U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Wing Yu
CIRS GROUP USA INC
4250 Fairfax Drive, Suite 600
Arlington, VA 22203

Re: GRAS Notice No. GRN 001305

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001305. We received the notice that you submitted on behalf of Inner Mongolia Kingdomway Pharmaceutical Co., Ltd. (Inner Mongolia Kingdomway) on November 14, 2025, and filed it on April 30, 2026. Inner Mongolia Kingdomway submitted amendments to the notice on July 7, 2026, and July 31, 2026, providing additional information about the manufacturing process, specifications, intended uses, production microorganism, and margin of safety.

The subject of the notice is brazzein preparation produced by *Komagataella phaffii* GDMCC 70101 expressing a gene encoding for brazzein from *Pentadiplandra brazzeana* (brazzein preparation) for use as a general-purpose sweetener in foods at levels consistent with current 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 Inner Mongolia Kingdomway's view that this use of brazzein preparation is GRAS through scientific procedures.

Our use of the terms, "brazzein preparation produced by *Komagataella phaffii* GDMCC 70101 expressing a gene encoding for brazzein from *Pentadiplandra brazzeana*," or "brazzein preparation," in this letter is not our recommendation of those terms 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 (NCE). The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for "brazzein preparation."

Inner Mongolia Kingdomway provides information about the identity and composition of brazzein preparation. Inner Mongolia Kingdomway states that brazzein preparation is a white to light gray powder containing ≥90% total protein (on a dry weight basis

(DWB)), of which ≥90% is brazzein. Inner Mongolia Kingdomway states that brazzein preparation contains the 54-amino-acid isoform of brazzein, naturally present in the fruit of *P. brazzeana*, known as oubli fruit.

Inner Mongolia Kingdomway describes the production organism used in the manufacturing process of brazzein preparation, stating that *K. phaffi* GDMCC 70101 is deposited at the Guangdong Microbiological Culture Collection Center (GDMCC) under the deposition number GDMCC 70101. Inner Mongolia Kingdomway explains that *K. phaffi* GDMCC 70101 was genetically engineered to express the brazzein gene, which was synthesized based on the genetic sequence from *P. brazzeana*, through homologous recombination integration technology. Inner Mongolia Kingdomway states that all genetic modifications were verified by polymerase chain reaction and that *K. phaffi* GDMCC 70101 is non-pathogenic and non-toxigenic.

Inner Mongolia Kingdomway states that brazzein preparation is manufactured through controlled fermentation of *K. phaffii* GDMCC 70101. Following fermentation, the production strain is inactivated by heating and pH adjustment, and the biomass is removed by solid-liquid separation using centrifugation to obtain a supernatant containing brazzein. The supernatant is subjected to ultrafiltration to concentrate the brazzein, followed by chromatographic separation to remove protein impurities. The eluent is then decolorized with activated carbon and subsequently subjected to nanofiltration for desalination and concentration to remove small molecule impurities. The resulting concentrated liquid is dried, sieved to obtain a fine powder, and passed through a magnet to remove potential metal contamination. Inner Mongolia Kingdomway states that brazzein preparation is manufactured according to good manufacturing practices and that all raw materials, processing aids, and food contact substances 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. Inner Mongolia Kingdomway states that brazzein preparation does not contain any of the nine major food allergens.

Inner Mongolia Kingdomway provides specifications for brazzein that include total protein (≥90% DWB), brazzein (≥90% of total protein), and limits for moisture (≤10%), ash (≤5%), glycerol (≤200 mg/kg), methanol (≤20 mg/kg), heavy metals, including lead (≤0.1 mg/kg), and microorganisms. Inner Mongolia Kingdomway provides results from the analyses of three non-consecutive batches to demonstrate that brazzein preparation can be manufactured to meet the specifications.

Inner Mongolia Kingdomway provides estimates of dietary exposure to brazzein preparation based on the relative sweetness intensity of the notified substance and the methodology presented in a published study (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

[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 an assumption of its substitutional use. Based on the methodology described in Renwick, 2008 and the estimated relative sweetness intensity of brazzein preparation (approximately 500 times sweeter than sucrose), Inner Mongolia Kingdomway estimates the average and upper 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 mg/kg bw/d, respectively), and diabetic children (1.34 and 1.82 mg/kg bw/day, respectively).

Inner Mongolia Kingdomway discusses publicly available data and information supporting the safety of brazzein preparation and its production organism, *K. phaffii* GDMCC 70101. Inner Mongolia Kingdomway describes brazzein as the principal sweetening component of brazzein preparation and notes that it is equivalent to native brazzein protein found in the fruit of the *P. brazzeana* plant. We note 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.

Inner Mongolia Kingdomway summarizes the results of a comprehensive literature search through October 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. Inner Mongolia Kingdomway provides a summary of multiple published 90-day subchronic oral toxicity and genotoxicity studies to support the safety of the intended use of brazzein preparation. Based on the available toxicological data, Inner Mongolia Kingdomway derives an acceptable daily intake (ADI) of 20 mg/kg bw/d and concludes that the dietary exposure to brazzein from the intended use of brazzein preparation is below the ADI and does not present a safety concern. Based on the weight of evidence, including the results of an *in vitro* digestibility study and *in silico* sequence-alignment-based approaches to assessing allergenicity, Inner Mongolia Kingdomway concludes that brazzein and copurified *K. phaffii* proteins do not pose an allergenic or toxigenic risk to consumers. Inner Mongolia Kingdomway states that the safety of brazzein preparation is further supported by other GRAS conclusions for precision fermentation derived brazzein preparations.[2] Additionally, Inner Mongolia Kingdomway 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* (see GRNs 000967, 001056, 001104, 001142, 001154, 001167, 001183, 001200, 001201, 001202, and 001219).[3]

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[2] The subjects of GRNs 001142, 001167, and 001207 are brazzein preparation produced by *K. phaffii* P-BRZ-013, *K. phaffii* strain "BG12," and *Aspergillus oryzae* 90402, respectively, expressing a gene encoding for brazzein from *Pentadiplandra brazzeana*. We evaluated these notices and responded in letters dated March 11, 2022, October 8, 2024, and April 10, 2025, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

[3] The subjects of each of these GRNs are produced by *K. phaffii*. We evaluated each of these notices and responded in letters stating that we had no questions at those times regarding the notifiers' GRAS conclusions. Additional information on these GRNs is available at https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices.

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

Standards of Identity

In the notice, Inner Mongolia Kingdomway 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 NCE. 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 Inner Mongolia Kingdomway'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 Inner Mongolia Kingdomway provided, as well as other information available to FDA, we have no questions at this time regarding Inner Mongolia Kingdomway'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 001305 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

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