

Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document, contact (CDER) Office of Compliance, 301-796-3400.

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

**May 2023
Compliance
Revision 1**

Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2023
Compliance**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	REGULATORY REQUIREMENTS	3
IV.	RECOMMENDATIONS TO SAFEGUARD THE QUALITY AND SAFETY OF MEDICINES FROM DEG AND EG CONTAMINATION	6

Contains Nonbinding Recommendations

**Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol
Immediately in Effect Guidance for Industry¹**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to alert pharmaceutical manufacturers, compounders, repackers, and suppliers to the potential public health hazard of glycerin and other high-risk drug components contaminated with diethylene glycol (DEG) or ethylene glycol (EG).^{2,3} FDA has received and continues to receive (most recently in early 2023) reports about fatal poisonings of consumers who ingested drug products in a liquid dosage form (such as cough, allergy, analgesic, and antiemetic drug products) that were manufactured with DEG- or EG-contaminated components.⁴

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

² For purposes of this guidance, “high-risk drug components” are components that, through historical experience, have been found to be at higher risk of DEG or EG contamination compared to other drug components. For brevity, the title of this guidance does not list all high-risk drug components.

³ Many, but not all, high-risk drug components have a United States Pharmacopeia or National Formulary (USP-NF) monograph that includes testing for DEG and EG. USP-NF refers to the combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). The USP-NF monographs establish identity testing for drugs listed therein, in addition to other tests and methods for determining the strength, quality, and purity of those products. The USP-NF monographs for the high-risk drug components listed by name in the title of this guidance include DEG and EG limit testing as part of the specific identification tests. There are additional high-risk drug components whose corresponding USP-NF monographs include testing for DEG and EG in either the identification test or the impurities tests, such as sorbitol sorbitan solution, noncrystallizing sorbitol solution, polyethylene glycol, and diethylene glycol stearates. FDA expects manufacturers to ensure they are referencing the current USP-NF when determining which testing is required to be performed.

⁴ See, e.g., *WHO urges action to protect children from contaminated medicines*, World Health Organization, Jan 23, 2023, available at <https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines>.

Contains Nonbinding Recommendations

This guidance provides information on compliance with applicable regulatory requirements and recommendations to help pharmaceutical manufacturers, repackers, other suppliers of high-risk drug components, and compounders prevent the use of glycerin and other high-risk drug components that are contaminated with DEG or EG. These requirements and recommendations, along with other appropriate measures under current good manufacturing practice (CGMP), are vital to prevent further consumer poisonings.

In general, FDA's guidance documents 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 (FD&C Act or Act), which included a provision requiring that drugs be demonstrated to be 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.⁵ 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 manufacturers of the liquid drug products 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 manufacturers of the liquid drug products containing contaminated glycerin relied on the certificate of analysis (COA) provided by the supplier of the glycerin.
- The origin of the glycerin was not readily apparent from the COA. The COA obtained by the manufacturers of the liquid drug products was often a copy of a COA on the letterhead of the distributor from whom they had purchased the glycerin and not the COA provided by the original manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known, often because the glycerin might have been sold

⁵ World Health Organization (WHO), *Report of the Diethylene Glycol Contamination Prevention Workshop*, 1997, p. xi.

Contains Nonbinding Recommendations

multiple times between its manufacture and its use in manufacturing the finished drug product.

In 2022 and 2023, numerous countries reported incidents of oral liquid drug products, primarily indicated for children, with confirmed or suspected contamination with high levels of DEG and EG.⁶ The cases of contamination, spanning at least seven different countries, were associated with more than 300 fatalities—mostly in children under the age of 5.⁷ In October 2022, and as part of the investigation into these cases, the Indonesian health authorities identified the presence of DEG and EG in a propylene glycol excipient used in manufacturing oral liquid drug products.⁸ At the time of issuance of this guidance, FDA had no indication that any contaminated products connected to the recent international incidents have entered the U.S. drug supply chain.

The 2022 outbreak resembles previous ones, as manufacturers of oral liquid drug products relied upon COAs provided by suppliers where the chain of custody or distribution history of the high-risk drug component was also not readily known or apparent from the COA. For example, in one instance, the appearance of the label and COA of propylene glycol, used as a component of a drug product, suggested the component container's content might differ from what the container label and COA stated. As a result of these practices, DEG- and EG-contaminated components, such as propylene glycol, entered the pharmaceutical raw material supply chain.

III. REGULATORY REQUIREMENTS

The FD&C Act and its implementing regulations contain many drug manufacturing requirements. This guidance highlights certain key provisions that are critical to ensuring the detection of DEG- and EG-contaminated drug components and avoiding additional poisoning incidents. However, this guidance is not intended to be an all-inclusive list of drug

⁶ See *WHO urges action to protect children from contaminated medicines*, World Health Organization, Jan 23, 2023, available at <https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines>. The WHO has issued global medical alerts addressing incidents in The Gambia (Oct 5, 2022), Indonesia (Nov 6, 2022), Uzbekistan (Jan 11, 2023), and the Marshall Islands and Micronesia (Apr 25, 2023). See *Medical Product Alert N°6/2022: Substandard (contaminated) paediatric medicines*, World Health Organization, Oct 5, 2022, available at [https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-\(contaminated\)-paediatric-medicines](https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines); *Medical Product Alert N°7/2022: Substandard (contaminated) paediatric liquid dosage medicines*, World Health Organization, Nov 2, 2022, available at [https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-\(contaminated\)-paediatric-liquid-dosage-medicines](https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines); *Medical Product Alert N°1/2023: Substandard (contaminated) liquid dosage medicines*, World Health Organization, Jan 11, 2023, available at [https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-\(contaminated\)-liquid-dosage-medicines](https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines); and *Medical Product Alert N°4/2023: Substandard (contaminated) syrup medicines*, World Health Organization, Apr 25, 2023, available at [https://www.who.int/news/item/25-04-2023-medical-product-alert-n-4-2023--substandard-\(contaminated\)-syrup-medicines](https://www.who.int/news/item/25-04-2023-medical-product-alert-n-4-2023--substandard-(contaminated)-syrup-medicines).

⁷ See *WHO urges action to protect children from contaminated medicines*, World Health Organization, Jan 23, 2023, available at <https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines>.

⁸ See *Indonesia revokes firms' fever syrup licences amid inquiry into 150 deaths*, Reuters, Oct 31, 2022, available at <https://www.reuters.com/world/asia-pacific/indonesia-revokes-firms-fever-syrup-licences-amid-probe-into-150-deaths-2022-10-31/>.

Contains Nonbinding Recommendations

manufacturing requirements. Drug manufacturers are responsible for ensuring their drug products are manufactured in compliance with all applicable FDA laws and regulations.

Manufacturers (including outsourcing facilities) of drugs, as defined in section 201(g) of the FD&C Act, must ensure that the drugs they manufacture comply with drug CGMP under section 501(a)(2)(B) of the FD&C Act.⁹ For purposes of section 501(a)(2)(B) of the FD&C Act, CGMP includes “oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.”^{10,11} Further, bulk or repackaged high-risk drug components intended as excipients or other components of a drug product are drugs as defined by section 201(g)(1)(D) of the FD&C Act. Testing bulk or repackaged high-risk components for DEG and EG content is consistent with the CGMP requirement under section 501(a)(2)(B) of the FD&C Act.

Manufacturers of finished drug products must also comply with the CGMP regulations codified in 21 CFR Parts 210 and 211.¹² To comply with FDA’s CGMP regulations, identity testing must be conducted to verify each component of a drug product.¹³ Specific identity tests, if they exist, must be used.¹⁴ Identity testing confirms that the component is what it is labeled to be. A component’s identity can be described as its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry.¹⁵ To comply with CGMP regulations, representative samples of each shipment of each lot of a component must undergo appropriate identity testing before use in drug product manufacturing.¹⁶ These requirements apply irrespective of the route of administration or

⁹ Under section 201(g) of the FD&C Act, the term “drug” means “(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).” Thus, a high-risk component that is intended as an excipient or other component of a drug product is a drug as defined by section 201(g) of the FD&C Act.

¹⁰ Section 501 of the FD&C Act, as amended in 2012.

¹¹ In accordance with section 501(a)(2)(B) of the FD&C Act, a drug is adulterated “if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”

¹² FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. Until these final regulations are promulgated, outsourcing facilities are subject to the CGMP requirements in parts 210 and 211.

¹³ See 21 CFR 211.84(d)(1).

¹⁴ *Id.*

¹⁵ See FDA’s website addressing *Questions and Answers on Current Good Manufacturing Practice Requirements | Control of Components and Drug Product Containers and Closures*, available at <https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-control-components-and-drug>.

¹⁶ Under 21 CFR 211.84(a), “[e]ach lot of components ... shall be withheld from use until the lot has been ... tested ... as appropriate.” Under 21 CFR 211.84(b), “[r]epresentative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed

Contains Nonbinding Recommendations

dosage form of the finished drug product (e.g., topical).¹⁷ Furthermore, manufacturers of finished drug products must have a quality unit that is responsible for approving or rejecting incoming lots of materials (including components) for use in manufacturing operations.¹⁸ The quality unit must have written procedures and follow those written procedures in carrying out its responsibilities.¹⁹ For example, any lot of a component that does not meet the appropriate written specifications must not be used in drug product manufacturing.²⁰

In addition, a drug, including a drug component, with a name recognized in the United States Pharmacopeia-National Formulary (USP-NF) must comply with compendial identity standards or be deemed adulterated, misbranded, or both.²¹

We note that all drug component that is used to manufacture a drug must either conform to an applicable USP-NF monograph, including the DEG and EG limits if specified, or conform to appropriate acceptance criteria if a DEG and EG test or limit has not been established in an applicable USP-NF monograph.²² Accordingly, any container sampled and tested by FDA must conform to these safety limits or will be deemed adulterated, misbranded, or both.²³

Some USP-NF monographs include, as part of the applicable identity testing, a limit test for DEG and EG. The relevant safety limit for DEG and EG is not more than (NMT) 0.10%, as recognized by the applicable USP-NF monograph for each high-risk drug component identified in the title of this guidance.²⁴ Accordingly, when a limit test for DEG and EG is included in the identity testing of a component's applicable USP-NF monograph, a drug manufacturer must perform the DEG and EG limit test on representative samples of each shipment of each lot of the component and find that the component contains no more than 0.10% of DEG and EG before using that component in drug product manufacturing.²⁵

for analysis and reserve where required by § 211.170.” Because DEG and EG contamination presents a serious hazard and FDA has seen wide variability of DEG and EG contamination from container to container, the Agency recommends that the representative sample collected for testing is of each container of each lot of a high-risk component. See *Police arrest two fugitives over kidney failure case*, ANTARA Indonesian News Agency, Jan 30, 2023, available at <https://en.antaranews.com/news/271113/police-arrest-two-fugitives-over-kidney-failure-case>, (noting that nine drum samples were found to contain a wide variability of DEG and EG over the safety limit.)

¹⁷ 21 CFR 211.84. See also Schier, J.G., Barr, D.B., Li, Z. et al. Diethylene Glycol in Health Products Sold Over-the-Counter and Imported from Asian Countries. *J. Med. Toxicol.* 7, 33–38 (2011). <https://doi.org/10.1007/s13181-010-0111-9> (noting that DEG-contaminated topical products have caused toxicity).

¹⁸ See 21 CFR § 211.22.

¹⁹ See *id.*

²⁰ See 21 CFR 211.84(e).

²¹ See section 501(b) and 502(a) of the FD&C Act; see also 21 CFR 299.5(a) and (b).

²² See footnote 11. A drug, including an inactive ingredient, with a name recognized in USP-NF must comply with compendial standards or be deemed adulterated, unless the difference in strength, quality, or purity from such standard is plainly stated on its label. Note that such “differences” do not extend to the drug’s identity. See section 501(b) of the FD&C Act.

²³ See sections 501(a)(2)(B) and 502(a) and (g) of the FD&C Act.

²⁴ At the time of issuance of this guidance, USP identified 0.10% as the DEG and EG limit in the identification section of the USP-NF monographs for Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, and Sorbitol Solution.

²⁵ See section 501(b) and 502(a) of the FD&C Act; see also 21 CFR 299.5(a) and (b); see also 21 CFR 211.84(a) and (b).

Contains Nonbinding Recommendations

For example, the United States Pharmacopeia (USP) monograph for glycerin provides a three-part identity test, including test A using “Infrared Absorption” and test B using gas chromatography that references the “Limit of Diethylene Glycol and Ethylene Glycol.”²⁶ Though the infrared absorption test (test A) identifies glycerin, it is not suitable for detection or quantitation of DEG or EG. Test B allows for quantitation of DEG and EG, if present, individually, down to the identified safety limit (NMT 0.10%).²⁷ Thus, representative samples of each shipment of each lot of glycerin intended to be used as a component in drug product manufacturing must be tested and found to meet the DEG and EG limit included in the identity testing in the USP Glycerin Monograph before use in drug product manufacturing.

If any testing reveals that their distributed drug products contain DEG or EG levels in excess of the applicable safety limit, manufacturers of New and Abbreviated New Drug Application products must submit a Field Alert Report (FAR).²⁸ FDA’s guidance for industry *Field Alert Report Submission: Questions and Answers* addresses how to submit a FAR.²⁹

Pharmacies that compound drug products that meet the conditions under section 503A of the FD&C Act must compound drug products using bulk drug substances that comply with the standards of an applicable USP or NF monograph, if a monograph exists (section 503A(b)(1)(A)(i)(I)), and using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if a monograph exists (section 503A(b)(1)(B)). This includes compliance with DEG and EG limits when specified in an applicable USP-NF monograph. Accordingly, any drug sampled and tested by FDA must conform to the applicable USP-NF safety limit for DEG and EG or will be deemed adulterated, misbranded, or both.³⁰

IV. RECOMMENDATIONS TO SAFEGUARD THE QUALITY AND SAFETY OF MEDICINES FROM DEG AND EG CONTAMINATION

It is critical for safeguarding the quality and safety of medicines that all manufacturers and others using high-risk drug components to manufacture or prepare drug products be aware of the importance of preventing the use of DEG- and EG-contaminated components.

In addition to the requirements listed above, in order to prevent the use of DEG- and EG-contaminated components, the Agency recommends:

1. Ensure the specific identity analysis for each lot, which includes a limit test for DEG and EG, incorporates testing of samples from **all containers of all lots** of a high-risk drug component

²⁶ Test C is an examination of the Test B chromatograms.

²⁷ Although the USP test 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.

²⁸ 21 CFR 314.81(b)(1)(ii).

²⁹ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

³⁰ See sections 501(b) and 502(a) and (g) of the FD&C Act.

Contains Nonbinding Recommendations

before the high-risk drug component is used in the manufacture or preparation of drug products.³¹

2. For high-risk drug components where the DEG and EG tests are not included in the identification test of the USP-NF monograph for the component,³² a manufacturer uses a suitable and equivalent procedure that includes a test to detect and quantify DEG and EG. The Agency recommends that any tests to detect and quantify DEG and EG use a safety limit for DEG and EG of NMT 0.10%.
3. Drug product manufacturers maintain current knowledge of their supply chain for high-risk drug components (i.e., the identity of the original manufacturer of the component and any subsequent repackers or distributors).
4. All personnel in pharmaceutical manufacturing facilities (especially personnel directly responsible for receipt, testing, and release of components) be made aware of the importance of proper DEG and EG contamination testing, and the potential hazards if this testing is not done.
5. Repackers, and others who distribute and prepare high-risk components for use in drug products, test the high-risk components that are used, sold for use, or intended for use in drug products. Accurate and complete COAs that identify the original manufacturer of the components should be issued for each component lot shipment.³³
6. Pharmacies that compound drug products that meet the conditions under section 503A of the FD&C Act (21 U.S.C. 353a) and that use high-risk components in compounding those drug products either test each lot of each high-risk component for DEG and EG content, or ensure that such testing was properly done by a reliable supplier.

The foregoing recommendations are also important precautions when determining supplier and lot acceptability of other components (e.g., polyethylene glycol 40 castor oil) that may be at risk for DEG or EG contamination and are not specifically named in this guidance.

³¹ 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 and FDA has seen wide variability of DEG and EG contamination from container to container, the Agency recommends that the representative sample collected for testing is of each container of each lot.

³² At the time of publication of this guidance, some examples of such components include, but are not limited to, high-risk components for which the USP-NF monograph includes testing for DEG and EG in the impurities tests (rather than the identities tests) (e.g., Polyethylene Glycol (MW <1000 only), Diethylene Glycol Stearates, Polyethylene Glycol Monomethyl Ether 350/550 (MW <600 only), and Polyoxyl 35 Castor Oil), high-risk components that have USP-NF monographs and testing procedures described in a USP-NF General Chapter (e.g., Polysorbate 20/40/60/80, Polyoxyl 15 Hydroxystearate, Polyoxyl 20 Cetostearyl Ether, Polyoxyl 8 Stearate, Octoxynol 9, and Nonoxynol 9), and high-risk components that do not have USP-NF monographs at all. USP monographs and standards are periodically updated. FDA expects manufacturers to ensure they are referencing the current USP-NF when determining which testing to perform.

³³ See, for example, section XI (11.4) and XVII (17.2 and 17.6) of FDA's guidance for industry, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

Contains Nonbinding Recommendations

If any testing of any drug component identifies DEG or EG levels at or above the USP-NF monograph limit, the manufacturer should notify CDER-DEG-EG-Reporting@fda.hhs.gov of the finding. Manufacturers should also contact the [appropriate Division of Pharmaceutical Quality Operations](#) if any drug product batches made with components whose testing identifies DEG or EG levels at or above the USP-NF monograph limit are already in distribution, to discuss appropriate next steps, such as voluntary initiation of a recall.