U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Katrina Emmel, PhD
KemmelCal Inc.
947 Martina Circle
Corona, CA 92879

Re: GRAS Notice No. GRN 001286

Dear Dr. Emmel:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001286. We received the notice that you submitted on behalf of GreenLab Inc. (GreenLab) on June 11, 2025, and filed it on December 1, 2025. GreenLab submitted amendments to the notice on March 13, 2026, March 24, 2026, and May 30, 2026, providing clarifying information regarding the materials used in the manufacturing process, specifications, analytical data, and a recently published study.

The subject of the notice is brazzein preparation produced by *Zea mays* expressing a gene encoding for brazzein from *Pentadiplandra brazzeana* (brazzein preparation) for use as a general-purpose sweetener in food 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 GreenLab's view that this use of brazzein preparation is GRAS through scientific procedures.

Our use of the terms, "brazzein preparation produced by *Zea mays* 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."

GreenLab provides information about the identity and composition of brazzein preparation. GreenLab states that brazzein preparation is a white to off-white powder containing ≥80% (on a dry basis) brazzein, small amounts of inorganic salts, and minor amounts of residual corn proteins carried over from the manufacturing process. GreenLab states that brazzein preparation contains the Type 3 isoform of brazzein,

naturally present in the fruit of *P. brazzeana*, known as oubli fruit. GreenLab states that the primary sequence of brazzein is 53 amino acids with a molecular weight of 6.5 kDa.

GreenLab describes the production organism, *Zea mays*, commonly referred to as maize or corn, and notes that it is widely used worldwide for a variety of food products with no carcinogenic, toxigenic, or highly allergenic properties. GreenLab states that the production organism is constructed through a series of transformation steps with different expression constructs to enable the biosynthesis of brazzein. GreenLab confirmed the genetic sequence of the transformed plants using N-terminal sequencing by Edmond degradation along with mass spectrometry of trypsin fragments.

GreenLab states that the manufacturing process starts with corn expressing brazzein that has been spatially segregated from all other corn. The corn is milled into flour, which subsequently undergoes aqueous extraction. The solids are then removed by filtration, and the extract is purified using ion exchange chromatography. The resulting eluate is desalted, lyophilized, and packaged. GreenLab states that all raw materials and processing aids used in the production of brazzein preparation are food grade and are approved for their respective uses via a regulation in Title 21 of the U.S. Code of Federal Regulations, are the subject of an effective food contact notification, or are GRAS for their intended use.

GreenLab provides specifications for brazzein preparation that include purity (≥ 80% brazzein on a dry basis), brazzein as percent of total protein (≥ 90%), and limits for inorganic salts (≤ 20%), arsenic (≤ 0.2 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), lead (≤ 0.5 mg/kg), aflatoxin (≤ 0.02 mg/kg), fumonisin (≤ 4 mg/kg) and microorganisms, including Enterobacteriaceae (< 10 CFU/g), *Salmonella* serovars (negative/25 g), and *Bacillus cereus* (< 100 CFU/g). GreenLab provides the results from the analyses of three non-consecutive batches to demonstrate that brazzein preparation can be manufactured to meet the stated specifications.

GreenLab provides estimates of 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 and an assumption of its substitutional use. Based on the methodology described in Renwick, 2008, and the estimated relative sweetness intensity of brazzein preparation (1200 times sweeter than sucrose), GreenLab estimates the average and upper percentile dietary exposure to brazzein preparation for non-diabetic adults (0.21 and 0.56 mg/kg body weight (bw)/day (d), respectively), diabetic adults (0.23 and 0.75 mg/kg bw/d, respectively), non-diabetic children (0.35 and 0.83 mg/kg bw/d, respectively), and diabetic children (0.56 and 0.76 mg/kg bw/d, respectively).

[1] Renwick AG, 2008, Food Chem Toxicol, 46 Suppl 7: S61-9.

GreenLab discusses publicly available data and information supporting the safety of brazzein preparation. GreenLab describes brazzein as the principal sweetening component of brazzein preparation and notes that it is similar to native brazzein protein found in the fruit of the West African *P. brazzeana* plant. GreenLab notes 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. GreenLab incorporates relevant safety information from GRN 001142[2] into the notice. GreenLab describes the biochemical mechanism of brazzein' s effect on sweet taste perception and notes that the mechanism is similar to that of other known sweet proteins.

GreenLab states that the safety of corn is well established, with an extensive history of safe use in food production and numerous GRAS conclusions for corn-derived ingredients (GRNs 000240,[3] 000427,[4] 000615,[5] 000616,[6] 000792,[7] 000793,[8]

[2] The subject of GRN 001142 is Brazzein produced by *Komagataella phaffii* expressing a gene encoding for brazzein from *Pentadiplandra brazzeana*. We evaluated this notice and responded in a letter dated March 11, 2024, stating that we had no questions at that time regarding the notifiers' GRAS conclusion. FDA notes reference to pending GRAS notifications for brazzein preparations, GRN 001167 and GRN 001207, at the time of submission. Since submission, we completed our evaluations of GRN 001167 and GRN 001207 and responded in letters dated October 8, 2024 and May 23, 2025, respectively, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

[3] The subject of GRN 000240 is corn, cane, or beet sugar cultured with *Lactobacillus paracasei* subsp. *paracasei*, *Bacillus coagulans* LA-1, or *Propionibacterium freudenreichii* subsp. *Shermanii*, or mixtures of these microorganisms. We evaluated this notice and responded in a letter dated October 24, 2008, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[4] The subject of GRN 000427 is corn hull fiber. We evaluated this notice and responded in a letter dated September 12, 2012, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[5] The subject of GRN 000615 is high-amylose cornstarch. We evaluated this notice and responded in a letter dated June 24, 2016, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[6] The subject of GRN 000616 is high-amylose cornstarch acetate. We evaluated this notice and responded in a letter dated June 24, 2016, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[7] The subject of GRN 000792 is *Corynebacterium glutamicum* corn syrup fermentation product. We evaluated this notice and responded in a letter dated April 26, 2019, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[8] The subject of GRN 000793 is *Corynebacterium stationis* corn syrup fermentation product. We evaluated this notice and responded in a letter dated April 26, 2019, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

000900,[9] 001069,[10] 001073,[11] and 001133[12]). GreenLab summarizes the results of a comprehensive literature search through May 2025, to identify available safety information relevant to brazzein preparation and does not identify any safety concerns or information that would contradict its GRAS conclusion. GreenLab acknowledges the well-characterized metabolic fate of dietary proteins and provides evidence of brazzein's susceptibility to enzymatic digestion. GreenLab provides a summary of the literature, including published genotoxicity and subchronic oral toxicity studies of brazzein to support the safety of the intended use of brazzein preparation. This evaluation did not include other uses of corn expressing brazzein preparation or byproducts of brazzein preparation production from corn.

Based on the weight of evidence, GreenLab concludes that brazzein preparation does not pose an allergenic or toxigenic risk to consumers.

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

Standards of Identity

In the notice, GreenLab 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 (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. 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

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[9] The subject of GRN 000900 is corn oil. We evaluated this notice and responded in a letter dated October 30, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[10] The subject of GRN 001069 is ethanol-extracted corn gluten meal containing ≥65% protein. We evaluated this notice and responded in a letter dated February 5, 2024, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[11] The subject of GRN 001073 is corn bran arabinoxylan. We evaluated this notice and responded in a letter dated March 21, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[12] The subject of GRN 001133 is resistant dextrin from corn. We evaluated this notice and responded in a letter dated January 22, 2024, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

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 GreenLab'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 GreenLab provided, as well as other information available to FDA, we have no questions at this time regarding GreenLab'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 001286 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

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