U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

John R. Endres ND
GRASroots Consulting, LLC
2543 Paramount Dr.
Enumclaw, WA 98022

Re: GRAS Notice No. GRN 001292

Dear Mr. Endres:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001292. We received HealthTech Bio Actives, S.L.U. (HealthTech)'s notice on July 23, 2025, and filed it on December 19, 2025. HealthTech submitted amendments to the notice on March 10, 2026, March 30, 2026, and April 12, 2026, that clarified the manufacturing process, specifications, intended use, dietary exposure, and aspects of the safety narrative.

The subject of the notice is a compounded sweetener made with neohesperidin dihydrochalcone (NHDC) and gamma cyclodextrin (GCD) (citrus-derived compounded sweetener) for use as a sweetener at levels ranging from 33.3 - 3333.3 mg/kg or L in various foods as described in Table 1, excluding use in infant formula or in products under the jurisdiction of the United States Department of Agriculture. The notice informs us of HealthTech's view that these uses of the citrus-derived compounded sweetener are GRAS through scientific procedures.

Table 1. Intended food categories and maximum use levels for the citrus-derived compounded sweetener.

Food Category	Maximum Use Levels (mg/kg or L)
Sweet crackers	166.6
Biscuits, cornbread, tortillas, corn muffins, other muffins, popovers, and quick breads	166.6
Fruit juices (with and without citrus) and nectars	33.3
Carbonated soft drinks, fruit drinks and nonfruit beverages	33.3
Nutrition drinks and powders	166.6
"Energy" drinks and sports drinks	166.6

Cakes, cookies and pies	166.6
Cobblers, eclairs, turnovers, pastries, danish, doughnuts and coffee cake	166.6
Sugar replacements or substitutes	3333.3
Jellies, jams and preserves	66.6
Ices and popsicles	66.6
Candies	166.6
Cottage cheeses	66.6
Yogurt	66.6
Flavored milk and milk drinks	33.3
Frozen milk desserts	66.6
Puddings, custards and other milk desserts	66.6
Soups with legumes as major ingredient, soups with grain as major ingredient, dark-green vegetable soups, deep-yellow vegetable soups, tomato soups, vegetable soups and Puerto Rican stews/soups with starchy vegetables (viandas)	33.3

Our use of the term, "citrus-derived compounded sweetener" in this letter is not our recommendation of this 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 for Excellence. The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for "citrus-derived compounded sweetener".

HealthTech describes the citrus-derived compounded sweetener as a white or yellowish-white powder comprised of NHDC (CAS number 20702-77-6) and gamma cyclodextrin (GCD, CAS number 17465-86-0) at a ratio of approximately 30:70 by weight. HealthTech indicates that NHDC and GCD are the subject of GRNs 000902[1] and 000046,[2] respectively. In GRN 000902, HealthTech indicates that the manufacturing process for NHDC uses purified neohesperidin crystals as the starting material. These crystals were derived from dried, immature fruits of *Citrus aurantium* via a multi-step extraction process. The citrus-derived compounded sweetener that is the subject of GRN

[1] The subject of GRN 000902 is NHDC. We evaluated this notice and responded in a letter dated November 23, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[2] The subject of GRN 000046 is GCD. We evaluated this notice and responded in a letter dated September 22, 2000, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

001292 is an inclusion complex of NHDC and GCD held together by electrostatic (Van der Waals and/or hydrogen bonds) interactions.

HealthTech provides a description of the manufacturing process for the citrus-derived compounded sweetener. GCD is dissolved in water and NHDC is added to the solution. The resulting mixture is spray-dried to obtain a powder of the citrus-derived compounded sweetener. HealthTech states that the citrus-derived compounded sweetener is manufactured according to current good manufacturing practices, and all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their respective uses, or are the subject of an effective food contact notification. HealthTech states that none of the raw materials used during the manufacturing process are derived from major allergens and the citrus-derived compounded sweetener does not contain any major allergens.

HealthTech provides specifications for the citrus-derived compounded sweetener that include the content of NHDC (28-33%; anhydrous basis), GCD (67-72%; anhydrous basis), water (≤10%), sulphated ash (≤0.5%), and limits for arsenic (≤0.1 mg/kg), cadmium (≤0.1 mg/kg), lead (≤0.3 mg/kg), mercury (≤0.1 mg/kg), and microorganisms. HealthTech provides results from the analyses of five batches[3] to demonstrate that the citrus-derived compounded sweetener can be manufactured to meet these specifications.

HealthTech estimates the dietary exposure to the citrus-derived compounded sweetener using food consumption data from the 2021-2023 National Health and Nutrition Examination Surveys. HealthTech reports the mean and 90th percentile dietary exposures to the citrus-derived compounded sweetener for the U.S. population aged 2 years and older to be 41 mg/person (p)/d (0.67 mg/kg body weight (bw)/d) and 93 mg/p/d (1.5 mg/kg bw/d), respectively. HealthTech states that the intended use of the citrus-derived compounded sweetener is substitutional for the current uses of NHDC in GRN 000902 and therefore, the cumulative dietary exposure to NHDC is not expected to increase. Given that the uses of GCD are only partially substitutional for those in GRN 000046, HealthTech estimates the cumulative mean and 90th percentile dietary exposure to GCD for the U.S. population aged 2 years and older to be 2.8 g/p/d (44 mg/kg body weight (bw)/d) and 5.8 g/p/d (97 mg/kg bw/d), respectively.

HealthTech discusses publicly available data and information supporting the safety of the citrus-derived compounded sweetener. HealthTech states that the citrus-derived compounded sweetener is expected to breakdown into its NHDC and GCD components following ingestion. Therefore, HealthTech discusses the well-characterized safety profiles of NHDC and GCD to support the safety of the NHDC/GCD complex.

[3] HealthTech provides data from five batches of citrus-derived compounded sweetener to demonstrate compliance with the specifications. Three of the batches had the same date and we inquired as to whether they were non-consecutive batches. HealthTech indicated that citrus-derived compounded sweetener is manufactured by a contract manufacturing organization, and the date reflects when the HealthTech facility received the batch and that each batch was produced using different raw material batches of GCD and NHDC. Therefore, each batch is unique.

HealthTech states the safety of NHDC is supported by the GRAS conclusions for both NHDC and GCD[1,2] and incorporates relevant safety information from those notices. HealthTech summarizes the results of a comprehensive literature search through May 2025 to identify available safety information relevant to the citrus-derived compounded sweetener and does not identify any safety concerns or information that would contradict its GRAS conclusion. HealthTech provides a summary of the literature, including published genotoxicity, acute, subchronic, chronic, and developmental toxicity studies of NHDC and/or GCD to support the safety of the intended use of citrus-derived compounded sweetener. HealthTech also summarizes the results of unpublished genotoxicity, subchronic, and developmental toxicity studies for NHDC and/or GCD as additional corroborative evidence of safety. HealthTech describes the results of published clinical studies reporting that under the conditions of the study, GCD was well tolerated, and no adverse effects were reported. Additionally, HealthTech discusses the safety evaluations of NHDC and GCD by other authoritative regulatory bodies as further evidence of safety.

Based on the totality of information, HealthTech concludes that the citrus-derived compounded sweetener is GRAS for its intended use.

Standards of Identity

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

Conclusions

Based on the information that HealthTech provided, as well as other information available to FDA, we have no questions at this time regarding HealthTech's conclusion that citrus-derived compounded sweetener is GRAS under its intended conditions of use. This letter is not an affirmation that citrus-derived compounded sweetener 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 001292 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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