



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

November 16, 2009

Lynnae M. Mahaney, MBA, FASHP  
President  
American Society of Health-System Pharmacists  
7272 Wisconsin Avenue  
Bethesda, MD 20814

Dear Ms. Mahaney:

In light of recent reports on diethylene glycol (DEG) poisonings associated with contaminated glycerin in pharmaceutical syrups, we ask that you inform your members about a guidance issued by FDA "Testing of Glycerin for Diethylene Glycol." This guidance recommends certain precautions be taken to prevent the use of glycerin that is contaminated with DEG and applies to other excipients, such as propylene glycol, at risk for such contamination. We have composed a letter for you to share with your members that contains pertinent information. Thank you in advance for your help in this matter.

Sincerely,

A handwritten signature in black ink, appearing to read "M. Levy", with a stylized flourish at the end.

Michael M. Levy  
Director  
Division of New Drugs and Labeling Compliance  
CDER, Office of Compliance  
U.S. Food and Drug Administration

Attachment

Dear Member:

This letter is to remind you of the information provided by the agency in its 2007 guidance “Testing of Glycerin for Diethylene Glycol (Glycerin Guidance).” This guidance recommends certain precautions be taken to prevent the use of glycerin that is contaminated with diethylene glycol (DEG) and applies to other excipients, such as propylene glycol, at risk for such contamination. Glycerin and propylene glycol are drug components that are used in the preparation of drug products by both pharmacy compounders and manufacturers. While the FDA has no reason to believe that the U.S. supply of glycerin is contaminated with DEG, the agency has been aware of reports from other countries in which DEG-contaminated glycerin or propylene glycol caused a number of human deaths.

DEG is a relatively toxic industrial chemical which has been implicated in numerous mass poisonings. In 1937, an outbreak of DEG poisoning occurred in the U.S., during which over 100 people, many of them children, died after ingesting elixir of sulfanilamide containing DEG as a solvent. This incident led to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938 requiring drugs be proven safe before marketing. Since that date, there are no drugs with approved applications that contain DEG and the Agency position remains that due to its toxicity, DEG should not be used to manufacture or compound any drug intended to be administered to U.S. consumers.

More recently, several foreign countries have reported and continue to report fatal DEG poisonings of consumers ingesting medicines contaminated with DEG that had been intentionally added to one of the medicine components without recognition by the producer of the consumer product. Between 1990 and 1998, such DEG poisoning occurred in Argentina, Bangladesh, Haiti, India, and Nigeria, resulting in the deaths of hundreds of children. One of the most recent outbreaks of DEG poisoning occurred in Panama in 2006, resulting in numerous hospitalizations for serious injury and more than 40 deaths. High levels of DEG were invariably traced to excipients commonly used as sweeteners in formulations of many pharmaceutical syrups (e.g., cough syrup, acetaminophen syrup). DEG has very similar physical and chemical properties to glycerin and propylene glycol and is not readily detected without performing a specific chemical analysis. Although reports of mass poisoning to date have involved either glycerin or propylene glycol, other liquid polyol sweeteners having similar properties to DEG also appear to be vulnerable to DEG contamination.

FDA considers the presence of toxic levels of DEG in any drug product to be an important public safety issue. Given the serious hazard of DEG poisoning and the complexity of certain globalized pharmaceutical supply chains, the agency issued the 2007 Glycerin Guidance. The intent of this guidance is to alert manufacturers, pharmacy compounders, and all suppliers including repackers and distributors, to the potential public health hazard of DEG contamination. The guidance aims to assist such entities in avoiding the use or distribution of DEG-contaminated glycerin through supply chain vigilance and testing. The guidance recommends that proper precautions be taken for all components at-risk of being intentionally contaminated with DEG.

The guidance discusses that the incidents of DEG contamination share the following similarities:

- The manufacturers of the syrups containing contaminated glycerin did not perform any test that would have allowed them to detect the gross amount of DEG present in the raw material.
- Instead of performing any testing upon receiving the glycerin, the manufacturers used the contaminated glycerin strictly based upon the data provided on a certificate of analysis (COA) from the glycerin supplier. It was unclear at which point in the distribution history the falsification of information on the COA making the glycerin appear suitable for pharmaceutical use had occurred.
- Often, the distributor letterhead appeared on the COA but the COA did not reveal the original manufacturer’s identity. In addition, there was no documentation provided to show the distribution history of the glycerin such that the recipients were not aware that in fact the glycerin had probably changed hands multiple times.

All pharmacy compounders using glycerin, propylene glycol and other liquid polyols such as sorbitol solution, to prepare drug products must be aware of the importance of properly testing at-risk excipients to detect DEG contamination. FDA recommends that pharmacy compounders that use any at-risk component in compounding drug products either test for DEG content or ensure that such testing was properly done by the direct supplier. The Agency recommends that pharmacy compounders only accept at-risk components from suppliers that have been

verified as providing reliable information. The USP monographs for Glycerin and Propylene Glycol require testing for DEG as part of the identity test requirement. On February 1, 2010, such testing will also be required for sorbitol and maltitol solutions. In previous incidents, it was nearly impossible to trace the point in the supply chain at which gross contamination had taken place. DEG testing is particularly important for all at-risk pharmaceutical excipients not sourced directly from the excipient manufacturer. Knowledge about the reliability of the manufacturer of any at-risk component, including any subsequent repackers, relabelers, and distributors is recommended.

FDA's guidance on Testing of Glycerin for Diethylene Glycol can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070347.pdf>. The guidance also provides information on other controls to identify potential DEG contamination. Information on those pharmaceutical excipients at-risk for DEG contamination, including appropriate test methods, can be found in the latest United States Pharmacopeia revision bulletin at <http://www.usp.org/hottopics/propyleneGlycolSorbitolInformation.html>.

The FDA also asks that any complaints or adverse events associated with DEG contamination be reported to MedWatch, the FDA's voluntary reporting program, by calling 800-FDA-1088, or electronically at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm). In addition, when filing the report, please also provide the sources of any contaminated pharmaceutical ingredients identified by your firm to Maria Edisa L. Gozun, Consumer Safety Officer at [fda.cpdingteam@fda.hhs.gov](mailto:fda.cpdingteam@fda.hhs.gov). This information will facilitate the agency's efforts to investigate reports of DEG contamination.