U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Wing Yu
CIRS GROUP USA INC
4250 Fairfax Drive, Suite 600
Arlington, VA 22203

Re: GRAS Notice No. GRN 001253

Dear Wing Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001253. We received the notice that you submitted on behalf of Wuhan Hesheng Technology Co., Ltd. (Hesheng) on February 22, 2025 and filed it on March 24, 2025. Hesheng' submitted an amendment to the notice on May 27, 2025 clarifying the specifications, storage conditions, dietary exposure, intended uses, manufacturing process, and provided references to safety data cited.

The subject of the notice is a lycopene preparation produced by *Saccharomyces cerevisiae* "JZL03" (lycopene preparation) for use as an ingredient at levels ranging from 5 mg/kg to 575 mg/kg in a variety of food categories as described in Table 1 (excluding use in infant formula and products under the jurisdiction of the United States Department of Agriculture). The notice informs us of Hesheng's view that these uses of lycopene preparation are GRAS through scientific procedures.

Table 1. Food categories and intended use levels

Food Category	Proposed Food Use	Use Level (mg/kg)
Baked goods and baking mixes	Nutrition bars	50
	Crackers	30
Beverages and beverage bases	Meal replacements	25
Breakfast cereals	Ready-to-eat cereals	50
Cheeses	Processed cheese spread	5
Condiments and relishes	Sauces, seasonings, relishes, and pickles	50
Confections and frostings	Decorations, fillings, and icings	25
Fats and oils	Table fat spreads	5
	Low fat salad dressings	20
Frozen dairy desserts and mixes	Frozen dairy desserts	25
Gelatins, puddings, and fillings	Gelatin desserts, puddings, and custards	25
Gravies and sauces	Tomato-based, gravies, and specialty sauces	50
Hard candy	Hard candy	25
Milk products	Dairy-based fruit drinks	50
	Milk-based meal replacements	25
	Cultured dairy drinks	20
Plant protein products	Meat substitutes	50
Processed fruits and fruit juices	"Energy", sports, and isotonic drinks	25
	Fruit-flavored drinks	25
	Fruit juices	25
	Nectars	25
Snack foods	Salty snacks	30
Soft candy	Jelly products	25
Soups and soup mixes	Prepared and condensed soups	7
	Dry soup mixes	575

Our use of the term, "lycopene preparation," 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 Nutrition Center of Excellence. The Office of Pre-

Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for "lycopene preparation."

Hesheng describes the lycopene preparation as a red to dark-red powder containing ≥ 96% lycopene ($C_{40}H_{56}$, CAS Registry Number 502-65-8). Hesheng states that lycopene derived from *Saccharomyces cerevisiae* "JZL03" is identical to the lycopene found in tomatoes.

Hesheng states that *S. cerevisiae* "JZL03" is nonpathogenic and nontoxigenic and is genetically engineered from the taxonomically identified host strain, *S. cerevisiae* "HESHEHG001". Hesheng states that the production microorganism was constructed through the integration of five endogenous genes from *S. cerevisiae* for enhancing expression, five marker genes for strain construction, and three *de novo* synthesized exogenous genes encoding three enzymes (geranylgeranyl pyrophosphate GGPP synthase, phytoene synthase, and phytoene desaturase) for the biosynthesis of lycopene. Hesheng indicates that the integrated genes in the host strain are stable as evidenced by gene transcription, protein expression and lycopene production.

Hesheng describes the manufacturing process for lycopene preparation, which is produced by fermentation of *Saccharomyces cerevisiae* "JZL03" under controlled conditions. Following fermentation, the yeast cells are collected by centrifugation and dried to obtain a powder. Lycopene is extracted from the yeast cells using ethyl acetate and then filtered. The filtrate is concentrated, crystallized with ethanol, and vacuum dried to yield the final product. Hesheng states that lycopene preparation is manufactured in accordance with current good manufacturing practices (cGMP) and that all raw materials, processing aids, and food contact substances are food-grade, and comply with applicable U.S. regulations, are GRAS for the intended uses, or are the subject of effective food contact notifications.

Hesheng provides specifications for lycopene preparation that include total lycopene (≥ 96%), all-trans-lycopene (≥ 90%), ethanol (≤ 0.5%), ethyl acetate (≤ 0.5%), lead (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), loss on drying (≤ 0.5%), and limits for microorganisms. Hesheng provides results from the analyses of three non-consecutive batches to demonstrate that lycopene preparation can be manufactured to meet these specifications. Based on the results of stability studies, Hesheng concludes that lycopene preparation remains stable for six months when stored at 4 °C or -20 °C under vacuum and in the dark.

Based on food consumption data from the 2017-2020 National Health and Nutrition Examination Survey (NHANES), Hesheng estimates the eaters-only dietary exposure to lycopene from the intended uses for the U.S. population aged 2 years and older to be 5.9 mg/person(p)/d (0.10 mg/kg body weight (bw)/d) at the mean and 13.1 mg/p/d (0.23 mg/kg bw/d) at the 90th percentile. Hesheng indicates that the intended uses of lycopene preparation are substitutional for the existing uses of lycopene described in GRN 000173[1] and, therefore, not expected to increase the current cumulative dietary exposure to lycopene.

In support of the safety of consumption of lycopene, Hesheng discusses published and unpublished acute and subchronic animal toxicity studies; reproductive, developmental and genotoxicity studies; and information on the absorption, distribution, metabolism, and elimination of dietary lycopene. Hesheng further discusses human tolerance studies with tomato-based products or capsules and concludes that long-term consumption of lycopene products is well-tolerated without reports of any adverse effects. Hesheng also refers to several lycopene GRAS notices[2] (GRNs 000119, 000156, 000173, 000185) for which FDA had no questions on the notifiers' GRAS conclusion.

Based on the totality of the data and information, Hesheng concludes that lycopene preparation is GRAS for its intended use.

Standards of Identity
In the notice, Hesheng states its intention to use lycopene preparation 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 lycopene preparation 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 the Nutrition Center of Excellence. 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, Hesheng describes lycopene preparation as a dark red powder. As such, the use of lycopene preparation 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 001253 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 Hesheng's notice concluding that lycopene preparation 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 lycopene preparation. Accordingly, our response should not be construed to be a statement that foods containing lycopene preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hesheng provided, as well as other information available to FDA, we have no questions at this time regarding Hesheng's conclusion that lycopene preparation is GRAS under its intended conditions of use. This letter is not an affirmation that lycopene preparation 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 001253 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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Date: 2025.07.21 15:10:01 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program

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1. ^ Lycopene from *Blakeslea trispora* was the subject of GRN 000173. We evaluated this notice and responded in a letter dated December 1, 2005, stating that we had no questions at that time regarding the notifier's GRAS conclusion.
2. ^ The subjects of GRNs 000119, 000156, 000173, and 000185 are various forms of lycopene. We evaluated these notices and responded in letters dated May 22, 2003,

February 7, 2005, December 1, 2005, and May 30, 2006, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusion.