U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Trung Vo
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Mississauga, Ontario, L5N 2X7
CANADA

Re: GRAS Notice No. GRN 001293

Dear Mr. Vo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001293. We received the notice that you submitted on behalf of Sweegen, Inc. (Sweegen) on July 23, 2025, and filed it on February 27, 2026. Sweegen submitted amendments to the notice on May 1, 2026, and May 15, 2026, providing additional information regarding the analytical methods, specifications, intended use, production organism, stability data, and safety narrative.

The subject of the notice is brazzein preparation produced by *Komagataella phaffii* "RA-b" expressing a gene encoding for brazzein from *Pentadiplandra brazzeana* (brazzein preparation) for use as a general-purpose sweetener in foods at levels consistent with good manufacturing practices (excluding use in infant formula and products under the jurisdiction of the United States Department of Agriculture). The notice informs us of Sweegen's view that this use of brazzein preparation is GRAS through scientific procedures.

Our use of the term, "brazzein preparation produced by *Komagataella phaffii* "RA-b" expressing a gene encoding for brazzein from *Pentadiplandra brazzeana*," or "brazzein preparation," in this letter is not our recommendation of that term as an appropriate common or usual name 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 name for "brazzein preparation."

Sweegen provides information about the identity and composition of brazzein preparation. Sweegen states that brazzein preparation is a white to off-white powder containing ≥90% total protein, of which ≥90% is brazzein, and small amounts of carbohydrates, ash, fat, and residual *K. phaffii* "RA-b" proteins carried over from the fermentation process. Sweegen states that brazzein preparation contains the 53-amino-

acid isoform of brazzein naturally present in the fruit of *P. brazzeana*, known as oubli fruit.

Sweegen states that brazzein preparation is produced from fermentation of a non-pathogenic and non-toxigenic *K. phaffii* "RA-b." Sweegen describes the genetic construction and integration of brazzein expression cassettes into the genome of *K. phaffii* ATCC 20864 which is derived from *K. phaffii* NRRL-Y-11430. Sweegen states that *K. phaffii* NRRL-Y-11430 is well characterized with a history of safe use in the food industry and that the bioengineering steps do not introduce any plasmids or antibiotic resistance genes into the production strain.

Sweegen describes the method of manufacture of brazzein preparation by controlled fermentation of *K. phaffii* "RA-b." During fermentation, brazzein is secreted into the fermentation medium. At the end of fermentation, the whole cell broth is centrifuged to isolate the production cells, and the resulting supernatant is heat treated to denature residual proteins, cooled, centrifuged, and filtered via membrane filtration to remove impurities. The filtered supernatant is further purified through ion exchange chromatography, and a salt gradient is used to elute the bound brazzein. The eluate is filtered using membrane filtration to concentrate the brazzein and remove residual salts. The concentrated brazzein solution is then decolorized, dried, ground, and sifted to obtain the final powder. Sweegen states that none of the raw materials used in the fermentation media are derived from major food allergens. Sweegen states that brazzein preparation is manufactured according to good manufacturing practices and all raw materials, processing aids, and food contact substances used in the manufacturing process are food grade and are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

Sweegen provides specifications for brazzein preparation that include total protein (≥90%), brazzein (≥90% of total protein), and limits on loss on drying (≤6%), fat (≤1%), ash (≤2%), carbohydrates (≤5%), heavy metals, including lead (<0.1 mg/kg), and microorganisms, including *Salmonella* serovars (negative in 10 g). Sweegen provides the results from the analyses of four non-consecutive batches to demonstrate that brazzein preparation can be manufactured to meet the stated specifications. Sweegen states that the shelf life of brazzein preparation is 23 months when stored under ambient conditions (room temperature and 40% relative humidity).

Sweegen estimates dietary exposure to brazzein from the intended uses of brazzein preparation based on the relative sweetness intensity of the notified substance and the methodology presented in Renwick, 2008.[1] This study reported average and upper percentile (i.e., 90th percentile and higher) estimates of dietary exposure to intense sweeteners among children and adults with and without diabetes and estimated the dietary exposure to a sweetener based on its relative sweetness to sucrose and an assumption of its substitutional use. Based on the methodology described in Renwick, 2008, the estimated relative sweetness intensity of brazzein (1,125 times sweeter than

[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.

sucrose), and brazzein content (approximately 92%) in brazzein preparation, Sweegen estimates the average and high percentile dietary exposures to brazzein for non-diabetic adults (0.21 and 0.55 mg/kg body weight (bw)/d, respectively), diabetic adults (0.23 and 0.73 mg/kg bw/d, respectively), non-diabetic children (0.35 and 0.81 mg/kg bw/d, respectively), and diabetic children (0.55 and 0.74 mg/kg bw/d, respectively).

Sweegen discusses publicly available data and information supporting the safety of brazzein and its production organism, *K. phaffii* "RA-b." Sweegen describes brazzein as a protein and the principal sweetening component of brazzein preparation and notes that it is equivalent to native brazzein-53, the minor isoform naturally occurring in the fruit of *P. brazzeana*. Sweegen notes the previous human consumption of *P. brazzeana* fruit as part of the diet in endemic regions of Africa, suggesting a history of consumption of brazzein as a component of human food. Sweegen describes the biochemical mechanism of brazzein effects on sweet taste perception and notes that this mechanism is similar to that of other known sweet proteins.

Sweegen states that brazzein preparation is similar to the brazzein preparations that are the subjects of GRN 001142 and GRN 001167[2] and incorporates relevant safety information from those notices into the subject GRN. Sweegen summarizes the results of a comprehensive literature search conducted through July 2025, covering multiple scientific databases, to identify available safety information relevant to brazzein, and does not identify any safety concerns or information that would contradict its GRAS conclusion.

Sweegen provides a summary of toxicology studies with brazzein preparation, including a bacterial reverse mutation test, an *in vitro* mammalian cell micronucleus test, and a repeated-dose 90-day oral toxicity study in rats. Sweegen concludes that brazzein preparation is non-mutagenic, non-clastogenic, and non-aneugenic based on the results of the genotoxicity studies. In the 90-day repeated-dose oral toxicity study the no observed adverse effect level (NOAEL) for brazzein was concluded to be 2,000 mg/kg bw/d, the highest dose tested.

Additionally, Sweegen describes corroborative safety information from published studies on brazzein preparations, derived from other strains of *K. phaffii,* that are similar to the subject of this notice. Sweegen notes that these published findings are consistent with those of its own published pivotal toxicology studies on the subject of this notice. Based on the weight of evidence, including the results of *in silico* sequence-alignment-based approaches and an *in vitro* digestibility evaluation, Sweegen concludes that brazzein does not pose an allergenic or toxigenic risk to consumers.

Based on the totality of information, Sweegen concludes that brazzein preparation is GRAS for its intended use.

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[2] The subjects of GRNs 001142 and 001167 are brazzein preparations produced by *K. phaffii* P-BRZ-013 and *K. phaffii* strain "BG12" respectively, expressing the gene encoding for brazzein from *Pentadiplandra brazzeana*. We evaluated these notices and responded in letters dated and March 11, 2024, and October 8, 2024, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Sweegen states its intention to use brazzein preparation 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.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing brazzein preparation bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of ONFL in the Nutrition Center of Excellence. OPMAS did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to 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 Sweegen's notice concluding that brazzein preparation 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 brazzein preparation. Accordingly, our response should not be construed to be a statement that foods containing brazzein preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Sweegen provided, as well as other information available to FDA, we have no questions at this time regarding Sweegen's conclusion that brazzein preparation is GRAS under its intended conditions of use. This letter is not an affirmation that brazzein preparation 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 001293 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

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