Ricardo Carvajal
Hyman, Phelps & McNamara, P.C.
700 13th Street NW, Suite 1200
Washington, DC 20005-5929

Re: GRAS Notice No. GRN 000679

Dear Mr. Carvajal:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000679. We received the notice that you submitted on behalf of Sumol + Compal Marcas S.A. (S+C) on November 14, 2016, and filed it on December 14, 2016. We received an amendment to the notice on February 21, 2017. The amendment contains additional information relevant to use levels, the manufacturing process, analytical methods, and results of analyses for potential by-products.

The subject of the notice is orange juice desugared by fermentation with *Schizosaccharomyces pombe* PYCC4197 (OJ-DF) for use as an ingredient at varying levels in carbonated and non-carbonated beverages such as fruit drinks, fruit-flavored drinks and drinks that contain fruit juice in part, and that contain <0.5% (volume/volume (v/v)) ethanol;[1] levels are limited by the content of ethanol <0.5% (v/v) in the finished product. The notice informs us of the view of S+C that this use of OJ-DF is GRAS through scientific procedures.

Our use of the term, "orange juice desugared by fermentation (OJ-DF)," 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 juice desugared by fermentation (OJ-DF).

S+C describes the identity and composition of OJ-DF as orange juice that has had essentially all of its natural sugars removed by fermentation but retains all other nutritionally relevant components. S+C describes the method of manufacture for OJ-DF, which is produced through a fermentation process utilizing a wild-type yeast strain,

[1] S+C cites FDA's Compliance Policy Guide (CPG) Sec. 510.400 "Dealcoholized Wine and Malt Beverages - Labeling," which states that "non-alcoholic" beverages may contain traces of alcohol (less than 0.5 percent alcohol by volume). Non-alcoholic beverages are distinct from "alcohol-free" beverages which contain no detectable alcohol.

S. pombe PYCC4197. The genome of *S. pombe* has been fully sequenced. The life cycle, main metabolic pathways, and genotypic and phenotypic diversity of natural isolates of *S. pombe* have been characterized in the published literature. S+C notes that *S. pombe* has been previously used in fermenting cider and in winemaking. S+C describes the production of the *S. pombe* PYCC4197 biomass, growth media, and the fermentation process. S+C states that all starting materials and ingredients used in the production of *S. pombe* PYCC4197 biomass are food-grade and the growth medium does not contain any common allergens. *S. pombe* PYCC4197 growth is monitored in order to determine the endpoint of biomass harvesting. The biomass is collected by centrifugation and washed with sterile saline. The starting material, orange juice or orange juice for manufacturing,[2] is pasteurized and treated with *S. pombe* PYCC4197 biomass to ferment natural sugars to ethanol and carbon dioxide. After removal of the biomass, the fermented orange juice is heat-treated for pasteurization and dealcoholization, and standardized to the original volume of the starting material by addition of water. C+S states that production of OJ-DF is conducted in accordance with current good manufacturing practice and a Hazard Analysis Critical Control Point (HACCP) system. S+C notes that for preserving the organoleptic quality of OJ-DF, storage at 0–4 °C prior to its use in a beverage should not exceed 30 days.

C+S provides specifications for OJ-DF including limits on sugars (≤2 g/L), ethanol (≤ 1% (v/v)), yeast and mold (<100 Colony Forming Units (CFU/mL), and bacteria (<1000 CFU/mL). Additionally, S+C provides results of analyses for potential by-products of the fermentation process (ethyl carbamate, biogenic amines, and methanol) for two non-consecutive batches of OJ-DF to demonstrate that these by-products are lower or similar to those found in commonly consumed foods and beverages.

C+S estimates the dietary exposure to OJ-DF based on published estimates of intake of beverages that are 100% fruit juice generated using the data from the National Health and Nutrition Examination Survey (NHANES). Among the estimates cited by C+S, the highest intake of 100% fruit juice (331 mL/p (person)/d at the mean for consumers only) was estimated based on the NHANES 2007–2010 data for the population aged 9–18 years old. The intake of orange juice for the population aged 19 years old and above was estimated to be 210 mL/p/d at the mean and 259 mL/p/d at 75th percentile for consumers only based on the NHANES 2003–2006 data. C+S concludes that the intake of OJ-DF will be similar to published estimates of orange juice consumption.

S+C discusses the safety of OJ-DF. S+C states that there are three potential undesirable by-products of the fermentation process utilized to desugar orange juice: ethyl carbamate, biogenic amines, and methanol. According to S+C, these by-products, if present, would be at levels lower or similar to those found in commonly consumed foods and beverages. S+C states that OJ-DF under the intended conditions of use and at the estimated highest achievable levels is not associated with any risk to human health.

[2] The starting materials, orange juice and orange juice for manufacturing, are defined in 21 CFR 146.135 and 21 CFR 146.151, respectively.

C+S includes the statement of a panel of individuals (C+S's GRAS panel). Based on its review, C+S's GRAS panel concluded that OJ-DF is safe under the conditions of its intended use.

Based on publicly available information pertaining to the safety of the starting material, *S. pombe* used for the production of OJ-DF, and the potential by-products of fermentation, S+C concludes OJ-DF is GRAS for its intended use in food.

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, S+C states that OJ-DF, when used as a substitute for regular orange juice, helps reduce the intake of sugar and thus energy (calories), and provides all the nutrients (other than sugars) for which orange juice is a significant dietary source. If products containing OJ-DF 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. The 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.

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

Conclusions

Based on the information that S+C provided, as well as other information available to FDA, we have no questions at this time regarding S+C's conclusion that OJ-DF is GRAS under its intended conditions of use. This letter is not an affirmation that OJ-DF 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 000679 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042713, cn=Michael A. Adams -S
Date: 2017.05.10 11:35:35 -04'00'

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