

# FDA Guidance Outlines Expectations to Mitigate the Risk of Diethylene Glycol and Ethylene Glycol Contamination of Drug Products

---

*August 16, 2023*

Throughout 2022 and 2023, various countries reported confirmed or suspected cases of diethylene glycol (DEG) and ethylene glycol (EG) contamination in drug products that resulted in over 300 fatalities, drawing several similarities to the 1937 case of DEG poisoning in the United States that led to the enactment of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1938. The World Health Organization also reported, on [April 30, 2023](#), and [June 16, 2023](#), that the risks associated with toxic EG and DEG-containing cough syrup are still present in multiple countries. On July 28, Bloomberg news published an extensive [article](#) related to such contamination found in market samples in some jurisdictions.

These recent incidents of DEG and EG contamination due to high-risk drug components, such as glycerin and propylene glycol, have prompted the U.S. Food and Drug Administration (FDA) to issue new guidance for pharmaceutical manufacturers, compounders, repackers, and suppliers. Specifically, in May 2023, the FDA published, for immediate implementation, its guidance for industry, [Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol](#).

FDA's guidance identifies certain practices that have allowed DEG- and EG-contaminated drug components to enter the pharmaceutical supply chain, including

- drug manufacturers failing to perform full identity testing on high-risk drug components to be used in manufacturing drug products (i.e., glycerin) to verify purity and to quantify EG and/or DEG present
- drug manufacturers relying on the certificate of analysis (COA) provided by the supplier of high-risk drug components that does not reveal the origin of the raw material or its chain of custody

FDA's guidance highlights existing regulations and requirements drug manufacturers should follow to mitigate the risks of DEG and EG contamination of drug products. These include

- full identity testing, in conformance with FDA's current good manufacturing practice regulations, 21 CFR Parts 210 and 211
- compliance with compendial identity standards and any specified DEG or EG limits for drugs, including drug components, recognized in the [USP-NF](#)
- an effective quality unit responsible for approving or rejecting incoming materials for use in drug manufacturing

FDA's guidance goes further and provides additional recommendations that may exceed the scope of the existing requirements, which speaks to the agency's focus and attention on preventing further incidents of such contamination. For example, FDA's guidance recommends the following:

- For high-risk components, the representative sample collected for testing should be for all containers of all lots.
- For high-risk components where the DEG and EG tests are not included in the identification test of the USP-NF monograph for the component, a manufacturer should use a suitable and equivalent method that includes a test to detect and quantify DEG and EG.
- Any tests to detect and quantify DEG and EG should use a safety limit for DEG and EG of NMT 0.10%.
- Repackers, and others who distribute and prepare high-risk components for use in drug products, should 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.
- Pharmacies that compound drug products that meet the conditions under Section 503(A) of the FD&C Act (21 U.S.C. 353a) and that use high-risk components in compounding those drug products should 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.

FDA has also recently issued warning letters to various drug manufacturers that make products containing high-risk components and that have failed to comply with identity testing requirements or establish reliability of the test analyses of a component's supplier. Notable examples of [warning letters](#) issued in 2023 include these:

- [Champaklal Maganlal Homeo Pharmacy Private Limited](#), dated May 18, 2023 — issued for failure to demonstrate adequate testing of glycerin used to manufacture drug products
- [Drivergent, Inc.](#), dated May 1, 2023 — issued for failure to determine whether component(s) conformed with written specifications for purity, strength, and quality before using them; it was noted the drug products contain glycerin
- [Accra-Pac, Inc.](#), dba Voyant Beauty, dated April 20, 2023 — issued for failure to include a DEG and EG limit test on all lots of glycerin before its use in the manufacture of drug products
- [Pharmaplast S.A.E.](#), dated April 13, 2023 — issued for failure to perform adequate identity

testing of each component used in drug products, including testing for methanol content in ethanol and presence of DEG and EG in glycerin

FDA's guidance and recent warning letters make clear the agency's compliance and enforcement focus on DEG and EG contamination controls and oversight. We expect FDA's continued focus on this issue, and we expect FDA inspections to delve deeply into a drug manufacturing facility's compliance with FDA's guidance document. Accordingly, it will be critical for drug manufacturers to, among other things, proactively ensure compliance with the expectations detailed in FDA's guidance, including maintaining 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), evaluating specifications to ensure they align with FDA's guidance, and ensuring a testing regimen that includes sampling from each container of each lot.

Our recent experiences indicate that FDA is using various tools such as records requests under 704(a)(4) to request specific information related to the firm's controls of such high-risk components prior to release for manufacturing. FDA is also detaining suspected products and requesting information related to DEG and EG levels in the specific lots of high-risk components used in the manufacture of the detained lots and, if applicable, finished product testing.

---

*Thank you to Ava Romanelli, intern for Sidley's Food, Drug and Medical Device practice group, for her significant contribution to this Update.*

## CONTACTS

If you have any questions regarding this Sidley Update, please contact the Sidley lawyer with whom you usually work, or

<b>James R. Johnson</b> , Partner	+1 202 736 8022, <a href="mailto:james.johnson@sidley.com">james.johnson@sidley.com</a>
<b>Daniel J. Roberts</b> , Sr. Director, Reg. Compliance	+1 415 772 7487, <a href="mailto:droberts@sidley.com">droberts@sidley.com</a>
<b>Stephanie Slater</b> , Sr. Director, Reg. Compliance	+1 213 896 6746, <a href="mailto:sslater@sidley.com">sslater@sidley.com</a>

---

Attorney Advertising—Sidley Austin LLP is a global law firm. Our addresses and contact information can be found at [www.sidley.com/en/locations/offices](http://www.sidley.com/en/locations/offices).

Sidley provides this information as a service to clients and other friends for educational purposes only. It should not be construed or relied on as legal advice or to create a lawyer-client relationship. Readers should not act upon this information without seeking advice from professional advisers. Sidley and Sidley Austin refer to Sidley Austin LLP and affiliated partnerships as explained at [www.sidley.com/disclaimer](http://www.sidley.com/disclaimer).

© Sidley Austin LLP