Alan B. Richards, Ph.D.
Vanguard Regulatory Services, Inc.
1311 Iris Circle
Broomfield, CO 80020

Re: GRAS Notice No. GRN 000901

Dear Dr. Richards:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000901. We received the notice that you submitted on behalf of Hayashibara Co., Ltd. (Hayashibara) on December 12, 2019, and filed it on February 19, 2020. Hayashibara submitted amendments to the notice on May 29, 2020, June 24, 2020, July 27, 2020, and September 7, 2020, that clarified aspects of the intended use, materials used in manufacturing processes, specifications, safety studies, and provided English translations of published studies cited in the notice.

The subject of the notice is glucosyl hesperidin for use as an antioxidant, coloring adjunct,[1] flavor enhancer, and flavoring agent and adjuvant in yogurts; chocolates; soft and hard candies; instant and bottled/canned coffees; instant and bottled/canned teas; carbonated waters; soft drinks; fruit and vegetable juice drinks and lemonade; fruit flavored drinks; beverage powders; "fortified" waters; nutritional, "energy," and "sports" drinks and powders; fluid replacement drinks; and other "functional" beverages at levels up to 500 mg per serving. The notice informs us of Hayashibara's view that these uses of glucosyl hesperidin are GRAS through scientific procedures.

Our use of the term, "glucosyl hesperidin," 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 Title 21 of the Code of Federal Regulations (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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "glucosyl hesperidin."

[1] Hayashibara states that the intended use of glucosyl hesperidin as a coloring adjunct is to improve the stability of colors added to food and that the use of glucosyl hesperidin does not itself impart color.

Hayashibara provides information regarding the identity and composition of glucosyl hesperidin. Hayashibara describes glucosyl hesperidin as a pale yellow to yellow-brown powder containing 75 to 85% monoglucosyl hesperidin. Monoglucosyl hesperidin (CAS No. 161713-86-6) has the chemical name (2*S*)-7-({6-O-[6-deoxy-α-L-mannopyranosyl-(1→]-4-*O*-[α-D-glucopyranosyl-(1→]-β-D-glucopyranosyl-(1→}oxy)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4H-chromen-4-one. Hayashibara discusses the results of compositional analyses of glucosyl hesperidin to demonstrate that it also contains approximately 14% hesperidin and minor amounts of di- and maltooligosyl hesperidin, other monoglycosyl flavonoids, β- and γ-cyclodextrins, and other saccharides.

Hayashibara provides a description of the manufacturing method for glucosyl hesperidin from hesperidin. Hayashibara states that glucosyl hesperidin is manufactured following current good manufacturing practices and all materials used in the manufacturing processes are food-grade and are authorized for their respective uses in the U.S. Hayashibara states that hesperidin is first extracted from orange peel with an alkaline solution, followed by acid precipitation and several steps of crystallization and washing. The crystalline hesperidin is then heated with sodium pyrosulfite in an aqueous solution of sodium hydroxide. Ascorbic acid and magnesium chloride are added to the solution, followed by the addition of dextrin. The pH of the resulting solution is optimized with sulfuric acid and cyclodextrin glucanotransferase[2] (EC 2.4.1.19) is then added to catalyze the transfer of oligosaccharides from the dextrin (starch) to the C4 position of the glucose unit of the hesperidin. After further adjusting the pH, glucoamylase[3] (EC 3.2.1.3) is added to catalyze the cleavage of any excess terminal glucose moieties from the formed glucosyl hesperidin. The reaction mixture is then heated to inactivate the enzymes and then the solution is cooled, filtered through diatomaceous earth, and subjected to an adsorption resin. Glucosyl hesperidin and hesperidin are eluted from the resin using ethanol. Ethanol is then removed by distillation and the remaining solution is decolorized and treated with powdered cellulose and activated carbon. The resulting glucosyl hesperidin solution is concentrated and spray-dried.

Hayashibara provides specifications for glucosyl hesperidin that include the content of monoglucosyl hesperidin (75–85% on a dry basis (db)) and total hesperidin (≥70% db), limits for pH (5.0 to 7.0), loss on drying (≤6%), residue on ignition (≤2%), lead (≤0.1 mg/kg), arsenic (≤1.5 mg/kg), as well as limits on microorganisms. Hayashibara provides results from analysis of five nonconsecutive batches to demonstrate that

[2] Hayashibara states that cyclodextrin glucanotransferase (EC 2.4.1.19) is isolated from a non-genetically engineered strain of *Bacillus stearothermophilus* (currently referred to as *Geobacillus stearothermophilus*). Hayashibara states that *G. stearothermophilus* is a non-pathogenic and non-toxigenic soil organism in the order of Firmicutes.

[3] Hayashibara states that glucoamylase (EC 3.2.1.3) is a carbohydrase obtained from the fermentation of *Rhizopus oryzae*, which is a non-pathogenic and non-toxigenic filamentous fungus. According to 21 CFR 173.130, carbohydrase from *Rhizopus oryzae* is approved for use in food as a secondary direct food additive.

glucosyl hesperidin can be manufactured to meet specifications.

Hayashibara provides estimates of the background dietary exposure to hesperidin based on its occurrence in food, and dietary exposure to glucosyl hesperidin based on the intended uses. Using food consumption data from the 2013–2016 National Health and Nutrition Examination Survey (NHANES) and data on the hesperetin[4] concentrations in food (USDA Database for the Flavonoid Content of Selected Foods), Hayashibara estimates the mean and 90th percentile background dietary exposure to hesperidin from the diet for the total population to be approximately 29 and 79 mg/person (p)/day (d), respectively. Based on NHANES food consumption data and the intended uses, Hayashibara estimates the mean and 90th percentiles dietary exposures to glucosyl hesperidin for the total population (users only) to be 826 and 1725 mg/p/d, respectively; this is equivalent to 603 and 1259 mg/p/d, respectively, on a hesperidin basis. In an amendment, Hayashibara discusses the intended use of the subject of GRN 000796,[5] which is specified to be ≥85% hesperidin. Hayashibara concludes that the intended use of glucosyl hesperidin is substitutional and is not expected to affect cumulative dietary exposure on a hesperidin basis.

Hayashibara discusses publicly available publications and supportive unpublished data supporting the safety of its intended use of glucosyl hesperidin. Hayashibara states that the publicly available information was gathered during literature searches which were most recently updated in December 2019. Their literature searches included information about glucosyl hesperidin as well as safety information about hesperidin.

Hayashibara discusses published and corroborative unpublished rat and human studies to support their conclusion that ingested glucosyl hesperidin is first metabolized to hesperidin and then to hesperetin, which is subsequently absorbed. Hayashibara states that the exposure to hesperetin is 3 to 3.7-fold higher after the ingestion of glucosyl hesperidin relative to the exposure following the ingestion of equivalent amounts of hesperidin. Hayashibara concludes that glucosyl hesperidin is absorbed into and metabolized in the body by the same pathway as hesperidin, which provides a basis to incorporate hesperidin safety assessments into their glucosyl hesperidin safety assessment.

Hayashibara discusses the results of a published study in which no toxicity was observed after 90 days of dietary administration of up to 3084 mg/kg bw/d glucosyl hesperidin to rats of both sexes. Hayashibara also states that no reproductive or teratogenic effects were found after administration of up to 1000 mg/kg bw/d of glucosyl hesperidin to gestating female rats. Hayashibara discusses published studies showing lack of genetic toxicity for glucosyl hesperidin. Hayashibara also discusses unpublished absorption, distribution, metabolism, and excretion as well as genetic toxicology studies which supported their conclusions drawn from published literature. Discussing the results of

[4] Hayashibara states that hesperetin is a direct metabolite of hesperidin and uses the ratio of molecular weights of hesperetin to hesperidin to estimate the background dietary exposure to hesperidin.
[5] The subject of GRN 000796 was orange extract containing ≥85% hesperidin. We evaluated GRN 000796 and responded in a letter dated February 20, 2019, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

both clinical and rat physiologic studies, Hayashibara found no evidence that glucosyl hesperidin affected blood pressure, serum triglycerides or had cardiovascular or clinical toxicity.

Hayashibara states that the safety information for structurally related hesperidin and methyl hesperidin are relevant for safety conclusion of glucosyl hesperidin. Hayashibara notes that the safety narratives in GRNs 000719[6] and 000796 contained detailed discussions of the safety of hesperidin. Hayashibara provides a similar discussion of the safety of hesperidin and methyl hesperidin based on a discussion of the published literature. Based on their discussion of glucosyl hesperidin, hesperidin and methyl hesperidin, Hayashibara concludes that the absence of an increase in cumulative exposure to hesperidin as hesperetin provides evidence for the safety of their intended use of glycosyl hesperidin.

Hayashibara includes the report and the statement of a panel of individuals (Hayashibara's GRAS panel).[7] Based on its review, Hayashibara's GRAS panel concluded that glucosyl hesperidin is safe under the conditions of its intended use.

Based on the totality of the available scientific information, Hayashibara concludes that glucosyl hesperidin is GRAS under the conditions of its intended use.

Standards of Identity

In the notice, Hayashibara states its intention to use glucosyl hesperidin in several food categories, including foods for which standards of identity exist, located in 21 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(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if it contains any chemical preservative, unless the label states that fact. Under section 403(i)(2) of the FD&C Act, a food is misbranded unless its label bears the common or usual name of each ingredient. Further, under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any way. Hayashibara's intended use of glucosyl hesperidin constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing glucosyl hesperidin must comply with the labeling regulations implemented in sections 403(k) and 403(i)(2) of the FD&C Act. For example, 21 CFR 101.22(j) requires that the label of a food with an added chemical preservative must declare both the common or usual name of the

[6] The subjects of GRN 000719 were orange pomace and enzyme-treated orange pomace. We evaluated GRN 000719 and responded in a letter dated December 26, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[7] Hayashibara includes in the notice the statement of Hayashibara's GRAS panel dated December 1, 2019, which refers to its GRAS panel report from December 15, 2009. Hayashibara provided its 2009 GRAS Panel report in the amendment dated May 29, 2020.

ingredient and a separate description of its function. Further, food that is subjected to any form of preservation, except as provided in 21 CFR 101.95(c), may not be labeled as "fresh." Questions related to food labeling should be directed to ONFL in CFSAN.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Hayashibara describes glucosyl hesperidin as a pale yellow to yellow-brown powder. As such, the use of glucosyl hesperidin in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000901 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

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 Hayashibara's notice concluding that glucosyl hesperidin 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 glucosyl hesperidin. Accordingly, our response should not be construed to be a statement that foods containing glucosyl hesperidin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hayashibara provided, as well as other information available to FDA, we have no questions at this time regarding Hayashibara's conclusion that glucosyl hesperidin is GRAS under its intended conditions of use. This letter is not an affirmation that glucosyl hesperidin 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 000901 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.11.09 17:10:13 -05'00'

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Director
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