



John R. Endres, ND
AIBMR Life Sciences, Inc.
2800 E. Madison Street
Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000796

Dear Dr. Endres:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000796. We received the notice that you submitted on behalf of Interquim d/b/a Ferrer HealthTech (Ferrer HealthTech) on July 2, 2018, and filed it on August 6, 2018. Ferrer HealthTech submitted amendments to the notice on September 14, 2018, and February 6, 2019, that include clarification on specifications and references, discussion of two additional studies, and the timeframe for the literature search conducted.

The subject of the notice is orange extract for use as an ingredient in flavored milk and imitation milk drinks; dry powdered milk mixtures; yogurts; coconut beverages; cookies; cereals; cereal, granola, and nutrition bars; fruit, fruit-flavored, and vegetable juices and drinks; table fats and vegetable oils; chocolate and dietetic candies; teas; carbonated soft drinks; “fortified” waters; nutrition drinks; nutrition powders; “energy” drinks; and “sport” drinks at a level of 500 mg per serving. The notice informs us of Ferrer HealthTech’s view that this use of orange extract is GRAS through scientific procedures.

Our use of the term, “orange extract,” 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 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 “orange extract.”

Ferrer HealthTech provides information on the source, identity, and composition of orange extract. Orange extract is a light brown to yellowish powder obtained from the exocarp and mesocarp of immature, dried fruits of sweet orange (*Citrus sinensis*). Orange extract contains $\geq 85\%$ hesperidin (CAS Registry Number 520-26-3), including

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

both the 2*S*- and 2*R*-diastereomer with ≥85% as the 2*S*-diastereomer. Orange extract also contains ≤8% of narirutin (CAS Registry Number 14259-46-2) and ≤3% of minor extractable material from the mesocarp of immature orange, such as the flavonoids didymin and diosmin.

Ferrer HealthTech provides a description of the manufacturing method for orange extract. Sweet orange fruits are harvested at an immature age, dried, and extracted with water under alkaline conditions. The resulting aqueous extract is treated with sulfuric acid to precipitate 2*S*-hesperidin. The mixture is submitted to heat treatment, filtered, and the product is dried to the final orange extract.

Ferrer HealthTech provides specifications for orange extract that include a minimum content of total hesperidin (≥85% on dry weight basis), 2*S*-hesperidin (≥85% of total hesperidin), limits for narirutin (≤8%), ash (≤0.2%), loss on drying (≤5%), lead (≤0.5 mg/kg), arsenic (≤0.2 mg/kg), cadmium (≤1 mg/kg), mercury (≤0.1 mg/kg), as well as limits on microorganisms. Ferrer HealthTech provides the results of four nonconsecutive batch analyses to demonstrate that orange extract can be manufactured to meet specifications.

Ferrer HealthTech provides estimates of dietary exposure to hesperidin based on its occurrence in the diet, the intended use of orange extract, and food consumption data from 2013–2014 National Health and Nutrition Examination Survey (NHANES). Based on published data for the concentration of hesperidin and NHANES consumption data for various citrus fruits, Ferrer HealthTech estimates the 90th percentile dietary exposure to hesperidin for the total population to be 72.1 mg/person (p)/day (d) (1.4 mg/kg body weight (bw)/d). Based on an assumption that orange extract contains 100% hesperidin, Ferrer HealthTech estimates the combined 90th percentile dietary exposure to hesperidin from current consumption and from the intended uses of orange extract for the total population to be 2,608 mg/p/d (39.5 mg/kg bw/d).

Ferrer HealthTech discusses data and information relevant to the safety of orange extract. Ferrer HealthTech states that no statistically significant adverse effects were reported in the following studies discussed in the 1982 safety assessment of hesperidin, naringin, and citrus bioflavonoid extracts; or in GRN 000719¹: (1) a published 200-day study in rats fed up to approximately 1,000 mg/kg bw/d hesperidin or naringin (toxicologically related to narirutin), (2) published 13-week and 96-week studies in mice fed up to approximately 7,500 mg/kg bw/d methyl hesperidin (toxicologically related to hesperidin), (3) an unpublished 400-day study in rats fed approximately 2,000–5,000 mg/kg bw/d hesperidin or naringin, and (4) an unpublished reproductive study in mice fed approximately 1,300–3,600 mg/kg bw/d hesperidin complex² for 158 days or naringin for 219 days. In addition, Ferrer HealthTech discusses published 13-week and 6-month studies in rats fed up to 1,250 mg/kg bw/d naringin that did not report

¹GRN 000719 describes uses of orange pomace (containing hesperidin as a minor component) in foods. FDA evaluated this notice and responded in a letter dated December 26, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

²A crude hesperidin preparation with an average hesperidin content of 72%.

statistically significant adverse effects. Ferrer HealthTech also summarizes several published human clinical studies using levels of up to 800 mg of 80% pure hesperidin for 4 weeks (highest dose) or 200 mg hesperidin and 1,152 mg naringin for 60 days (longest duration) and states that no adverse effects were reported in these studies. Ferrer HealthTech states that published mutagenicity and genotoxicity studies on hesperidin and hesperetin (hesperidin aglycone) found them to be nongenotoxic. Ferrer HealthTech reports that they conducted a literature search on the safety of orange extract through May 2018.

Based on the information presented in the notice, Ferrer HealthTech concludes that orange extract is GRAS for its intended use in foods.

Standards of Identity

In the notice, Ferrer HealthTech states its intention to use orange extract 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.

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). The notice raises a potential issue under these labeling provisions. In the notice, Ferrer HealthTech cites a study that describes hesperidin, a main component of orange extract, as having certain health benefits. If products containing orange extract 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. OFAS 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Ferrer HealthTech describes orange extract as light brown to yellowish. As such, the use of orange extract 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 000796 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 Petition Review in OFAS.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Ferrer HealthTech's notice concluding that orange extract is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing orange extract. Accordingly, our response should not be construed to be a statement that foods containing orange extract, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Ferrer HealthTech provided, as well as other information available to FDA, we have no questions at this time regarding Ferrer HealthTech's conclusion that orange extract is GRAS under its intended conditions of use. This letter is not an affirmation that orange extract 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 000796 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Dennis M.
Keefe -S**

Digitally signed by Dennis M.
Keefe -S
Date: 2019.02.20 14:14:08 -05'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition