Kathryn Davis
Senior Regulatory Manager
Apeel Sciences
71 S. Los Carneros Rd.
Goleta, CA 93117

Re: GRAS Notice No. GRN 000886

Dear Ms. Davis:

This letter revises our response letter to GRN 000886 signed on July 13, 2020. The purpose of this revised letter is to clarify the statements pertaining to intended use and usage levels on page 1, paragraph 3 and in footnote 1 of this letter, and to add the references cited on page 2, paragraph 4 of this letter.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000886. We received Apeel Sciences' notice on October 15, 2019 and filed it on December 9, 2019. Apeel Sciences submitted amendments to the notice on March 1, 2020 and March 29, 2020 that clarified the identity, provided limits of detection for analytical methods, revised manufacturing specifications, and updated the literature search.

The subject of the notice is a mixture of mono- and diacylglycerides derived from grape seed (MDAG) for use as a component of a surface finishing agent to protect the freshness and extend the shelf life of fresh produce at levels not to exceed good manufacturing practice (GMP).[1] MDAG forms a thin, edible physical barrier against moisture loss and oxidation when applied to the surfaces of certain fruits and vegetables. The notice informs us of Apeel Sciences' view that this use of MDAG is GRAS through scientific procedures.

Our use of the term, "a mixture of mono- and diacylglycerides derived from grape seed" or "MDAG" 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 did not consult with ONFL regarding the appropriate common or usual name for a mixture of mono- and

[1] Apeel Sciences states that the use of MDAG is self-limiting for technological reasons and that MDAG will be used at a level up to 1.52 grams per kilogram of produce.

diacylglycerides derived from grape seed.

Apeel Sciences describes MDAG as yellow liquids, white to pale yellow-colored plastics, or ivory, white or pale yellow solids. Apeel Sciences provides a general chemical structure of monoglycerides, as well as the chemical structure and chemical and physical properties for two representative monoacylglycerides derived from grape seed. Apeel Sciences describes the manufacturing process. Apeel Sciences states that grapeseed oil is extruded from grape seeds by mechanical pressing. The oil is processed to generate a mixture of mono- and diacylglycerides containing the same naturally-occurring fatty acids as in the grape seed oil, but in their saturated form. Apeel Sciences first adds glycerol and a catalyst to the grape seed oil. Then, a neutralizing agent is added to quench the catalyst. A liquid–liquid extraction with water and heptane or ethyl acetate is then performed to remove unreacted glycerol, residual catalyst, and the residual neutralizing agent. The saturated forms of the naturally-occurring fatty acids are then formed in the presence of hydrogen gas and a catalyst (20% w/w palladium hydroxide supported on carbon), and then the catalyst and residual solvent are removed to yield the final MDAG. Apeel Sciences states that MDAG is manufactured under current good manufacturing practices using food grade ingredients and processing aids.

Apeel Sciences has established specifications for MDAG as follows: total glycerides (≥ 90 wt %); mono- and diesters (≥ 70 wt %); α-monoglyceride content (≥ 30 wt %); total glycerol (16–33 wt %); free glycerol (≤ 7 wt %); soap (≤ 6 wt %); residue on ignition (≤ 0.5% determined at 800 ± 25°C); acid value (≤ 6); iodine value (≤ 4); water content (≤ 2%); ethyl acetate (≤ 1,000 mg/kg); heptane (≤ 1,000 mg/kg); palladium (≤ 5 mg/kg); arsenic (≤ 3 mg/kg); lead (≤ 2 mg/kg); cadmium (≤ 1 mg/kg); and mercury (≤ 1 mg/kg). The notifier provides analytical data from three nonconsecutive lots to demonstrate that the product can be manufactured to meet the stated specifications.

MDAG will be applied to the external surfaces of produce that may be consumed with or without peels. For those foods where the peel or rind is removed prior to consumption, MDAG is not expected to migrate to the edible portion, and the main source of consumer exposure will be in products with edible peels.

Apeel Sciences states that based on a study by Kimmons et al. (2009) (Ref.1) of the top ten reported fruits and vegetables for adolescents 12-18 years of age, men over 19 years of age, and women over 19 years of age, apples, grapes, and strawberries are the only fruits on this list with edible peels. Similarly, potatoes and beans were the only vegetables on the list that had edible peels. Therefore, these foods were chosen as representative foods for fruits and vegetables containing edible peels. Apeel Sciences estimates the dietary exposure to MDAG using: 1) the average daily intake of the representative fruit or vegetable as listed in Smiciklas-Wright et al. (2002) (Ref. 2) ; 2) the stated use level for the ingredient on the representative fruits and vegetables; and 3) the assumption that the percent of fruits and vegetables containing an edible peel in the list of the top ten fruits and vegetables represents the percent of fruits and vegetables in the diet containing an edible peel. Apeel Sciences estimates that the exposure to MDAG is 54 mg/p/d from use on fruit and 55 mg/p/d from use on vegetables. Apeel Sciences multiplied these values by two to derive the exposures for a high consumer of fruits and

vegetables and then summed the values to derive an overall exposure for a high consumer. Apeel Sciences states that the total amount of MDAG consumed by a high consumer of both fruits and vegetables would be 218 mg/day.[2]

Apeel Sciences states that monoacylglyceride derivatives are components of dietary fats (plant oils and animal fats) commonly found in food and are also endogenously formed in the human body, and that the absorption, digestion, and metabolism of dietary fats applies to monoglycerides and serves to support the safety of the consumption of MDAG.

Apeel Sciences references the safety and toxicity data described in previous related GRAS notices (GRN 000056, GRN 000115, GRN 000131, GRN 000192, GRN 000269 and GRN 000648)[3] for which FDA had no questions, to corroborate the safety of MDAG at use levels proposed by Apeel Sciences.

Apeel Sciences discusses findings from a published 90-day rat study, chronic toxicity studies in rats and dogs, and 12 human studies lasting 3-12 months, on orally administered diacylglycerol oils to further support the safety of the intended use of MDAG. Apeel Sciences concludes that these diacylglycerol oil studies also support that there are no adverse effects resulting from the monoacylglyceride component thereof. Based on the findings from these diacylglycerol studies containing 5% monoacylglycerides, Apeel Sciences concludes that the associated monoacylglyceride exposure can be considered safe.

Apeel Sciences includes the statement of a panel of individuals (Apeel Sciences' GRAS panel). Apeel Sciences' GRAS Panel evaluated the data and information and concluded that MDAG is safe for the intended use.

Based on the totality of the data and information described above, Apeel Sciences concludes that the intended use of MDAG is GRAS.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Apeel Sciences' notice concluding that

[2] FDA also estimated exposure for MDAG using food consumption data from the 2013-2016 National Health and Nutrition Examination Survey and including all food codes for fruits and vegetables with an edible peel. FDA estimated an eaters-only exposure to MDAG from the use on fresh produce to be 131 mg/p/d at the mean and 281 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older.

[3] We evaluated GRNs 000056, 000115, 000131, 000192, 000269, and 000648 and responded in letters dated December 4, 2000, February 24, 2003, December 4, 2003, August 3, 2006, May 21, 2009 and December 13, 2016, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

MDAG 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 MDAG. Accordingly, our response should not be construed to be a statement that foods containing MDAG, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Apeel Sciences provided, as well as other information available to FDA, we have no questions at this time regarding Apeel Sciences' conclusion that MDAG is GRAS under its intended conditions of use. This letter is not an affirmation that MDAG 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 000886 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.09.11 17:40:03 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

References

1. Kimmons et al. 2009. Fruit and vegetable intake among adolescents and adults in the United States: Percentage meeting individualized recommendations. The Medscape Journal of Medicine 11(1): 26.

2. Smiciklas-Wright. et al. 2002, Foods Commonly Eaten in the United States: Quantities Consumed Per Eating Occasion and in a Day, 1994-1996. U.S. Department of Agriculture NFS Report No. 96-5, 252 pp. Available at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/Portion.pdf.