U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Wenwen Ma, Ph.D.
PureNutrix+ Inc
400 West Capitol Avenue, Suite 1700
Little Rock, AR 72201

Re: GRAS Notice No. GRN 001295

Dear Dr. Ma:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001295. We received the notice that you submitted on behalf of MicroFarmtory LLC (MicroFarmtory) on July 29, 2025, and filed it on February 27, 2026. MicroFarmtory submitted an amendment to the notice on May 11, 2026, providing additional information about the identity, intended use, relative sweetness, analytical methods, specifications, production organism, and safety narrative.

The subject of the notice is brazzein preparation produced by *Komagataella phaffii* CCTCC M 20241743 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 MicroFarmtory's view that this use of brazzein preparation is GRAS through scientific procedures.

Our use of the terms, "brazzein preparation produced by *Komagataella phaffii* CCTCC M 20241743 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 (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for "brazzein preparation."

MicroFarmtory provides information about the identity and composition of brazzein preparation. MicroFarmtory states that brazzein preparation is a yellowish-brown powder containing ≥90% total protein, of which ≥90% is brazzein, and small amounts of carbohydrates, ash, and fat, as well as residual *K. phaffii* CCTCC M 20241743 proteins carried over from the fermentation process. MicroFarmtory states that brazzein

preparation contains the 53-amino-acid isoform of brazzein, naturally present in the fruit of *P. brazzeana*, known as oubli fruit.

MicroFarmtory states that brazzein preparation is produced from fermentation of a non-pathogenic and non-toxigenic *K. phaffii* CCTCC M 20241743. MicroFarmtory describes the genetic modification and integration of the brazzein gene into the genome of *K. phaffii* GS115 which is derived from *K. phaffii* NRRL-Y-11430. MicroFarmtory states that *K. phaffii* NRRL-Y-11430 and GS115 are 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.

MicroFarmtory describes the method of manufacture of brazzein preparation by controlled fermentation of *K. phaffii* CCTCC M 20241743. The culture broth is centrifuged to separate the biomass from the supernatant. The supernatant is then heat treated, cooled, and centrifuged. The resulting supernatant is then subjected to ultrafiltration to remove macromolecular proteins, followed by purification using ion exchange chromatography. The eluates containing brazzein are subjected to nanofiltration, and then dried, ground, and sifted to obtain the final powder. MicroFarmtory states that none of the raw materials used during the manufacturing process are, or are derived from, major food allergens. MicroFarmtory states that brazzein preparation is manufactured according to good manufacturing practices and that all starting materials and processing aids 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.

MicroFarmtory provides specifications for brazzein preparation that include total protein (≥90%), brazzein (≥90% of total protein), and limits for loss on drying (≤10%), fat (≤1%), ash (≤5%), carbohydrates (≤5%), heavy metals, including lead (≤0.1 mg/kg), and microorganisms, including *Salmonella* serovars (not detected in 25 g). MicroFarmtory provides the results from the analyses of three non-consecutive batches to demonstrate that brazzein preparation can be manufactured to meet the specifications.

MicroFarmtory estimates dietary exposure to 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 and the estimated relative sweetness intensity of brazzein (500 times sweeter than sucrose), MicroFarmtory estimates the average and high percentile dietary exposures to brazzein preparation for non-diabetic adults (0.51 and 1.35 mg/kg body weight (bw)/d, respectively), diabetic adults (0.56 and 1.79 mg/kg bw/d, respectively), non-diabetic children (0.85 and 1.98

[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.

mg/kg bw/d, respectively), and diabetic children (1.34 and 1.82 mg/kg bw/d, respectively).

MicroFarmtory discusses publicly available data and information supporting the safety of brazzein preparation and its production organism, *K. phaffii* CCTCC M 20241743. MicroFarmtory describes brazzein as a principal sweetening component of brazzein preparation and notes that it is similar to native brazzein protein found in the fruit of *P. brazzeana*. MicroFarmtory notes the previous human consumption of *P. brazzeana* fruit as part of the diet in endemic regions of Africa, suggesting previous consumption of brazzein as a component of human food. MicroFarmtory states that brazzein preparation is similar to the subject of GRN 001142 and GRN 001167[2] and incorporates relevant safety information into the notice. MicroFarmtory describes the biochemical mechanism of brazzein effects on sweet taste perception, and notes that the mechanism is similar to that of other known sweet proteins.

MicroFarmtory summarizes the results of a comprehensive literature search through July 2025 to identify available safety information relevant to brazzein preparation produced by *K. phaffii* and does not identify any safety concerns or information that would contradict its GRAS conclusion. MicroFarmtory provides a summary of published 90-day subchronic oral toxicity studies, genotoxicity studies including bacterial reverse mutation assays (or Ames tests), *in vitro* micronucleus assays, and an *in vitro* chromosome aberration assay, to support the safety of the intended use of brazzein preparation. Additionally, MicroFarmtory summarizes additional corroborative safety information in the form of unpublished genotoxicity and repeat-dose oral toxicity studies of brazzein preparation.

Based on the weight of evidence, including the results of *in silico* sequence-alignment-based approaches and an *in vitro* digestibility study, MicroFarmtory concludes that brazzein preparation does not pose an allergenic or toxigenic risk to consumers. MicroFarmtory states that the safety of *K. phaffii* and any derived proteins is further supported by other GRAS conclusions for protein ingredients produced by *K. phaffii*.

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

[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 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, MicroFarmtory 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 MicroFarmtory'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 MicroFarmtory provided, as well as other information available to FDA, we have no questions at this time regarding MicroFarmtory'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 001295 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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