DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Bentsen FDA
official

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The Honorable Kenneth E. Bentsen, Jr.
House of Representatives
Washington, D.C. 20515-4325

Dear Mr. Bentsen:

Thank you for your letter of April 2, 1999, addressed to Ms. Sara Bianchi in the Office of the Vice President, which was sent to us on December 2, 1999, on behalf of Mr. Mark E. Wilson, Managing Director for Argyll Scientific, L.L.C., of Houston, Texas, regarding the use of propylene glycol in over-the-counter (OTC) drug products. Mr. Wilson is concerned that the Food and Drug Administration's (FDA or the Agency) regulations do not require manufacturers to label propylene glycol as "alcohol" on their OTC drug products. Ms. Bianchi has asked us to respond directly to you. We apologize for the delay in this response.

Propylene glycol, United States Pharmacopeia (USP), is a clear, colorless, viscous liquid with a slightly acrid taste. Because of its solubility in aqueous and nonaqueous media and its hygroscopicity (ability to absorb moisture), propylene glycol has multiple uses in foods and drugs. Propylene glycol is used as a solvent for oral and injectable drugs, and is also used in cosmetics, lotions, and ointments. As a food ingredient, propylene glycol is an emulsifying and plasticizing agent, surfactant, humectant, and solvent for flavoring compounds. It has been used as a drug ingredient for more than fifty years and as a food ingredient in the United States since at least 1920.

Mr. Wilson criticizes FDA's approach to the regulation of propylene glycol. He argues that propylene glycol is an alcohol and should be labeled as such. As a corollary, he argues that no drug product should be labeled as alcohol-free if it contains propylene glycol. At the same time, Mr. Wilson also suggests that the scientific evidence on toxicity of propylene glycol is sufficiently compelling to ban its use as an ingredient in drug products.

FDA does not agree that propylene glycol should be identified as "alcohol" on food or drug product labeling. Although propylene glycol is, as a matter of scientific nomenclature, a member of the class of hydroxyl compounds identified as alcohols, propylene glycol is not alcohol, as the word is commonly understood. As commonly and usually understood, "alcohol" means ethyl alcohol, (i.e., the type found in alcoholic beverages). The Agency's labeling policies reflect this common understanding of the word. See Title 21, Code of Federal Regulations (CFR) § 328.3(a) (defining the term "alcohol" under FDA's over-the-counter drug labeling rules as "ethanol, ethyl alcohol, or Alcohol, USP"). The USP, the officially recognized pharmaceutical compendium, defines alcohol as ethyl alcohol or ethanol. (The USP has established a separate monograph for propylene glycol.) Thus, FDA does not believe it is misleading to label propylene glycol-containing products that do not contain ethyl alcohol as "alcohol-free." See 21 CFR § 328.50(e).

Mr. Wilson has raised concerns about the safety of propylene glycol. Scientists in both FDA's Center for Food Safety and Applied Nutrition and Center for Drug Evaluation and Research (CDER) have considered the safety of propylene glycol and have determined that the ingredient is safe when used in amounts consistent with good manufacturing practices (GMP). 21 CFR Section 184.1666 indicates the types of foods and levels of propylene glycol considered in affirming the status of the ingredient as "generally recognized as safe" (GRAS).

Prompted by earlier correspondence from Mr. Wilson on propylene glycol, CDER scientists reviewed the safety of the compound in drug products. The scientists considered the available body of evidence, including animal toxicity data and clinical experience, and concluded that, in the amounts that propylene glycol is commonly used in drug products, the chemical poses no unacceptable risks. As with all excipients, excessive or irresponsible use can lead to harm. Also, a few cases of allergic reactions will be seen with virtually any substance. The Agency continues to monitor the safety of propylene glycol as a drug inactive ingredient, both in its review of new drug products containing propylene glycol and in its surveillance of marketed products containing propylene glycol.

Mr. Wilson is correct that FDA recently amended regulations governing the use of propylene glycol in cat food. This action was taken because propylene glycol is known to cause toxicity in cats when ingested in substantial quantities. Specifically, propylene glycol ingestion by cats results in the development of

"Heinz bodies," which are projections extending from erythrocytes, and indicate oxidation of hemoglobin. Differences between cat and human hemoglobins may explain why cats may be more sensitive to propylene glycol; cat hemoglobin is relatively easily oxidized. Exposure to propylene glycol at levels that are consistent with GMP regulations does not appear to induce the formation of Heinz bodies in humans. FDA took action to respond to the marketing of pre-moistened cat food that contained very high levels of propylene glycol. The Agency notes that propylene glycol remains GRAS for use in other veterinary products. Furthermore, FDA's action on propylene glycol in cat food has no bearing on propylene glycol's status as an ingredient in FDA-regulated articles for human consumption.

The Agency shares Mr. Wilson's concern that ingredients in OTC drug products be safe and suitable. Under the OTC labeling regulations, 21 CFR §201.66, manufacturers are required to include all inactive ingredients in the product labeling. Therefore, consumers will be able to determine which inactive ingredients, such as propylene glycol, are present in OTC drug products. FDA notes that few ingredients are completely risk free. As discussed, the Agency continues to believe that when used in appropriate amounts, propylene glycol is both safe and suitable.

For your information, we are enclosing a copy of the Final Rule: "OTC Drug products Intended for Oral Ingestion That Contain Alcohol," published March 13, 1995.

We trust this information responds to your concerns. If we may be of any further assistance, please contact us again.

Sincerely,

Karen B. Mercier
for

Melinda K. Plaisier
Associate Commissioner
for Legislation

cc: Ms. Sarah Bianchi
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