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FDA Alerts Pharmaceutical Manufacturers to Risk of Benzene in Certain Drugs

FDA Continues to Focus on Identifying and Controlling Trace Impurities in Drugs

On December 23, 2021, the U.S. Food and Drug Administration ("FDA") alerted drug manufacturers that FDA was investigating the root cause of benzene contamination in certain drugs.[1] FDA's alert continues the Agency's increased focus on identifying and controlling trace-level impurities, including nitrosamines,[2] per- and polyfluoroalkyl substances ("PFAS"),[3] and other potentially toxic substances, in drug products. In addition to advances in analytical technology that allow manufacturers to detect impurities at very low levels, FDA's heightened interest has been prompted, in part, by a series of findings by the Agency of benzene in consumer health products such as hand sanitizers and aerosol products.[4] In addition to FDA's findings, private analytical laboratories have filed Citizen Petitions with FDA under 21 C.F.R. § 10.30, which lead directly to personal injury, consumer class action, and attorney-general lawsuits against product manufacturers.

FDA REGULATION OF BENZENE IN DRUGS

FDA, adopting the International Conference on Harmonization (ICH) *Q3C Impurities: Residual Solvents Guidance*, classifies benzene as a Class 1 solvent, meaning it falls within one of the following three categories: known human carcinogens, strongly suspected human carcinogens, or environmental hazards.[5] Under this classification, the use of benzene in the manufacture of drugs should be avoided to the extent possible. However, if use of benzene cannot be avoided, FDA requires manufacturers to have controls in place to ensure that benzene levels do not surpass 2 parts per million (ppm), unless the manufacturer justifies and FDA agrees with the use of a higher limit.

POSSIBLE ROOT CAUSES OF BENZENE PRESENCE

When benzene is intentionally used during the manufacturing process, drug manufacturers can readily identify the risk and evaluate whether – and what – controls may be necessary. FDA, however, has identified several potential sources that may cause benzene to be present even if the solvent is not intentionally used. Specifically, FDA identified that ingredients that are within a chemical class known as "hydrocarbons" or other ingredients manufactured with benzene may act as potential sources of benzene. Additionally, FDA has found that some ingredients, such as sodium benzoate, may react to form benzene under certain conditions.

RECOMMENDATIONS FOR ASSESSING RISK FOR PRESENCE OF BENZENE

FDA recommends that drug manufacturers conduct risk assessments to identify the potential for the presence of benzene in prescription and over-the-counter (OTC) drug products. Although the risk assessment focuses on final drug products, manufacturers must also assess whether any raw materials may introduce benzene. If a risk of benzene being present is identified, drug manufacturers should conduct confirmatory testing to assess whether benzene is actually present and at what levels. If testing confirms benzene's presence, FDA established how manufacturers should contact the Agency about the issue. These options include contacting a dedicated email for sharing test results and methods (when benzene is below the allowable limit) to contacting the appropriate Office of Regulatory Affairs Division Recall Coordinator (if benzene is detected above the allowable limit) to discuss the initiation of a voluntary recall. Additionally, even if the drug manufacturers can rule out the risk of benzene being present, they should continue to assess whether benzene presence is possible anytime there are changes in raw materials, including changes in raw material suppliers. FDA also expressed that the Agency intends to release further guidance on recommended test methods and appropriate steps to modify formulations to limit and control the presence of benzene.

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 benzene exposure lawsuits. We expect the FDA alert to draw even more attention to the issue of benzene contamination and create additional regulatory and litigation risk for manufacturers. Please contact us if we can assist your company.

[1] 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.
[2] U.S. FOOD & DRUG ADMIN., CONTROL OF NITROSAMINE IMPURITIES IN HUMAN DRUGS (Sept. 2020), https://www.fda.gov/media/141720/download.
[3] U.S. FOOD & DRUG ADMIN., *Per- and Polyfluoroalkyl Substances (PFAS)*, (Current as of Oct. 18, 2021), https://www.fda.gov/food/chemical-contaminants-food/and-polyfluoroalkyl-substances-pfas.
[4] *E.g.*, U.S. FOOD & DRUG ADMIN., *FDA updates on hand sanitizers consumers should not use*, (Current as of Dec. 22, 2021), https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use.
[5] U.S. FOOD & DRUG ADMIN., Q3C IMPURITIES: RESIDUAL SOLVENTS (Dec. 1997); U.S. FOOD & DRUG ADMIN., Q3C – TABLES AND LIST (Aug. 2018), https://www.fda.gov/media/133650/download.