
Guidance for Industry

Testing of Glycerin for Diethylene Glycol

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2007**

Compliance

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I. INTRODUCTION

This guidance is intended to alert pharmaceutical manufacturers, pharmacy compounders, repackers, and suppliers to the potential public health hazard of glycerin contaminated with diethylene glycol (DEG), a poison. FDA has received and continues to receive (most recently in October 2006) reports about fatal DEG poisoning of consumers who ingested medicinal syrups, such as cough syrup or acetaminophen syrup, that were manufactured with DEG-contaminated glycerin. This guidance provides recommendations that will help pharmaceutical manufacturers, repackers, and other suppliers of glycerin, and pharmacists who engage in drug compounding, avoid the use of glycerin that is contaminated with DEG and prevent incidents of DEG poisoning.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In 1937, an outbreak of DEG poisoning occurred in the United States, which resulted from people ingesting elixir of sulfanilamide that contained DEG as a solvent. A total of 107 people died, many of them children. This event led to the enactment of the Federal Food, Drug, and Cosmetic Act (the Act), which included a provision requiring that drugs be demonstrated to be

¹ This guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration.

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safe before marketing. In late 1995 and early 1996, many children were admitted to hospitals in Port-au-Prince, Haiti, with sudden kidney failure, resulting in at least 80 fatalities. An investigation by Haitian health officials, the Centers for Disease Control (CDC), and FDA discovered that the cause was DEG-contaminated glycerin in acetaminophen syrup manufactured in Haiti. Between 1990 and 1998, similar incidents of DEG poisoning occurred in Argentina, Bangladesh, India, and Nigeria and resulted in the deaths of hundreds of children.² In October 2006, an outbreak of DEG poisoning occurred in Panama, resulting in multiple cases of illness and death.

These cases reveal the following similarities:

- The pharmaceutical manufacturers of the syrups that contained contaminated glycerin did not perform full identity testing on the glycerin raw material, including tests to quantify the amount of DEG present and to verify the purity of the glycerin received.
- The pharmaceutical manufacturers of the syrups containing contaminated glycerin relied on the certificate of analysis (COA) provided by the supplier.
- The origin of the glycerin was not easily apparent from the COA. The COA obtained by the pharmaceutical manufacturers of the syrups was often a copy of a COA on the letterhead of the distributor and not the COA provided by the manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known because the glycerin may have been sold several times between its manufacture and its use in medicinal syrup or other drug product.

As a result of these practices, DEG-contaminated glycerin entered the pharmaceutical raw material supply chain.

III. RECOMMENDATIONS

To avoid the use of DEG-contaminated glycerin, certain analytical testing procedures must be performed on all lots of glycerin (21 CFR 211.84(d)(1)). It is critical that all manufacturers and others using glycerin to manufacture or prepare drug products be aware of the importance of properly testing glycerin to detect DEG contamination.

The Agency recommends that:

1. Drug product manufacturers perform a specific identity test that includes a limit test for DEG on all containers of all lots of glycerin before the glycerin is used in the manufacture or preparation of drug products because of the serious hazard associated with DEG contamination.³ The relevant safety limit for DEG is 0.1%, as recognized by

² World Health Organization (WHO), *Report of the Diethylene Glycol Contamination Prevention Workshop*, 1997, p. xi.

³ FDA's regulation at 21 CFR 211.84(a) requires testing of each lot of components; 21 CFR 211.84(b) requires that a representative sample of each shipment of each lot be collected for testing and describes that the number of containers to be sampled shall be based upon appropriate criteria. Because DEG contamination presents a serious hazard, the Agency recommends that the representative sample collected for testing is of each container of each lot.

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the USP monograph for glycerin. The Agency recommends that a manufacturer perform the identity tests, including the limit test for DEG, which appear in the USP monograph for glycerin. Alternatively, a manufacturer may use an equivalent identification procedure that includes a test to detect and quantify DEG provided it meets the relevant safety limit. One alternative procedure is a thin-layer chromatography (TLC) method published in the *Journal of AOAC International*.⁴

This identification test is done in accordance with the CGMPs, which require that each lot of a component undergo testing to confirm its identity before use in drug product manufacturing (21 CFR 211.84(d)(1) requires that “[a]t least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used”). A specific identity test for glycerin is found in the *United States Pharmacopeia (USP)* monograph.⁵ The USP monograph for glycerin provides a two-part identity test: test A using “Infrared Absorption” and test B using gas chromatography that references the “Limit of Diethylene Glycol and Related Compounds.” The infrared absorption test identifies glycerin and DEG, but does not distinguish between the two. Test B distinguishes glycerin from DEG.⁶

2. Drug product manufacturers know their supply chain for glycerin (i.e., the manufacturer of the component and any subsequent distributor(s)).
3. All manufacturers take every opportunity to ensure proper testing of glycerin for DEG contamination. All personnel in pharmaceutical manufacturing facilities (especially personnel directly responsible for receipt, testing, and release of glycerin) should be made aware of the importance of proper testing and the potential hazards if the testing is not done.
4. Repackers, and others who distribute and prepare glycerin for use in drug products, test glycerin that is used, sold for use, or intended for use in drug products.

Alternatively, knowledge of shipping controls can help in the determination of a representative sample. See, for example, section XVII (17) of FDA’s guidance for industry on *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (Q7A). The Q7A guidance is available at <http://www.fda.gov/cder/guidance/index.htm>. We update guidances periodically. To make sure you have the most recent version of a guidance, check our Web site.

⁴ Kenyon et al., *J. AOAC Int’l*, vol. 81, no. 1, 1998, pp. 44 -50, available at <http://www.fda.gov/cder/offices/otr/default.htm>.

⁵ The United States Pharmacopeial Convention, Inc., *United States Pharmacopeia 29—National Formulary 24*, 2006. The current good manufacturing practice (CGMP) regulations recognize the use of *USP* and *NF* methods (see 21 CFR 211.194(a)(2)). Although a method other than that in the *USP-NF* may be used, the suitability of the testing method must be verified under actual conditions of use and must be accurate and reliable (21 CFR 211.194(a)(2) and (b)).

⁶ While the USP method is effective, there may be a potential for variability in the composition of products labeled as glycerin. Therefore, method modifications may be needed to the preparation of the *Resolution*, *Standard*, and *Sample solutions* and to the *Chromatographic system* to achieve suitable performance. Method modifications in analyses performed by FDA have included preparation of all solutions in methanol with appropriate modifications to the chromatographic system, as needed, such as temperature ramps and hold times.

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5. Pharmacies that use glycerin in compounding drug products either test the glycerin for DEG content or ensure that such testing was properly done by a reliable supplier.

Bulk or repackaged glycerin intended as an excipient or other component of a drug product is a drug as defined by section 201(g)(1) the Act (21 U.S.C. 321(g)(1)). Section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)) requires that the methods used in, or the facilities or controls used for a drug's manufacture, processing, packing, or holding conform to CGMP. Testing bulk or repackaged glycerin for DEG content is consistent with good manufacturing practice required under the Act.

For other components, such as propylene glycol, that in the past were found to be contaminated with DEG, precautions should also be taken to identify reliable suppliers and secure shipment to prevent similar occurrences.⁷

⁷ The August 2, 1996, CDC *Morbidity and Mortality Weekly Report* describes DEG-contamination of propylene glycol. The report is available at <http://www.cdc.gov/mmwr/mmwrpvol.html>. The TLC test mentioned in recommendation #1 will distinguish DEG from propylene glycol.