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 001309

Dear Wing Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001309. We received the notice that you submitted on behalf of Henan Zhongda Hengyuan Biotechnology Stock Co., Ltd. (Hengyuan) on November 18, 2025, and filed it on March 5, 2026. Hengyuan submitted an amendment to the notice on May 21, 2026, that clarified the natural occurrence of the ingredient, manufacturing process, specifications, intended use, and aspects of the safety narrative.

The subject of the notice is D-psicose, produced using D-psicose 3-epimerase expressed in *Bacillus subtilis* CGMCC 22577, for use as a sweetener in the food categories and at the maximum levels shown in Table 1, excluding use in infant formula, foods for infants and young children, and in products under the jurisdiction of the United States Department of Agriculture. The notice informs us of Hengyuan's view that these uses of D-psicose are GRAS through scientific procedures.

Table 1: Intended food categories and maximum use levels for D-psicose.

Food Category	Maximum Use Level (%)
Bakery products (rolls, cakes, pies, pastries, and cookies; low-calorie or dietetic)	10
Non-alcoholic beverages (low- and reduced-calorie, sugar-free)	3.5
Hard candy	50
Soft candy (low- and reduced-calorie, sugar-free)	25
Chewing gum	50
Cereals, regular	2
Cereals (low- and reduced-calorie, sugar-free)	5
Coffee mix	30
Confections and frostings	5
Dressings for salads	5
Frozen dairy desserts (ice cream, soft serve, sorbet; low- and reduced-calorie, sugar-free)	5
Gelatins, puddings, and fillings (low- and reduced-calorie, sugar-	10

Food Category	Maximum Use Level (%)
free)	
Fat-based creams	10
Jams and jellies	10
Sugar	10
Sugar substitutes	100
Sweet sauces and syrups (low- and reduced-calorie, sugar-free)	10
Yogurt and frozen yogurt (low- and reduced-calorie, sugar-free)	5
Alcoholic beverages (pre-mixed cocktails, wine coolers, and malt beverages; low- and reduced-calorie)	3.5

Hengyuan describes D-psicose (also known as D-allulose) as a white to yellow liquid containing ≥95% (dry weight basis (DW)) D-psicose or a white crystalline powder containing ≥98% (DW)) D-psicose. D-psicose is a monosaccharide (C-3 epimer of D-fructose) with a molecular weight of 180.16 g/mol and the CAS Registry No. 551-68-8.

Hengyuan describes the method of manufacture of D-psicose. D-psicose is manufactured from D-fructose by enzymatic epimerization in the presence of D-psicose 3-epimerase produced by *B. subtilis* CGMCC 22577 expressing a gene encoding D-psicose 3-epimerase from *Ruminococcus* sp. 5_1_39B_FAA. Hengyuan states that *B. subtilis* CGMCC 22577 is non-pathogenic and non-toxigenic.

The *B. subtilis* CGMCC 22577 cells are grown by fermentation, and then the culture broth is centrifuged, and the resulting pellet is immobilized using sodium alginate, calcium chloride, diatomaceous earth, and dipotassium phosphate, frame filtration, and drying. The immobilized cell system is used to convert a D-fructose aqueous solution (25-30% solids) to D-psicose at 60 °C. The resulting D-psicose solution is decolorized using activated carbon and subjected to ion exchange chromatography to remove impurities. The purified D-psicose solution is then further purified through separation chromatography to remove residual D-fructose and other sugars, subjected to an additional decolorization, ion-exchange chromatography, and concentrated to yield D-psicose syrup (≥70° Brix). For the crystalline powder, the syrup is further concentrated (≥80° Brix), crystallized, centrifuged, and dried using a fluidized bed. Hengyuan states that D-psicose is manufactured in accordance with current good manufacturing practices and that all raw materials and processing aids are food grade and are used in accordance with U.S. regulations, are GRAS for their intended use, or are the subject of an effective food contact notification. Hengyuan states that the fermentation media does not contain any major food allergens or substances derived from major food allergens.

Hengyuan provides specifications for D-psicose that include D-psicose content (≥95% in syrup or ≥98% in powder, DW), and limits for fructose (≤4.0% in syrup or ≤0.5% in powder, DW), glucose (≤0.5%, for both forms, DW), moisture (≤33% in syrup or ≤1.0% in powder), ash (≤0.5%), lead (≤0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤0.1 mg/kg), and microorganisms, including *Salmonella* serovars (absent in 25 g). Hengyuan provides the results from the analyses of three non-consecutive batches each of syrup and powder to demonstrate that D-psicose can be

manufactured to meet the specifications.

Hengyuan states that the intended uses of D-psicose are the same as those described in GRN 001024[1] and incorporates the dietary exposure estimates from GRN 001024 into the notice. Hengyuan states that the eaters-only dietary exposure to D-psicose from the intended uses is 9.4 g/person (p)/d (0.13 g/kg body weight (bw)/d) at the mean and 22.7 g/p/d (0.32 g/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). Hengyuan notes that because the intended uses of D-psicose are substitutional for the uses in GRN 001024, an increase in the cumulative dietary exposure to D-psicose is not expected. Hengyuan estimates the eaters-only cumulative dietary exposure from all uses of D-psicose to be 11.9 g/p/d at the mean and 23.9 g/p/d at the pseudo-90th percentile[2] for the U.S. population aged 2 years and older and notes that these estimates are similar to those in GRN 001057[3].

Hengyuan summarizes publicly available safety data for D-psicose from prior GRNs for D-psicose (see GRNs 000400, 000498, 000693, 000828, 001024, 001029, 001057, 001188, and 001193)[4] and from updated literature searches through September 2025. Hengyuan discusses studies on D-psicose absorption, distribution, metabolism, and excretion (ADME), acute (rats and dogs) and subchronic (rats and dogs) toxicity, reproductive and developmental toxicity, mutagenicity, genotoxicity, chronic toxicity in animals, and clinical studies involving human tolerance. Based on these data, Hengyuan concludes that D-psicose is non-genotoxic and non-carcinogenic. Hengyuan states that no adverse effects attributable to D-psicose were observed in multiple animal studies including in 90-day studies (1670-2000 mg/kg bw/d) and in a chronic study (approximately 1300 mg/kg bw/d). Additionally, Hengyuan discusses a reproductive toxicity study in rats in which no adverse effects were observed up to the highest dose tested (2000 mg/kg bw/d). Hengyuan discusses multiple human tolerance studies on the safety of orally consumed D-psicose. Hengyuan states that up to 0.5 g/kg bw for men and 0.6 g/kg bw for women of D-psicose were well tolerated. Hengyuan states that its intended conditions of use of D-psicose are identical to those previously evaluated by

---

[1] The subject of GRN 001024 is D-psicose. We evaluated GRN 001024 and responded in a letter dated March 2, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[2] The pseudo-90th percentile dietary exposure approximates the dietary exposure at the 90th percentile by doubling the mean dietary exposure as described in FDA's "Guidance for Industry: Estimating Dietary Intake of Substances in Food" (https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/guidance-industry-estimating-dietary-intake-substances-food).

[3] The subject of GRN 001057 is D-psicose. We evaluated GRN 001057 and responded in a letter dated January 25, 2024, stating that we had no questions at that time regarding the notifier's GRAS conclusion. FDA notes that the eaters-only cumulative dietary exposure in the GRN 001057 response letter was stated to be 12.3 g/p/d at the mean and 24.5 g/p/d at the pseudo-90th percentile for the US population aged 2 years and older.

[4] The subject of GRNs 000400,000498, 000693, 000828, 001029, 001188, and 001193 was D-psicose. We evaluated those GRNs and responded in letters dated June 18, 2012, June 12, 2014, August 28, 2017, March 2, 2020, August 4, 2023, November 19, 2024, and December 12, 2024, respectively, stating that we had no questions at that time regarding each notifier's GRAS conclusion.

FDA and does not identify additional issues of toxicological concern.

Based on the totality of information, Hengyuan concludes that D-psicose is GRAS for its intended use.

Standards of Identity

In the notice, Hengyuan states its intention to use D-psicose 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, & 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 D-psicose 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 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 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 Hengyuan's notice concluding that D-psicose 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 D-psicose. Accordingly, our response should not be construed to be a statement that foods containing D-psicose, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hengyuan provided, as well as other information available to FDA, we have no questions at this time regarding Hengyuan's conclusion that D-psicose is GRAS under its intended conditions of use. This letter is not an affirmation that D-psicose 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 001309 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

Digitally signed by SUSAN J. CARLSON -S
Date: 2026.07.06 10:20:54 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program