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4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-D-1573]

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; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a final guidance for industry entitled "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol." This guidance provides updated recommendations on testing and other activities that will help pharmaceutical manufacturers, repackers, other suppliers, and compounders prevent the use of high-risk drug components, including glycerin, propylene glycol, maltitol solution, hydrogenated starch hydrolysate, and sorbitol solution, that are contaminated with diethylene glycol (DEG) and ethylene glycol (EG). These and other appropriate measures under current good manufacturing practice (CGMP) are vital to prevent incidents of consumer poisoning.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-D-1573 for "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol." Received comments will be placed in the docket and, except for those submitted as

"Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New

Hampshire Ave., Bldg. 51, Rm. 4337, Silver Spring, MD 20993. Send two self-addressed adhesive labels to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Tara Gooen Bizjak, Office of Manufacturing Quality, Center for Drug Evaluation and Research (HFD-003), Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-3400.

SUPPLEMENTARY INFORMATION:

I. Background

We are announcing the availability of a guidance for industry entitled "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol." We are issuing this guidance consistent with our good guidance practices (GGP) regulation (§ 10.115 (21 CFR 10.115)). We are implementing this guidance without prior public comment because we have determined that prior public participation is not feasible or appropriate (§ 10.115(g)(2)). This guidance document is being implemented immediately to alert the industry to the potential public health hazard of DEG and EG contamination in certain drug components following international reports of children's oral liquid drug products with confirmed or suspected high levels of DEG or EG contamination. Although this guidance document is immediately in effect, it remains subject to comment in accordance with FDA's GGP regulation.

On May 2, 2007, FDA announced the availability of a guidance for industry entitled "Testing of Glycerin for Diethylene Glycol" (hereinafter, 2007 guidance) (72 FR 24316). As explained in detail in the 2007 guidance, and described further in this updated guidance, there have been repeated instances of DEG poisonings around the world, and even in the United States in 1937. Each outbreak resulted in numerous fatalities, many of them children. The 2007

guidance recommended that certain activities be performed on glycerin, including analytical testing, to avoid the use of DEG-contaminated 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.[1] 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.[2] At this time, FDA has no indication that any contaminated products connected to these recent international incidents have entered the U.S. drug supply chain.

This guidance is intended to replace the 2007 guidance and to alert the industry that in addition to glycerin, there are other components at a high risk of contamination with DEG and EG, including, but not limited to, propylene glycol, maltitol solution, hydrogenated starch hydrolysate, and sorbitol solution (hereinafter, "high-risk components"). This guidance provides recommendations, including analytical testing, to help pharmaceutical manufacturers, repackers, other suppliers of high-risk components, and compounders, prevent the use of glycerin and other high-risk components that are contaminated with DEG or EG.

The guidance represents the current thinking of FDA on "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-

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[1] See e.g., *WHO urges action to protect children from contaminated medicines*, World Health Organization, January 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 these incidents in The Gambia (October 5, 2022), Indonesia (November 6, 2022), Uzbekistan (January 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, October 5, 2022, available at 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, November 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; *Medical Product Alert N°1/2023: Substandard (contaminated) liquid dosage medicines*, World Health Organization, January 11, 2023, available at 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.

[2] See *WHO urges action to protect children from contaminated medicines*, World Health Organization, January 23, 2023, available at https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines.

Risk Drug Components for Diethylene Glycol and Ethylene Glycol." 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required for this guidance. The previously approved collection of information is subject to review by OMB under the PRA. The collection of information for CGMP requirements has been approved under OMB control number 0910-0139.

III. Electronic Access

Persons with access to the internet may obtain the guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: May 5, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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