to FDA, we have no questions at this time regarding Levinthal'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 001310 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

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