



Jim Lassiter
Rejimus, Inc.
600 W. Santa Ana Blvd.
Suite 1100
Santa Ana, CA 92701

Re: GRAS Notice No. GRN 001064

Dear Mr. Lassiter:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001064. We received the notice that you submitted on behalf of Verdure Sciences on March 28, 2022, and filed it on June 7, 2022. Verdure Sciences submitted amendments to the notice on October 7, 2022, October 28, 2022, November 9, 2022, April 19, 2023, April 28, 2023, May 26, 2023, July 28, 2023, July 31, 2023, and August 9, 2023 that provided additional information on the chemical composition, specifications, dietary exposure estimate, and various aspects of the safety data submitted in support of the notice.

The subject of the notice is whole fruit pomegranate extract for use as an ingredient in dairy milks, fruit and vegetable juices, and chocolate candies at levels up to 50 mg per serving.^{1, 2} The notice informs us of Verdure Sciences' view that these uses of whole fruit pomegranate extract are GRAS through scientific procedures.

Our use of the term, "whole fruit pomegranate 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 non-standardized 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 "whole fruit pomegranate extract."

Verdure Sciences describes whole fruit pomegranate extract (CAS No. 84961-57-9) as a

¹ Based on the Reference Amounts Customarily Consumed in 21 CFR 101.12 Table 2.

² Verdure Sciences states that whole pomegranate fruit extract is not intended for use in infant formula, foods formulated for infants and young children, and products under the jurisdiction of the United States Department of Agriculture.

yellowish-brown to brown powder derived from the whole pomegranate fruit (*Punica granatum* L.), including the rind. Verdure Sciences states that whole fruit pomegranate extract contains $\geq 50\%$ total polyphenols (including $\geq 30\%$ punicalagins), carbohydrates, and small amounts of protein, fat, and ash. Verdure Sciences states that the ratio of punicalagins to total polyphenols in whole fruit pomegranate extract is similar to that in commercial pomegranate juice derived from the whole fruit.

Verdure Sciences describes the method of manufacture for whole fruit pomegranate extract. Whole pomegranate fruits are washed, crushed, and extracted with 100% ethanol. The ethanolic extract is then filtered and concentrated by evaporation. The resulting concentrate is spray-dried and milled to produce the final whole fruit pomegranate extract powder. Verdure Sciences states that whole fruit pomegranate extract is manufactured according to current good manufacturing practices and that all processing aids are used in accordance with the appropriate U.S. regulations.

Verdure Sciences provides specifications for whole fruit pomegranate extract that include a minimum level of polyphenols ($\geq 50\%$) and limits for ethanol (≤ 1000 mg/kg), lead (< 0.1 mg/kg), mercury (< 0.1 mg/kg), arsenic (< 0.1 mg/kg), cadmium (< 0.1 mg/kg), and microorganisms. Verdure Sciences provides the results from the analyses of four non-consecutive batches to demonstrate that whole fruit pomegranate extract can be manufactured to meet these specifications. Verdure Sciences provides the results of a stability study and states that whole fruit pomegranate extract is stable for 4 years at 30 °C and 65% humidity.

Verdure Sciences estimates an eaters-only dietary exposure to whole fruit pomegranate extract from the intended uses to be 41 mg/person (p)/d at the mean and 96 mg/p/d at the 90th percentile for the U.S. population aged 2 years or older using food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES).³ In addition, Verdure Sciences provides an eaters-only estimate of dietary exposure to polyphenols from the intended uses of whole fruit pomegranate extract to be 55.1 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older.⁴ Verdure Sciences also estimates the cumulative dietary exposure to pomegranate polyphenols from the intended uses of whole fruit pomegranate extract and the background sources (pomegranate fruit and its juice) to be 54.5 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older.

Verdure Sciences discusses the absorption, distribution, metabolism, and excretion (ADME) of pomegranate fruit extract and its constituents, and states that the metabolites are excreted and not significantly retained in tissues. Verdure Sciences reviews several published oral toxicology studies in rodents, including a 90-day (subchronic) study, where the whole fruit pomegranate extract was orally administered.

³ Using food consumption data from the 2017-2018 NHANES, FDA estimated an eaters-only dietary exposure to whole fruit pomegranate extract from the intended uses to be 60 mg/p/d at the mean and 130 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older.

⁴ Verdure Sciences notes that the dietary exposure to polyphenols from the intended uses of whole fruit pomegranate extract was conservatively based on the highest total polyphenol content of 57.4% reported for one of the batches.

No treatment-related adverse effects were observed even at the highest dose in the subchronic study. Verdure Sciences states that pomegranate fruit extract is not genotoxic or cytotoxic. Verdure Sciences also cites several published studies performed in humans that were orally administered whole fruit pomegranate extract. No adverse events were reported in these studies. Verdure Sciences states that the occurrence of allergic reactions to pomegranate fruit is rare and that pomegranate fruit is not considered a major food allergen.

Based on the totality of evidence, Verdure Sciences concludes that whole fruit pomegranate extract is safe for its intended use.

Standards of Identity

In the notice, Verdure Sciences states its intention to use whole fruit pomegranate extract 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, 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). If products containing whole fruit pomegranate 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 in CFSAN. 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, Verdure Sciences describes whole fruit pomegranate extract as a yellowish-brown to brown dry powder. As such, the use of whole fruit pomegranate 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 001064 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 Verdure Sciences' notice concluding that whole fruit pomegranate extract 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 whole fruit pomegranate extract. Accordingly, our response should not be construed to be a statement that foods containing whole fruit pomegranate extract, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Verdure Sciences provided, as well as other information available to FDA, we have no questions at this time regarding Verdure Sciences' conclusion that whole fruit pomegranate extract is GRAS under its intended conditions of use. This letter is not an affirmation that whole fruit pomegranate 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 001064 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
Division of Food Ingredients
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