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 001318

Dear Ms. Si:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001318. We received the notice that you submitted on behalf of Delytose (Shanghai) Biotech. Co., Ltd. (Delytose) on December 1, 2025, and filed it on April 27, 2026. Delytose submitted an amendment to the notice on June 23, 2026, that provided additional information about the starting material, production strain, manufacturing process, updated batch analysis tables, and an updated literature search.

The subject of the notice is enzyme-modified steviol glycosides (EMSG) 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 Delytose's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 001318 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 EMSG, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "EMSG," "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 "EMSG," "steviol glycosides," and "SGs."

Delytose provides information about the identity and composition of EMSG. Delytose states that the subject of the notice is ≥95% total steviol glycosides (SGs) and consist of primarily rebaudioside M and rebaudioside D. Rebaudioside M (CAS No. 1220616-44-3) and rebaudioside D (CAS No. 63279-13-0) are glycosides of steviol and part of a group of known SGs, which differ from each other by the number of glycoside moieties and bonding order.

Delytose describes the method of manufacture for EMSG. Delytose states that EMSG 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* XT-EC101. Delytose provides information on the parent strain *E. coli* BL21(DE3) and describes the construction of the production strain that includes insertion of synthesized genes. The production microorganism is grown in a culture medium under controlled conditions and expression of the enzymes is induced with isopropyl β-D-1-thiogalactopyranoside. After the fermentation is complete, the broth is centrifuged to obtain the bacterial biomass. The biomass is resuspended in phosphate buffer and subjected to homogenization to lyse the cells. The lysate is centrifuged and the supernatant containing the enzymes is combined with rebaudioside A, sucrose, and other processing aids and the enzymatic reaction is conducted under controlled conditions. The enzymatic reaction results in the production of rebaudioside D and rebaudioside M. After the reaction is complete, the mixture is heated to inactivate the enzymes and then is filtered. Delytose states that the filtrate may be treated with chromatography and the eluate is concentrated and cooled to obtain a crystal product, or the filtrate is cooled to induce crystal formation and the crystals are then washed and redissolved in aqueous ethanol, filtered and recrystallized. The crystalline product is dried, heat treated, ground and sieved to obtain the EMSG product. Delytose notes that EMSG is produced to be predominantly rebaudioside M or rebaudioside D and that these may then be blended together and optionally with rebaudioside A to obtain EMSG formulations with the desired composition. Delytose states that EMSG is produced under current good manufacturing practices and that all raw materials and processing aids used to manufacture EMSG are food-grade, used in accordance with U.S. regulations.

Delytose provides specifications for EMSG that include four formulations with differing composition of SGs. EMSG is specified to contain ≥95 % total SGs on a dry matter basis and the four formulations are ≥95 % rebaudioside M, ≥95 % rebaudioside D, ≥50 % rebaudioside M and ≥5 % rebaudioside D, or ≥50 % rebaudioside D and ≥5 % rebaudioside M. Specifications for EMSG also include limits for ash (≤1 %), loss on drying (≤6 %), ethanol (≤3000 mg/kg), methanol (≤200 mg/kg), lead (≤0.3 mg/kg), arsenic (≤0.3 mg/kg), cadmium (≤0.3 mg/kg), mercury (≤0.3 mg/kg), and limits on microorganisms. Delytose provides results from the analyses of twelve non-consecutive batches (three each of the four formulations) to demonstrate that EMSG can be

[1] Delytose 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, 2023).

produced in accordance with the stated specifications.

Delytose provides estimates of dietary exposure to EMSG. Delytose discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Delytose estimates that the relative sweetness intensities of the four EMSG formulations to be in the range of 200–350 times sweeter than sucrose. Based on the methodology described in Ref. 1 and the relative sweetness intensities, Delytose estimates the maximum dietary exposure in adults (expressed as steviol equivalents) to be up to 1.12-1.26 mg/kg body weight (bw)/day (d) and in children to be 1.24-1.39 mg/kg bw/d. Delytose states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

Delytose summarizes published studies pertaining to the metabolic fate and safety of EMSG. Based on pharmacokinetic studies, Delytose concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. Delytose 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 EMSG. Delytose includes an update of the literature regarding the safety of SGs through June 2026, and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that EMSG is GRAS for the intended use, Delytose 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. Delytose 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, Delytose concludes that EMSG is GRAS for its intended use in foods.

Standards of Identity

In the notice, Delytose states its intention to use EMSG 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.

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

Conclusions

Based on the information that Delytose provided, as well as other information available to FDA, we have no questions at this time regarding Delytose's conclusion that EMSG is GRAS under its intended conditions of use. This letter is not an affirmation that EMSG 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 001318 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

Digitally signed by SUSAN J. CARLSON -S
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Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
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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