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Client Alert

FDA and Life Sciences

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FDA Releases Guidance on Testing High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

On May 10, the U.S. Food and Drug Administration ("FDA") released a new guidance document *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*.[1] This guidance recommends that companies immediately begin evaluation of "high-risk" drug components for the presence of diethylene glycol ("DEG") and ethylene glycol ("EG").

This guidance follows a series of actions by FDA focused on controlling potentially low-level impurities, such as benzene[2] and nitrosamines.[3] In addition to increased focus by FDA, private analytical laboratories with interest in litigation may begin testing products for DEG and EG to instigate potential litigation.

BACKGROUND

As discussed in the guidance, the concern of potential risks associated with DEG and EG date back to 1937 when DEG was used as a solvent for the drug sulfanilamide and resulted in 107 deaths. Indeed, this event prompted the enactment of the Federal Food, Drug, and Cosmetic Act. Since then, periodic contaminations with large concentrations of DEG and EG in other countries have stirred public health concerns. For instance, between 1995 and 1996 in Haiti, large concentrations of DEG contamination were purportedly linked to 80 fatalities. Between 1990 and 1998, a series of countries including Argentina, Bangladesh, India, and Nigeria observed hundreds of fatalities purportedly linked to large concentrations of DEG contamination. Now, just recently in 2022 and 2023, large concentrations of DEG and EG were purportedly linked to 300 fatalities in various countries outside the United States. In many instances, children were disproportionally impacted because DEG and EG

are more often used to manufacture liquid formulations intended for pediatric patients.

In all of these scenarios, regulators have suggested a similar fact pattern resulted in the contamination, namely that (1) manufacturers of liquid oral drug products relied on certificates of analyses provided by suppliers as opposed to the original manufacturer; and (2) the full chain of custody for the high-risk drug component was not readily known or included on the certificate of analysis.

DEFINING "HIGH RISK" DRUG COMPONENTS

The scope of FDA's guidance is limited to drug components which are at high risk of containing DEG or EG. The guidance discusses two ways to identify which drug components are at high risk. First, the guidance itself enumerates certain drug components which are considered high risk based on "historical experience," but notes that the guidance is not exhaustive. Second, FDA notes that many, but not all, high-risk drug components have an analytical method covering DEG or EG within the United States Pharmacopeia or National Formulary ("USP-NF") monograph for that component. FDA acknowledges that neither the guidance nor the USP-NF provide comprehensive lists, yet FDA still expects manufacturers to identify which components are at high risk and conduct the proper testing.

REGULATORY EXPECTATION FOR TESTING

The guidance emphasizes the Agency's expectation that manufacturers, including outsourcing facilities, comply with current Good Manufacturing Practices ("cGMP") for all drugs. FDA expects, in relevant part, testing of bulk or repackaged high-risk drug components and finished drug products for the presence of DEG and EG, as appropriate. Notably, FDA reports that the Agency has observed "wide variability of DEG and EG contamination from container to container." Thus, FDA expects manufacturers to test representative samples from every container of every lot of all high-risk drug components.

Moreover, FDA expects manufacturers to establish specifications, if not already established, requiring the concentrations of DEG or EG to be no more than 0.10% of the sample. If the concentration of DEG or EG surpass these levels in distributed drug products, FDA requires manufacturers to submit a Field Alert Report (FAR).

HOW WE CAN HELP

King & Spalding is at the forefront of legal issues surrounding impurities in pharmaceuticals, foods, and other consumer healthcare products. Our FDA and Life Sciences team can provide detailed risk-mitigation and best-practices assessments to comply with regulatory expectations for quality control in light of established and emerging FDA regulations. Additionally, our Trial & Global Disputes Practice group represents manufacturers in various litigations relating to trace level impurities and has decades of experience defending toxic tort lawsuits. We expect the FDA guidance to draw attention to the issue of DEG and EG contamination and potentially prompt testing by laboratories with ties to the Plaintiffs' bar. Please contact us if we can assist your company.

ABOUT KING & SPALDING

Celebrating more than 130 years of service, King & Spalding is an international law firm that represents a broad array of clients, including half of the Fortune Global 100, with 1,300 lawyers in 23 offices in the United States, Europe, the Middle East and Asia. The firm has handled matters in over 160 countries on six continents and is consistently recognized for the results it obtains, uncompromising commitment to quality, and dedication to understanding the business and culture of its clients.

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[1] U.S. FOOD & DRUG ADMIN, *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*, (May 2023), https://www.fda.gov/media/167974/download.
[2] U.S. FOOD & DRUG ADMIN., *FDA alerts drug manufacturers to the risk of benzene contamination in certain drugs*, (Sept. 2020), https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs.
[3] U.S. FOOD & DRUG ADMIN., *Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, Revision 1* (Feb. 2021), https://www.fda.gov/media/141720/download.