Memorandum

Date: February 17, 2005

From: Division of Petition Review (DPR; HFS-265), Chemistry Review Group and Toxicology Review Group I

Subject: **FAP 3A4749** (MATS #1148, M2.3.1): Comments from Hercules Incorporated dated 8/26/04, received 12/9/04 regarding Glycerol Ester of Gum Rosin for Use as an Additive in Oil-Based Citrus Flavorings for Beverages to Increase the Density of Citrus Oils.

To: Division of Petition Review
Regulatory Review Group I
Attn: A. Zajac, Ph.D.

This memorandum addresses comments received from Hercules Incorporated (Hercules) in response to food additive petition (FAP) 3A4749 submitted by Environ on behalf of T&R Chemical regarding glycerol ester of gum rosin (GEGR) for use as an additive in oil-based citrus flavorings for beverages to increase the density of citrus oils. Hercules disagrees with the conclusion reached by the petitioner and the FDA[1] that glycerol ester of wood rosin (GEWR) and GEGR are chemically similar.[2] Hercules also objects to what they view as the petitioner's reliance on a significant body of safety data generated by Hercules in support of the regulated use of GEWR as the basis for establishing the safety of GEGR. In addition, Hercules noted that without their written permission, neither the petitioner for GEGR nor the FDA can refer to such data in defining the safety of GEGR.

The agency's response to the comments submitted by Hercules is presented below.

Raw Material Sourcing Differences

Hercules states that they believe the data submitted by the petitioner are not representative of gum rosin sources and likely represent only one regional source. Hercules notes that wood rosin is derived almost exclusively from 2-3 related species of pine trees harvested in the southeastern

[1] Chemistry memorandum dated June 21, 2004 from D. McClain to C. Murray regarding FAP 3A4749.

[2] We have used the term "chemically similar" to refer to GEGR and GEWR in this memorandum and in previous memoranda regarding FAP 3A4749. However, the comments provided by Hercules use the term "chemically equivalent." Whether two substances are "equivalent" or "similar" is a matter of degree. For example, two similar substances may be equivalent with respect to the identity of the chemical components (i.e., the substances both contain the same components), but differ slightly in the relative amounts of those components. Based on the data provided by Environ, there is variability in the composition of the rosins from different sources and even from the same source (e.g., harvested at different times of the year). This natural variability in the rosins does not result in a qualitatively different composition of the rosin, but rather a typical range of values for the individual components of the rosin. Therefore, we used "chemically similar" as the basis for our conclusions reached regarding GEGR and GEWR. This variability in the rosin composition does not result in a significant difference in the estimated daily intake (EDI) for the individual resin acid components of GEGR and GEWR.

2003F-0471

BKG1

United States and Central America, while gum rosin is produced in a number of countries throughout the world from at least ten different species of pine trees. Hercules further comments that the chemical composition of gum rosin varies significantly depending on the geographical area. Therefore, there is no standard gum rosin source, nor a typical or characteristic gum rosin.

In our review of FAP 3A4749, we requested that the petitioner provide data on the typical variation in the composition of the resin acids present in gum rosin resulting from a variation in the source location. In their response dated 3/4/04, the petitioner noted that the GEGR they produce is typically from one source. However, the petitioner provided documentation of the variability of the individual resin acids in gum rosin based on the source of the pine trees (e.g., American, Mexican, etc.). We found that these data represent the comparability and natural variability in the composition of rosins.

Given that rosins are derived from a natural source, there will be some variability in the composition of the rosin. There are currently no source limitations placed on wood rosin, and no source limitations have been placed on gum rosin. Therefore, Hercules arguments regarding the variability of the chemical composition of gum rosin due to different sources would also apply to wood rosin. In our review of the subject petition, we determined that the representative ranges for the components of wood rosin and gum rosin were not significantly different, and thus, gum rosin and wood rosin could be considered chemically similar. In addition, GEGR is required to meet the same specifications as GEWR (i.e., acid number, color, softening point). If source variations would result in a product that cannot meet these specifications, those GEGR batches would not be regulated under 21 CFR 172.735, and beverages containing GEGR from those batches would be considered adulterated.

Hercules has also provided statements from the Natural Resources Institute, supported by the Food and Agricultural Organization (FAO), that state that there are no international standards for rosins, but that companies and traders in the rosin industry have their own "in-house" specifications, which vary from company to company, making it difficult to generate "typical data" for rosins. We note that these concerns apply to both wood rosin and gum rosin. The regulation in 21 CFR 172.735 for GEWR and the proposed wording for the regulation for GEGR list specifications that must be met for the additive to be safe for use in food.

In addition, Hercules provides a definition of GEWR from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) that Hercules claims recognizes the difference among the various rosin sources. This definition does not indicate that GEGR is different. Rather, GEGR is not included in this definition. We note that many of the general characteristics of GEWR described in this definition would also apply to GEGR.

Raw Material Processing Differences

Hercules states that gum rosin is generally manufactured via a single state "flash" distillation process where the terpene fraction is volatized leaving the rosin as a "bottom" product. Therefore, gum rosin may contain metals, less-volatile impurities, and chemical stimulants

(used to increase the flow of exudates from the tree) that were present in the crude oleoresin. In contrast, wood rosin is manufactured via a multistage purification and refining process involving solvent extraction of the pine wood chips followed by solvent-solvent refining of the crude rosin. This process removes the volatile terpene fractions, as well as the less-volatile impurities (e.g., metals and chromophoric, polar, and oxidized species), resulting in a more consistent, standardized raw material for subsequent esterification.

While we will not comment directly on the manufacturing process used by the petitioner, we note that the petitioner did provide data on heavy metals and impurities. The GEGR manufactured by the petitioner meets the specifications for GEGR listed in the Food Chemicals Codex (FCC, 5th Edition). We note that these are the same specifications as for GEWR. In addition, the petitioner provided a comparison of various physical and chemical properties for GEGR and GEWR (i.e., acid number, softening point, ash content, etc.). We note that these values are comparable for GEGR and GEWR.

Compositional Differences and Variation in Gum Rosin

Hercules provided a research report generated in 1989 that they claim demonstrates the differences among wood rosin, gum rosin, and tall oil rosin (Attachment 1). Tall oil rosin is not the subject of the current discussion, and will, therefore, not be considered any further. Hercules claims that these data show that gum rosin is more variable than wood rosin.

After reviewing these data, we agree that there are quantitative differences in the amount of individual resin acids in gum rosin and wood rosin. However, such differences would be expected, given that gum rosin is derived from a natural source and that different environmental factors (e.g., temperature, soil conditions, etc.) between sources could affect the amounts of the individual resin acids. Hercules only provided two chromatograms for wood rosin. However, these chromatograms also indicated quantitative differences in the amounts of the individual resin acids in wood rosin. Although there were differences in the amounts of the individual resin acids, in all cases the identity of the resin acids and the relative retention times for these resin acids were qualitatively similar for both the wood and gum rosin samples analyzed.

Hercules further states that the differences in sources for gum rosin can lead to significant performance differences in downstream processing and end use applications. This is not a regulatory issue. If GEGR meets the specifications listed under 21 CFR 172.735, and is manufactured in accordance with good manufacturing practices (GMP), then GEGR may be sold as an article of commerce and used in the manufacture of citrus flavorings. If the product is not performing to the standards of industry, then manufacturers will not purchase and use GEGR.

Esterification Differences

Hercules notes that variations in the rosin acid content of gum rosin can lead to variation during the esterification process, which leads to variation in the final product, GEGR. Hercules further notes that the total rosin acid content will determine the maximum amount of rosin triglycerides that would result from the esterification process, which would affect the softening point and acid

number of GEGR. Hercules states that the variability in the amount and distribution of rosin esters in GEGR results in a product that cannot be a unique or well-defined entity, as is GEWR. Hercules also speculates that to produce a consistent GEGR product that meets the specifications for softening point and acid number, the esterification process must be manipulated, altered or changed to compensate for the natural variation in rosin acid isomer content.

We agree that variation in the rosin acid content leads to variation in the amount and identity of the rosin triglycerides. However, we disagree with Hercules' assertion that this variation does not apply to GEWR so that GEWR is more "well defined" than GEGR. Variation in the rosin triglycerides is also expected for GEWR, as wood rosin has also been demonstrated to have variable rosin acid content, as discussed above. Any variation in the composition between GEGR and GEWR is due to the fact that rosins are derived from natural sources, as discussed above. In addition, Hercules did not provide any evidence that the esterification process for each batch of GEGR produced is actually being altered in order to meet the proposed specifications. Provided that GEGR meets the specifications set forth in the proposed regulation, and the additive is manufactured in accordance with GMP, GEGR can be introduced into commerce.

Comparison of Wood Rosin and Gum Rosin via Saponification and Gas Chromatography (GC) Analysis

Hercules claims that GEGR and GEWR cannot be analyzed using the traditional method of saponification followed by GC analysis. Hercules states that this technique can induce isomerization of the rosin acids, thereby changing the composition compared to the starting rosin. Hercules did not provide any literature references or data to support this statement. In addition, the procedure used by the petitioner included a methylation step which should decrease the amount of isomerization. The petitioner also used other analytical techniques to compare GEGR and GEWR. The data from these techniques, as well as the data from the GC analysis, were the basis of our conclusion that GEGR and GEWR are chemically similar.

Reliance on Safety Data Generated by Hercules

Hercules states that the petitioner for FAP 3A4749 is relying on a significant body of safety data generated by Hercules for GEWR (regulated under 21 CFR 172.735) as a basis for establishing the safety of GEGR. Hercules cites FDA regulations governing food additive petitions in 21 CFR 171.1(b) that state "any reference to unpublished information furnished [previously to FDA] by a person other than the applicant will not be considered unless use of such information is authorized in a written statement signed by the person who submitted it [previously to FDA]." Hercules also contends that "it would not be appropriate for FDA to refer to any previous toxicological evaluations conducted within the agency or FDA memoranda on the safety of the glycerol ester of wood rosin or gum rosin that were based on unpublished data submitted previously to the Agency."

In response to this comment, the agency does acknowledge the conditions defined within 21 CFR 171.1(b). However, we disagree with Hercules' contention that the agency is relying on

safety data previously submitted to FDA (by Hercules) in support of the regulated use of GEWR in order to establish the safe use of GEGR in oil-based citrus flavorings for beverages.

We note that in DPR's final toxicology memorandum dated August 16, 2004, brief reference is made to the safety data for GEWR (previously submitted to FDA by Hercules). However, the agency's decision regarding the safety of the petitioned use of GEGR is clearly based on information presented in DPR's final chemisty memorandum dated June 21, 2004. In that memorandum it is stated that GEGR and GEWR are chemically similar and that estimated daily intakes of the individual resin acids that are the major components of both GEGR and GEWR would not differ significantly were GEGR to be substituted for GEWR in oil-based citrus flavorings. Based on these determinations, the August 16, 2004 toxicology review closes by stating "We have no concerns about the safety of glycerol esters of gum rosin for the proposed, substitutional uses in citrus flavored beverages."

Conclusion

After reviewing the comments received by Hercules, we disagree with their conclusion that GEGR and GEWR are not chemically similar. Hercules did not provide any information to change the basis for our conclusions reached in our chemistry memorandum dated June 21, 2004.

Furthermore, based on the additional chemistry review provided above, we conclude that any minor differences in the composition of GEGR and GEWR are not significant to be of toxicological concern and that toxicity testing on GEGR is not required to establish the safety of the petitioned, substitutional use of this additive in oil-based citrus flavorings for beverages. Our conclusion that said use of GEGR is safe, as noted in our final toxicology memorandum of August 16, 2004, remains unchanged.

Diana L. Doell, Ph.D.

David B. Carlson, Ph.D.

HFS-245 (Perfetti); 205 (R/F)
HFS-265:DLDoell:436-1276:FAP3A4749_c_response to commentsfinal.doc
Init: SECarberry: 2/17/05
Final: dld: 2/17/05