Kayla Preece, ND
Scientific and Regulatory Consultant
AIBMR Life Sciences, Inc.
2800 East Madison Street, Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000902

Dear Dr. Preece:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000902. We received the notice that you submitted on behalf of HealthTech BioActives, S.L.U. (HealthTech) on January 8, 2020, and filed it on February 18, 2020. HealthTech submitted amendments to the notice on May 26, 2020, June 24, 2020, and September 28, 2020, that provided clarifications on information related to the intended use, manufacturing process, specifications, batch analyses, information on analytical methods validation, and safety studies.

The subject of the notice is neohesperidin dihydrochalcone (NHDC) for use as a sweetener in a variety of food categories (excluding infant formula, foods under the jurisdiction of the United States Department of Agriculture, and foods where standards of identity precludes such use) at levels ranging from 10 to 1000 milligrams per kilogram (mg/kg). The notice informs us of HealthTech's view that this use of NHDC is GRAS through scientific procedures.

Our use of the terms "neohesperidin dihydrochalcone" or "NHDC" in this letter is not our recommendation of these 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 Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "neohesperidin dihydrochalcone."

HealthTech provides information on the identity of NHDC. HealthTech describes NHDC as an off-white crystalline powder that is 950 to 1800 times sweeter than sucrose. NHDC has a molecular formula of $C_{28}H_{36}O_{15}$, CAS Registry No: 20702-77-6, and a molecular weight of 612.58 Da. NHDC has a chemical structure that consists of a 3, 2', 4', 6' -tetrahydroxy-4-methoxydihydrochalcone attached to the 4' position of neohesperidosyl via a glycosidic linkage.

HealthTech describes the manufacturing process for NHDC which uses purified neohesperidin crystals as the starting material. HealthTech uses a multi-step extraction process to make the neohesperidin crystals from dried, immature fruits of *Citrus aurantium*. The purified neohesperidin crystals are dissolved in a 4 % (w/w) potassium hydroxide solution to which a palladium-on-charcoal catalyst is then added under hydrogen gas pressure to facilitate hydrogenation. The mixture is neutralized with sulfuric acid, heated to 90 °C, and subjected to filtration to remove the catalyst. The solution is cooled and NHDC is crystallized from the solution. The crude crystals are then dissolved in water and filtered through a 0.6 μm filter to remove small particles and any microorganisms. The purified NHDC crystals are vacuum-dried, milled and packed. HealthTech states that NHDC is manufactured in accordance with current good manufacturing practices using food-grade materials.

HealthTech provides specifications for NHDC that includes assay for NHDC (96-102%), water (<12%), residue on ignition (<0.2%), neodiosmin (<2%), naringin dihydrochalcone (<2%), lead (≤2 mg/kg), arsenic (≤3 mg/kg), cadmium (≤1 mg/kg), and limits for microorganisms. HealthTech provides the results of the analyses of five nonconsecutive batches to demonstrate that NHDC can be manufactured to meet the stated specifications for NHDC, water, residue on ignition, neodiosmin, naringin dihydrochalcone, and microorganisms. HealthTech also provides the results of the analyses of three nonconsecutive batches of NHDC to demonstrate that the specifications for heavy metals are met. Additionally, HealthTech provides stability data indicating that NHDC is stable for up to five years when stored at 30 °C.

HealthTech estimates the dietary exposure for NHDC using food consumption data from the 2015-2016 National Health and Nutrition Examination Surveys. HealthTech estimates the mean and 90th percentile dietary exposures for the U.S. population aged 2 years and older to be 10 mg/person/d (0.15 mg/kg body weight (bw)/d) and 19 mg/person/d (0.33 mg/kg bw/d), respectively. HealthTech states that the use of NHDC in food is self-limiting due to organoleptic factors and consumer taste considerations.

HealthTech discusses the safety of NHDC. HealthTech discusses published toxicokinetic and metabolism data for NHDC and structurally related flavonoids and concludes that NHDC is rapidly excreted and unlikely to remain in any tissue for long periods. HealthTech discusses data from peer reviewed, published 90-day oral toxicity studies in rats. HealthTech concludes that no adverse effects were observed at doses up to 750 mg/kg bw/d. HealthTech also discusses a published rat embryotoxicity and teratogenicity study and concludes that there was no evidence of toxicity to dams or

fetuses at the highest dose of 3100 mg/kg bw/d. HealthTech concludes, based on results from genetic toxicity studies, that NHDC does not induce mutations in bacteria or chromosomal damage in mouse bone marrow.

To further support its view that NHDC is GRAS, HealthTech discusses data from published, non-peer reviewed toxicology studies, including a 2-year study in dogs, 1-year and 11-month studies in rats, as well as a reproductive toxicology study and a toxicokinetic study in rats. HealthTech also discusses the results from unpublished studies to corroborate the safety of NHDC. Additionally, HealthTech discusses safety evaluations by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in support of its review of several similarly structured flavor compounds and by the European Commission Scientific Committee for Food (SCF) in its evaluation of NHDC as a sweetener. HealthTech states that there is no reason to suspect that NHDC would pose a safety concern to diabetic consumers.

Based on the totality of data and information presented in the notice, HealthTech concludes that NHDC is GRAS for its intended use in food.

Standards of Identity

In the notice, HealthTech states its intention to use NHDC in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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.

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 NHDC 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 NHDC. Accordingly, our response should not be construed to be a statement that foods containing NHDC, 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 NHDC is GRAS under its intended conditions of use. This letter is not an affirmation that NHDC 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 000902 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.11.23 18:14:03 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition