U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

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Re: GRAS Notice No. GRN 001294

Dear Dr. Tafazoli:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001294. We received the notice that you submitted on behalf of Arzeda Corporation (Arzeda) on July 28, 2025, and filed it on January 13, 2026. Arzeda submitted an amendment to the notice on March 25, 2026 and April 13, 2026, that provided additional information about the production strain, fermentation process, specifications, and an updated literature search.

The subject of the notice is rebaudioside M produced by enzymatic treatment of steviol glycosides (SGs) 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 practices. The notice informs us of Arzeda's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 001294 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 did not consult with ONFL regarding the appropriate common or usual

names for “rebaudioside M,” “steviol glycosides,” and “SGs.”

Arzeda provides information about the identity and composition of rebaudioside M. Arzeda states that the subject of the notice is ≥95% total SGs and ≥90% rebaudioside M and minor amounts of other SGs. Rebaudioside M (CAS No. 1220616-44-3) is a glycoside of steviol and is one of a group of known SGs, which differ from each other by the number of glycoside moieties and bonding order.

Arzeda describes the method of manufacture for rebaudioside M. Arzeda states that rebaudioside M is obtained through the enzymatic conversion of SGs from an extract of *S. rebaudiana* leaves. The enzymes utilized include β-1,2-glucosyltransferase, β-1,3-glucosyltransferase, and sucrose synthase that are produced from fermentation of three genetically engineered *Escherichia coli* strains derived from the host *Escherichia coli* W3110 via gene deletion and plasmid insertion. Arzeda confirms that the production strains are non-pathogenic and non-toxicogenic. The production microorganisms are grown under sterile and controlled conditions. After the fermentation step is complete, the cells are lysed by homogenization and resuspended in buffer. The lysate is heat-treated and subjected to flocculation and centrifugation to remove cellular biomass. The lysate is then filtered to obtain the expressed enzymes. Arzeda states that any residual DNA from the production microorganisms is removed by treatment with a nuclease.[1] The enzyme mixture is then utilized in the enzymatic treatment of an *S. rebaudiana* extract. Arzeda states that the *S. rebaudiana* extract is obtained from a hot water extraction of the leaves of *S. rebaudiana* and meets Food Chemicals Codex (FCC, 14th edition) specifications for SGs. The *S. rebaudiana* extract and the enzyme mixture are combined, and Arzeda states that after the enzymatic reaction is complete, the product undergoes additional processing that includes heat treatment to inactivate the enzymes, centrifugation and/or filtration, concentration, solid-liquid separation, crystallization, dissolution, recrystallization, and drying to obtain the final rebaudioside M product. Arzeda states that rebaudioside M is produced under current good manufacturing practices and that all materials, processing aids, and equipment used to manufacture rebaudioside M are food-grade, permitted by U.S. regulations or have been previously determined to be GRAS for the respective use.

Arzeda provides specifications for rebaudioside M that include the content of total SGs (≥ 95 %, dry matter basis (DM)), rebaudioside M (≥ 90 % DM), limits for ash (≤ 1 %), loss on drying (≤ 6 %), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), and limits on microorganisms. Arzeda provides results from the analyses of three non-consecutive batches to demonstrate that rebaudioside M can be produced in accordance with the stated specifications.

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[1] In the amendment dated March 25, 2026, Arzeda states that the nuclease is commercially available and is obtained from a genetically engineered strain of *Komagataella phaffii*. Arzeda states that the nuclease conforms to specifications established in the Food Chemicals Codex (14th edition) and to the General Specifications and Considerations for Enzyme Preparations Used in Food(1 Processing established by the FAO/WHO Joint Expert Committee on Food Additives.

Arzeda provides estimates of dietary exposure to rebaudioside M. Arzeda 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 300 times that of sucrose, Arzeda estimates the maximum dietary exposure in adults (expressed as steviol equivalents) to be up to 1.11 mg/kg body weight (bw)/day (d) and in children to be 1.22 mg/kg bw/d. Arzeda states that the use of rebaudioside M in food is self-limiting due to organoleptic factors and consumer taste considerations.

Arzeda summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on the pharmacokinetic studies, Arzeda concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. Arzeda 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. Arzeda includes an update of the literature regarding the safety of SGs through March 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, Arzeda summarizes the decisions on the safety of SGs 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. Arzeda 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, Arzeda concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

In the notice, Arzeda 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.

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 Arzeda'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 Arzeda provided, as well as other information available to FDA, we have no questions at this time regarding Arzeda'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 001294 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