DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

AUG 1 8 2003

Anil J. Shrikhande
Vice President Research and Development
Polyphenolics, Inc.
12667 Road 24
Madera, CA 93637

Re: GRAS Notice No. GRN 000125

Dear Dr. Shrikhande:

The Food and Drug Administration (FDA) is responding to the notice, dated February 6, 2003, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on February 21, 2003, filed it on February 26, 2003, and designated it as GRAS Notice No. GRN 000125.

The subjects of the notice are grape seed extract (GSE) and grape pomace extract (GPE). The notice informs FDA of the view of Polyphenolics, Inc. (Polyphenolics) that GSE and GPE are GRAS, through scientific procedures, for use as antioxidants in fruit juices (for which no standard of identity exists), fruit flavored beverages, fruit flavored beverage mixes and carbonated fruit flavored beverages at a concentration of up to 210 parts per million (alone or in combination).

In a previous GRAS notice, dated December 12, 2001, Polyphenolics had informed FDA of the view that GSE and GPE are GRAS, through scientific procedures, for their intended use. FDA received the notice on December 17, 2001, and designated it as GRN No. 000093. FDA responded to Polyphenolics in a letter, dated June 5, 2002, stating that GRAS Notice GRN No. 000093 did not provide a sufficient basis to conclude that GSE and GPE are GRAS under the conditions of their intended use. In its letter, FDA noted that Polyphenolics provided insufficient information about the composition of GSE and GPE to evaluate safety. In addition, FDA noted that the studies most relevant to safety were not generally available to the expert scientific community. FDA also mentioned that the recommendation by the National Toxicology Program (NTP) that another grape seed extract product be subjected to substantial toxicity tests raised questions about consensus within the scientific community about the safety of chronic consumption in food of GSE and GPE.

As part of GRN No. 000093, Polyphenolics provided the report of a panel of individuals (Polyphenolics' GRAS panel) who evaluated the data and information that are the basis for Polyphenolics' GRAS determination. Polyphenolics considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Polyphenolics' GRAS panel evaluated published data and information about polyphenolic compounds in general, as well as results and analyses of two animal studies conducted with GSE and GPE. Based on this review, Polyphenolics' GRAS panel concluded that GSE and GPE that meet the appropriate food grade specifications are GRAS, through scientific procedures, for use in fruit juice and fruit flavored beverages as an antioxidant provided the extracts are used in accordance with the limitations of current good manufacturing practice. As part of GRN No.

000125, Polyphenolics' GRAS panel was provided with additional chemistry and safety data from newly published studies conducted with commercial grape seed extracts. In an addendum to the GRAS panel report provided in GRN No. 000125, Polyphenolics' GRAS panel acknowledged review of this additional data and information and affirmed its original conclusion that GSE and GPE are GRAS under the conditions of their intended use.

Polyphenolics describes GSE as a rose-beige powder with a bitter/astringent taste and GPE as a red-purple powder. Polyphenolics states that GSE and GPE are mixtures of chemicals comprised predominantly of polyphenolic compounds. Polyphenols are commonly found in higher plants, and are a diverse group of polymeric compounds containing multiple phenolic functionalities. Polyphenols are classified according to their repeating monomeric building blocks. In GSE and GPE, these monomers generally fall into two classes: flavonoids and non-flavonoids. The flavonoid polymers that are known as proanthocyanidins contain a specific type of flavonoid (called flavanols) as monomers. The non-flavonoid polymers that are known as anthocyanins are composed of esters of the monomers gallic acid or hexahydroxydiphenyl and a polyol (such as D-glucose). Other non-flavonoid polyphenols can be found in GSE and GPE and are composed of the monomers caffeic acid, chlorogenic acid and resveratrol. Based on the mean analytical profile of six lots of GSE, Polyphenolics states that GSE is composed of approximately 81 percent proanthocyanidins, 7 percent free flavanol monomers, and 6 percent non-flavonoid polyphenols. Based on the mean analytical profile of six lots of GPE, Polyphenolics states that GPE is composed of approximately 80 percent proanthocyanidins, 6 percent free flavanol monomers, 7 percent non-flavonoid polyphenols and 2 percent anthocyanins.

Polyphenolics describes the method of manufacture of GSE and GPE. The extracts are manufactured from fresh grapes, which are inspected for quality and screened for defects. The grapes are de-stemmed, crushed, and pressed, leaving a pomace residue of seeds and skin. The seeds are separated from the skins (for GSE), and the seeds or the pomace of seeds and skin (for GPE) are boiled in water to extract the polyphenolic constituents. The seeds are then removed, and the extract is cooled, enzymatically depectinized, and the pH is adjusted. The resulting extract is refrigerated and stored for one to three months. The extract is then filtered with diatomaceous earth and passed through a column of trimethylolpropane trimethacrylate (TMPTMA). Polyphenolics notes that grape phenolic constituents preferentially adsorb to the TMPTMA resin, while other grape constituents such as minerals and organic acids pass through the column and are discarded. The phenolic constituents are eluted from the resin using 75 percent (by volume) beverage-grade ethanol. The ethanol is then removed using a vacuum thermal evaporator, and the concentrate is spray dried to give the final GSE or GPE product.

Polyphenolics provides product specifications and analyses of two production lots of GSE and GPE. Specifications for both GSE and GPE include limits on the minimum level of total phenolics and maximum levels of moisture, microbial contaminants, and residual pesticides. Specifications also include ranges for the monomeric, oligomeric, and polymeric content of the phenol profile. An additional specification for GSE includes a limit on insoluble substances and for GPE a limit on total anthocyanins. Polyphenolics states that the heavy metals composition of GSE and GPE are within FDA tolerances for grapes. Polphenolics notes that another grape-derived extract (i.e., grape skin extract (enocianina)) is regulated for use under 21 CFR 73.170 as a color additive in still and carbonated drinks and ades, beverage bases, and alcoholic beverages.

Polyphenolics uses the United States Department of Agriculture (USDA) 1994-1996 Continuing Surveys of Food Intakes by Individuals and the 1998 Supplemental Children's Survey to estimate the intake of GSE and GPE from their intended use. Polyphenolics estimates the combined intake of GSE and GPE for the total population to be approximately 70 milligrams per person per day (mg/person/day) at the mean and approximately 130 mg/person/day at the 90th percentile. Polyphenolics notes that the average proanthocyanidin content of other foods and beverages (e.g., red wine, cranberry juice, chocolate and apples) has been reported to range from approximately 22 to 148 milligrams per serving and that the average dietary flavonoid intake in the United States has been reported to range from approximately 460 mg/person/day to 1000 mg/person/day. Polyphenolics concludes that the estimated intake of GSE and GPE compares favorably to the dietary intake of proanthocyanidins from other food sources and to the total dietary flavonoid consumption in the United States.

Polyphenolics discusses published information related to the absorption, distribution, metabolism, and excretion of polyphenolic compounds. Polyphenolics reports that there is indirect evidence of intestinal absorption of polyphenols and notes that the chemical structure and molecular weight of polyphenols determines the rate and extent of absorption. Following absorption, polyphenols are transported to the liver and other organs where they are further metabolized and subsequently excreted in the urine and feces.

Polyphenolics discusses published studies conducted with Polyphenolic's GSE and GPE[1] and other grape seed extract products or components in humans and various animal species and draws the following conclusions:

- Acute and subchronic oral toxicity studies conducted in animals fed GSE and GPE, other grape seed extracts, or substances that are components of GSE and GPE showed no relevant compound-related toxicological effects.
- Genotoxicity studies conducted *in vivo* and *in vitro* with GSE and GPE, other grape seed extracts, or substances that are components of GSE and GPE demonstrated no mutagenic effects.
- Nutritional and clinical studies conducted with substances that are components of GSE and GPE demonstrated no significant adverse effects.

Polyphenolics reports that the National Cancer Institute nominated a different grape seed extract for evaluation at the May 2001 meeting of the NTP Interagency Committee for Chemical Evaluation and Coordination. Polyphenolics states that the recommendation to evaluate grape seed extract was due in part to the widespread consumer use of the substance as a dietary supplement and to the absence, at the time of the nomination, of adequate published safety information. Polyphenolics considers that the recommendation by NTP is not inconsistent with its view that the intended use of GSE and GPE as antioxidants in fruit juices and fruit flavored beverages is GRAS because the specific charge to NTP was to evaluate a grape seed extract in the form of a dietary supplement. Furthermore, Polyphenolics notes that subsequent to NTP's nomination of grape seed extract, subchronic and genotoxicity studies have appeared in the

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[1]The subchronic and mutagenicity studies conducted with GSE and GPE, which were considered by Polyphenolics' GRAS panel to be the most relevant to safety, were unpublished at time GRN No. 000093 was submitted to FDA. These studies are now published.

published literature, the results of which show no evidence of toxicity or mutagenicity at oral doses many times the expected human exposure.

Potential requirement for a color additive petition

In its notice, Polyphenolics describes GPE as a red-purple powder. As such, the use of GPE in food products may constitute the use of a color additive under section 201(t)(1) of the Federal Food, Drug and Cosmetic Act (FFDCA) and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food; except that such term does not include any material which the Secretary,[2] by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempt from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Given the construct of section 201(t)(1) of the FFDCA and 21 CFR 70.3(f) and (g), the use of a substance that is capable of imparting color may constitute use as a color additive in addition to use as a food additive or GRAS substance. For example, beta-carotene is both approved for use as a color additive (21 CFR 73.95) and affirmed as GRAS for use as a nutrient supplement (21 CFR 184.1245); in some food products, beta-carotene is used for both purposes. Importantly, if the use of GPE constitutes use as a color additive within the meaning of section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR 70.3(f) and (g), section 721(a) of the FFDCA requires premarket review and approval of that use by FDA. Under section 402(c) of the FFDCA, a food product that contains an unapproved color additive would be deemed adulterated.[3]

In a telephone conversation on March 4, 2003, between representatives of FDA and Polyphenolics, FDA requested that Polyphenolics present its view on whether any of the intended uses of GPE would be exempt from the definition of color additive. Polyphenolics stated that although GPE has a natural red-purple color, it is intended to be used at low levels in food products and is not intended to be used as a color additive. Polyphenolics expressed its opinion that this issue does not interfere with the GRAS determination and, thus, it did not believe a response was warranted. Importantly, FDA's response to GRN 000125 does not include any comment by FDA about Polyphenolics' view on this issue. If, after receipt of this

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[2]The Secretary of the Department of Health and Human Services (DHHS). The Secretary of DHHS has delegated the authority for this provision of the FFDCA to FDA.

[3]We note that section 721(b)(4) of the FFDCA provides that a color additive shall be deemed to be safe and suitable for the purpose of listing under section 721(b) of the FFDCA while there is in effect a published finding of the Secretary declaring that the substance is exempt from the definition of "food additive" because of its being generally recognized by qualified experts as safe for its intended use as provided in section 201(s) of the FFDCA. Importantly, FDA's response to GRN 00125 does not constitute a "finding of the Secretary" within the meaning of section 721(b)(4) of the FFDCA.

letter, Polyphenolics has any specific questions about this issue, we recommend that Polyphenolics contact the Division of Petition Review (HFS-265), Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740. You can reach this division by telephone at (202)418-3035.

Potential labeling issues

The original subjects of the Polyphenolics' notice were described as grape seed extract (GSE) and grape skin extract (GSKE). Because a different preparation of grape skin extract (enocianina) is currently regulated for use under 21 CFR 73.170 as a color additive in beverages, the Office of Food Additive Safety (OFAS) consulted with the Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS) and Polyphenolics regarding the common or usual name of the notified substance, grape skin extract (GSKE). In a letter, dated April 30, 2003, Polyphenolics requested to change the common or usual name of the notified substance from grape skin extract (GSKE) to grape pomace extract (GPE).

Section 403(i)(2) of the FFDCA provides that a food shall be deemed to be misbranded unless its label bears the common or usual name of each ingredient. In addition, section 403(k) of the FFDCA provides that a food shall be deemed to be misbranded if it bears or contains any chemical preservative, unless it bears labeling stating that fact. Polyphenolics use of GSE and GPE as antioxidants constitutes use as a preservative. Therefore, the ingredient statement on labels of food products treated with GSE and GPE must comply with 21 CFR 101.22(j), which requires a food to which a chemical preservative is added to bear a label declaration stating both the common or usual name of the ingredient and a separate description of its function. If you have any questions about the appropriate labeling of these food ingredients, you should contact the staff in ONPLDS, Division of Food Labeling and Standards, 5100 Paint Branch Parkway, College Park, MD 20740. You can also reach this division by telephone at (301)436-2375.

Section 403(a) of the FFDCA provides that a food shall be deemed to be misbranded if its labeling is false or misleading in any particular. In addition, Section 403(r) of the FFDCA lays out the statutory framework for a health claim. In describing the intended use of GSE and GPE and in describing the information that Polyphenolics relies on to conclude that GSE and GPE are GRAS under the conditions of their intended use, Polyphenolics raises potential labeling issues under these provisions of the FFDCA. These labeling issues consist of Polyphenolics' assertion that GSE and GPE have physiological effects that Polyphenolics views as beneficial. If products that contain GSE or GPE bear any claims about such benefits on the label or in labeling, such claims are the purview of ONPLDS. OFAS neither consulted with ONPLDS on these labeling issues nor evaluated the information in Polyphenolics' notice to determine whether it would support any claims made about GSE and GPE on the label or in labeling.

Conclusions

Based on the information provided by Polyphenolics, as well as other information available to FDA, the agency has no questions at this time regarding Polyphenolics' conclusion that GSE and GPE are GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of GSE and GPE. As always, it is the continuing responsibility of Polyphenolics to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements. In particular, we note that any use of GPE that constitutes use as a color additive requires premarket review and approval by FDA.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,

Laura M. Tarantino, Ph.D.
Acting Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition