February 10, 2023

Ms. Jessica Simpson
Senior Manager, Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 02-23-001-PN

Dear Ms. Simpson:

The FDA has been closely monitoring recent poisoning incidents resulting from drug products contaminated with diethylene glycol (DEG) and ethylene glycol (EG). DEG and EG have long been recognized as highly toxic adulterants which can lead to renal failure and death if consumed even in small quantities. A mass poisoning incident caused by contamination of Elixir sulfanilamide with DEG in 1937 led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938. Following fatal DEG poisoning of consumers who ingested medicinal syrups in 2006, such as cough syrup or acetaminophen syrup that were manufactured with DEG-contaminated glycerin, the FDA published Guidance for Industry: Testing of Glycerin for Diethylene Glycol.[1]

In 2022, mass DEG and EG poisoning incidents continued, resulting in hundreds of cases of pediatric renal failure leading to death. Fraudulent substitution or contamination of drug product components such as propylene glycol have been implicated as potential sources of DEG and EG. On January 23, 2023, the World Health Organization issued a call-to-action warning of the risks of contaminated drugs and urging regulators to ensure their detection and removal from the market.[2]

To address this risk, the USP-NF includes identity testing requirements in the monographs for these components as well as several other potential sources such as the Maltitol Solution, Hydrogenated Starch Hydrolysate, and Sorbitol Solution monographs. The quality controls for components supported by the USP are also codified in the Code of Federal Regulations[3] requiring that finished drug manufacturers perform identity testing of each shipment of each lot of components of a drug product and that specific identity tests, if they exist, shall be used.

Similar to the above-mentioned monographs, the Polyethylene Glycol and the not yet official Polyethylene Glycol 40 Castor Oil monographs include impurity testing for DEG and EG. However, these monographs have limitations. For example, in the Polyethylene Glycol monograph, the limits only apply to molecular weights up to 1000. Additionally, these tests appear under the Impurities sections in the monographs. We request that these tests be included

[1] https://www.fda.gov/media/71029/download
[2] https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines
[3] 21 CFR 211.84(d)(1))

in the Identity sections of the Polyethylene Glycol and Polyethylene Glycol 40 Castor Oil monographs. Additionally, we request that the Polyethylene Glycol monograph be revised so that testing for DEG and EG should include all molecular weights as defined in the monograph, including greater than 1000.

In addition, we recommend that USP consider similar revisions to other articles which have USP/NF monographs which include a test for DEG and EG.

Because this is a current patient safety issue, we are requesting that this issue be discussed and addressed with urgency. We hope these comments will be helpful to USP and the Excipient Monographs Expert Committee. Please feel free to contact me at pallavi.nithyanandan@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan -S

Digitally signed by Pallavi Nithyanandan -S
Date: 2023.02.10 21:18:15 -05'00'

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