



Margien Mutter, PhD
G3P Inc.
20 Mall Road, Suite 220
Burlington, MA 01803

Re: GRAS Notice No. GRN 001199

Dear Dr. Mutter:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001199. We received G3P Inc. (G3P)'s notice on June 4, 2024, and filed it on September 30, 2024. G3P submitted an amendment on December 10, 2024, clarifying the intended use and providing additional information on the enzymes, manufacturing process, specifications, and safety.

The subject of the notice is rhamnogalacturonan-I (RG-I) enriched fraction from pumpkin purée (pRG-I) for use as an ingredient in instant coffee and tea at levels up to 1% and in bagels, English muffins, biscuits, bread and rolls (excluding sweet types), breadsticks, cornbread, corn muffins, tortillas, crackers, and pies; enhanced, flavored, carbonated, and fortified water; non-milk-based meal replacement, protein, and nutritional beverages; soft drinks; sports, electrolyte drinks, and fluid replacement drinks; breakfast cereals; non-dairy milk, cream, and yogurts; puddings and other milk-based desserts, and pie fillings; meal replacement, cereal, granola, "energy", and protein bars; macaroni and noodle products, and rice-based dishes; buttermilk and plain fermented milk; evaporated, condensed, and dry milk; flavored milk, milk drinks, and mixes; milk shakes; milk-based replacement, nutrition, and protein beverages; yogurt and yogurt drinks; milk-based snack dips; gummy candy; and soups at levels up to 2%.¹ The notice informs us of G3P's view that these uses of pRG-I are GRAS through scientific procedures.

Our use of the term, "pRG-I" 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 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 Nutrition Center of Excellence (NCE). The Office of Pre-Market Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "pRG-I."

¹ G3P states that pRG-I is not intended for use in infant formula or infant food products, products under the jurisdiction of the United States Department of Agriculture, or in foods for which standards of identity preclude its use.

G3P states that pRG-I is obtained by enzymatic extraction of pectin from pumpkin purée and is enriched in modified RG-I, which is a low-molecular weight fraction of pectin. G3P describes pRG-I as a dark orange or pale-yellow powder containing $\geq 45\%$ total carbohydrates with galactose, arabinose, uronic acid, rhamnose, and glucose being the predominant sugars.

G3P describes the manufacturing process for pRG-I. The pumpkin purée from *Cucurbita moschata* var. Dickinson is heated at 50 °C for 2 hours in the presence of a mixture of the three enzymes.^{2, 3} The enzymes are inactivated by heat treatment. The extract is separated from insoluble materials and the supernatant is filtered to remove remaining solids followed by ultrafiltration and concentration. The concentrated extract is then diafiltrated, homogenized, sterilized, pasteurized, and spray dried to yield pRG-I. G3P states that pRG-I is manufactured in accordance with current good manufacturing practices and that all starting materials and processing aids are food grade, and that they are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

G3P provides specifications for pRG-I that include total carbohydrates ($\geq 45\%$) and major monosaccharides (uronic acids ($\leq 30\%$), rhamnose (4-10%), arabinose (3-10%), galactose (10-36%), and glucose ($\leq 20\%$)), ratio of uronic acids vs. rhamnose (1-4), moisture ($\leq 10\%$), fat ($\leq 27\%$), protein ($\leq 15\%$, dry basis), ash ($\leq 7\%$), arsenic (≤ 0.1 mg/kg), mercury (≤ 0.01 mg/kg), cadmium (≤ 0.1 mg/kg), lead (≤ 0.15 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). G3P provides the results from the analyses of three non-consecutive batches to demonstrate that pRG-I can be manufactured to meet these specifications. Based on the results from the accelerated and real-time stability studies, G3P states that pRG-I is stable for at least 24 months.

G3P estimates the dietary exposure to pRG-I based on the intended uses of pRG-I and food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). G3P estimates the mean and 90th percentile eaters-only dietary exposure to pRG-I for the U.S. population aged 2 years and older to be 8.6 g/person (p)/d (128 mg/kg body weight (bw)/d) and 18.1 g/p/d (278 mg/kg bw/d), respectively. G3P states that the intended uses of pRG-I are substitutional to the current uses of other

² G3P Inc. states that the three enzyme systems used in the manufacturing of pRG-I include (i) a commercially available α -amylase and amyloglucosidase from *Aspergillus niger*; (ii) a commercially available multi-enzyme cellulase complex (containing endo-glucanase, exo-glucanases, glucosidase and several hemicellulases) derived from *Trichoderma longibrachiatum*; and (iii) a pectinase enzyme (containing endo-polygalacturonase and pectin esterase) derived from non-genetically engineered strains of *A. niger*.

³ G3P states that α -amylase and amyloglucosidase, and pectinase enzymes from *A. niger* meet the specifications for activity, purity and microbial content described in GRN 000089. We evaluated this notice and responded in a letter dated April 03, 2002, stating that we had no questions at that time regarding the notifier's GRAS conclusion. G3P states that the multi-enzyme cellulase complex is GRAS in accordance with 21 CFR 184.1250.

fiber-containing ingredients and therefore, there will be no increase in the cumulative dietary exposure to fiber.

G3P states that pectins generally, of which pRG-I is a family member, are part of the human diet, present in commonly consumed fruits and vegetables, with no report of adverse effects attributable to them. G3P also notes that pectins from different plant sources are considered GRAS with no limitation to inclusion in food. In addition, pRG-I is derived from puréed pumpkin, which is a part of the human diet. Further, G3P notes that pectins are not readily absorbed intact in the gastrointestinal tract but are digested by bacterial fermentation in the large intestine and converted to short chain fatty acids, which are normal metabolites in the human body. G3P also notes that compounds with molecular weights greater than 1 kiloDalton (kDa) are not readily absorbed by the gastrointestinal tract and that pRG-I contains the fractions with the molecular weights above 30 kDa that are unlikely to be absorbed.

G3P also conducted an *in vitro* fermentation assay on pRG-I using human intestinal microbiota and reports that it is fermentable by human gut microbiota. G3P discusses published toxicological studies using pRG-I as the test article to support their GRAS conclusion. G3P states that no toxicologically relevant adverse effects on the measured study parameters were reported following dietary administration of pRG-I to Sprague-Dawley rats at up to 36,000 ppm/d in a published 90-day study. G3P also states that pRG-I was non-mutagenic and non-clastogenic based on the results of testing in an *in vitro* bacterial reverse mutation assay and an *in vitro* micronucleus assay. G3P discusses the potential for pRG-I to be allergenic and notes that while allergenicity to pumpkin and pumpkin seed has been reported in the literature, pRG-I is unlikely to produce allergic reactions given the extensive processing and purification it undergoes. G3P summarizes the published literature on the safety of pectins from other sources and pumpkin pectin, and notes that none of the publications found in that search contradict its GRAS conclusion.

Based on the totality of the data and information, G3P concludes that pRG-I is GRAS for its intended use.

Standards of Identity

In the notice, G3P states its intention to use pRG-I 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 pRG-I

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 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, G3P describes pRG-I as a dark orange or pale-yellow powder. As such, the use of pRG-I 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 001199 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 OPMAS.

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 G3P's notice concluding that pRG-I 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 pRG-I. Accordingly, our response should not be construed to be a statement that foods containing pRG-I, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that G3P provided, as well as other information available to FDA, we have no questions at this time regarding G3P's conclusion that pRG-I is GRAS under its intended conditions of use. This letter is not an affirmation that pRG-I 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 001199 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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