U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Evangelia Pelonis
Keller and Heckman LLP
1001 G Street NW Suite 500
Washington, DC 20001

Re: GRAS Notice No. GRN 001260

Dear Ms. Pelonis:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001260. We received the notice that you submitted on behalf of PureCircle by Ingredion USA (PureCircle) on January 28, 2025 and filed it on July 11, 2025. PureCircle submitted an amendment to the notice on September 16, 2025 that included missing pages in the Annex section of the notice, provided additional information on the identity of rebaudioside V2, added a specification for the content of rebaudioside M, and provided an updated literature review.

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 good manufacturing practices. The notice informs us of PureCircle's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 001260 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."

PureCircle provides information about the identity and composition of rebaudioside M. PureCircle states that the subject of the notice is ≥95% total SGs with ≥90%

rebaudioside M and minor amounts of other SGs, including rebaudiosides B, D, I, V2, V3, and AM. 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.

PureCircle describes the method of manufacture for rebaudioside M. PureCircle states that rebaudioside M is obtained through the enzymatic conversion of SGs from an extract of *S. rebaudiana* leaves. The enzymes utilized include uridine monophosphate (UMP)-kinase, uridine diphosphate (UDP)-glucotransferases, and a sucrose synthase that are obtained from fermentation of non-pathogenic and non-toxicogenic strains of *Escherichia coli* derived from *E. coli* K-12 W3110. PureCircle provides information on the parent strain and describes the construction of the production organisms. The production organisms are grown in a culture medium and after the fermentation step is complete, the microbial biomass is separated from the media, homogenized, treated with a nuclease, and filtered to obtain the enzyme preparations. The enzyme preparations are combined with an extract of the leaves of *S. rebaudiana* that contains >95% SGs and is primarily rebaudioside A as well as sucrose and uridine-5′-diphosphate disodium salt. The reaction results in the conversion of the SGs present in the extract to rebaudioside M. The reaction mixture is subsequently heated to inactivate the enzymes, filtered, and subjected to a crystallization step to separate rebaudioside M. The crystals are separated by centrifugation or filtration and PureCircle notes the process may optionally use treatment with a macroporous adsorbent resin. The crystals are dried and sieved to obtain the final rebaudioside M product.

PureCircle 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 (< 1 mg/kg), arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), mercury (< 1 mg/kg), methanol (< 0.02 %), ethanol (< 0.3 %), and limits on microorganisms. PureCircle provides results from the analyses of three non-consecutive batches to demonstrate that rebaudioside M can be produced in accordance with the stated specifications.

PureCircle provides estimates of dietary exposure to rebaudioside M. PureCircle 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 as low as 200 times that of sucrose, PureCircle estimates the maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.10 mg/kg body weight (bw)/day (d) and in children to be 1.22 mg/kg bw/d. PureCircle states that the use of rebaudioside M in food is self-limiting due to organoleptic factors and consumer taste considerations.

PureCircle summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on the pharmacokinetic studies, PureCircle concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. PureCircle 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. PureCircle includes an update of the literature regarding the safety of SGs through September 2025 and reports that no studies relevant to safety were found that would alter its GRAS conclusion.

To further support its view that rebaudioside M is GRAS for the intended use, PureCircle 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. PureCircle 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, PureCircle concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

In the notice, PureCircle 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 PureCircle'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 PureCircle provided, as well as other information available to FDA, we have no questions at this time regarding PureCircle'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 001260 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2025.11.18 10:25:32 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
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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.