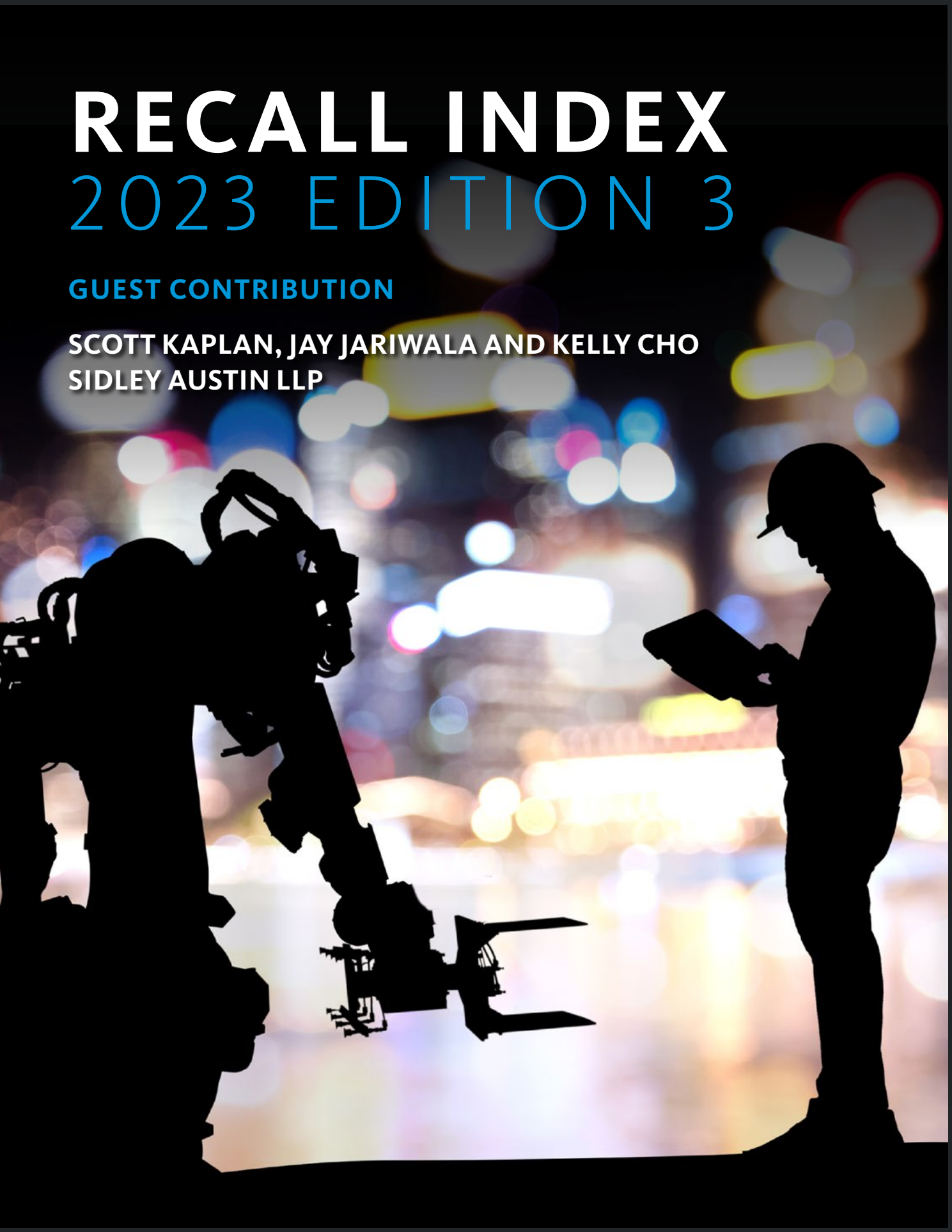
RECALL INDEX
2023 EDITION 3

GUEST CONTRIBUTION

SCOTT KAPLAN, JAY JARIWALA AND KELLY CHO
SIDLEY AUSTIN LLP



DATA, TRENDS & PREDICTIONS **FOR US INDUSTRIES**

sedgwick | brand protection

SCOTT KAPLAN, PARTNER; **JAY JARIWALA,** SENIOR DIRECTOR OF REGULATORY COMPLIANCE; AND **KELLY CHO,** MANAGING ASSOCIATE, WITH **SIDLEY AUSTIN LLP**

CONTROLLING CONTAMINANTS: RISKS TO YOUR SUPPLY CHAIN AND BEYOND

Drug contaminants continue to be a focus for the Food and Drug Administration (FDA). This year the agency has issued several guidances including one on testing for diethylene glycol (DEG) and ethylene glycol (EG) and more recently, one recommending acceptable intake limits for nitrosamine drug substance-related impurities (NDSRIs).

The FDA has also engaged in a stream of enforcement activities this year, issuing at least 30 warning letters regarding DEG/EG. In every case, the agency stated that drug manufacturers failed to comply with identity testing requirements or didn't establish the reliability of their suppliers' test analyses. In addition, multiple recalls were implemented by manufacturers due to continuous discovery of various nitrosamine related impurities.

This article reviews three recent case studies of contaminants that have highlighted supply chain vulnerabilities and shaken much of the drug industry: benzene, nitrosamine, and DEG/EG. In combination, these events remind drug manufacturers of the importance of maintaining current knowledge of their end-to-end supply chain and scrutinizing it for any high-risk components.

In the cases where contaminants are detected, these events also illustrate the need to be vigilant and develop control and response strategies for (a) recalls, (b) FDA information requests such as records requests or during inspections, (3) ensuing enforcement actions (e.g., warning letters and import alerts), (4) drug shortages, and/or (5) class-action lawsuits.

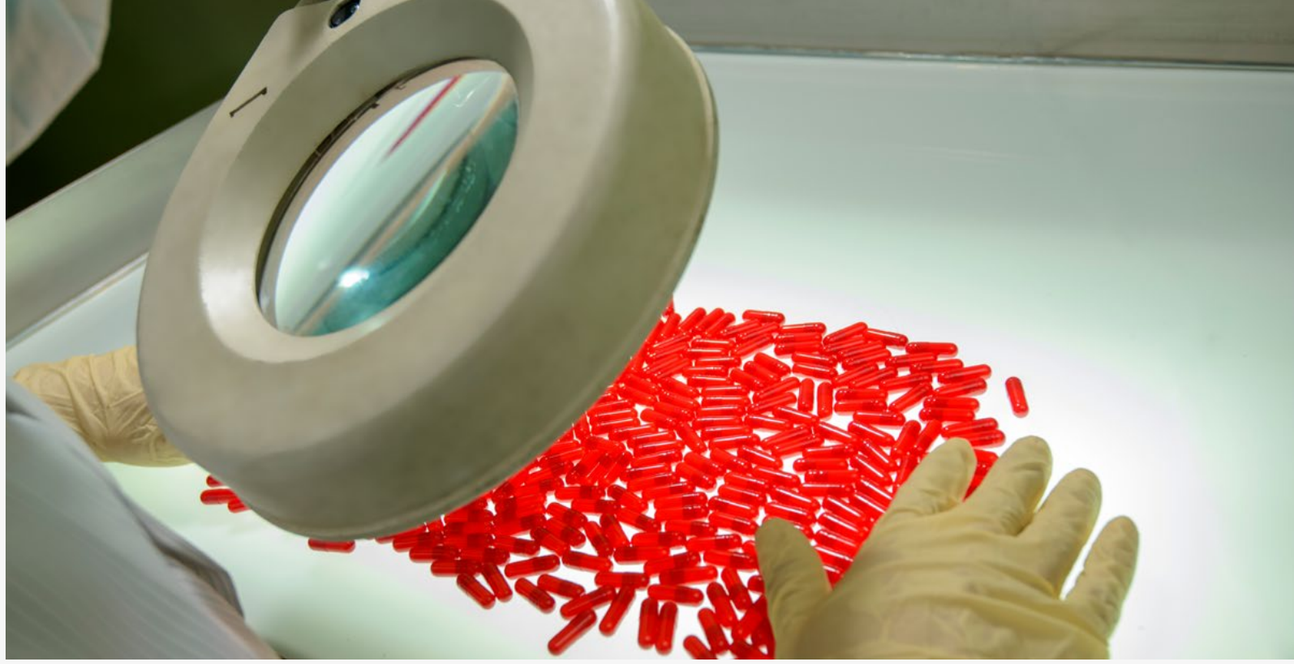
Benzene

In May 2021, one independent laboratory filed a citizen petition identifying as many as 78 sunscreen and after-sun care products after the laboratory's testing detected benzene at or above the limit set by FDA for Class 1 solvents of two parts per million. Benzene is a known human carcinogen that can lead to leukemia or other blood disorders. According to the World Health Organization, there is "no safe level of exposure" recommended. The laboratory's citizen petition asked the FDA to recall the identified batches of sunscreen products and publish rules and guidances for analysis of benzene in sunscreen products, among other actions.

While FDA has yet to provide a substantive response to the petition, the agency issued a statement later that year, stating that it was alerting manufacturers to the risk of benzene contamination from drug components and other potential risk factors. The statement pointed to inactive components as potential contaminant sources. These included carbomers (thickening agents), isobutane (a spray propellant), and other drug components made from hydrocarbons.

The agency reminded drug manufacturers to conduct risk assessments to determine they have the appropriate specifications, test methods, and controls to ensure drugs are free from contamination. It also recommended that they conduct testing of both raw materials and finished product batches and be vigilant about the changes in raw materials throughout the lifecycle of the drug. The FDA also cautioned about changes in suppliers, which could introduce contaminants into the supply chain.

The laboratory's citizen petition triggered a series of voluntary recalls by a number of manufacturers identified in the petition, as well as a wave of class action lawsuits. The FDA has issued new and revised guidance to emphasize the need to be recall ready and to be proactive with the implementation of recalls. These test cases underscore the delicate balance that is needed between carefully assessing public health risk at the outset and reaching a decision on whether a recall is necessary.



Nitrosamine

The FDA released guidance in August 2023 that recommended acceptable intake limits (AI limits) for nitrosamine drug substance-related impurities (NDSRIs). This is a class of nitrosamine impurities that share structural similarity to a particular active pharmaceutical ingredient (API). The guidance is incredibly broad in scope and applies to nearly all approved prescription and over-the-counter (OTC) drugs as well as those in development.

Nitrosamines are organic compounds that we are exposed to in our everyday lives through a range of sources including water and foods such as cured or grilled meats. Exposure to them above acceptable levels over long periods of time may increase the risk of cancer. In drug products, NDSRIs typically form during manufacturing as a result of a reaction between the API or API fragment and a nitrosating agent. There is limited safety data for most NDSRIs.

The FDA began investigating small molecule nitrosamine impurities in drug products in 2018. Since then, the agency has taken a number of steps to control this type of impurity in drug products. In 2019, the FDA issued numerous warning letters, mostly to manufacturing sites in China or India, for failure to have adequate controls against nitrosamine impurities. After identifying nitrosamine impurities, multiple manufacturers conducted recalls of several drug classes including angiotensin II receptor blockers (ARBs), ranitidine, nizatidine, and metformin based on unacceptable levels of nitrosamine impurities. In the case of ARBs, the recalls resulted in drug shortages.

The August 2023 guidance follows previous guidance the FDA issued in 2020 and revised in 2021 which recommends a three-step mitigation strategy to detect and prevent unacceptable levels of nitrosamine impurities. The process starts with the need for drug manufacturers to conduct a risk assessment that considers all potential causes of nitrosamine formation. This includes examining the supply chain, e.g., API, raw materials, and their vendors.

The recent guidance builds upon the established frameworks with specific advice on establishing AI limits for NDSRIs. With the FDA's and global heath regulatory authorities' understanding of NDSRIs evolving, the guidance establishes a recommended approach using predicted five carcinogenic potency categories to establish NDSRI AI limits.

It also sets guidelines for establishing a framework for drug sponsors to determine AI limits for NDSRIs. However, due to the changing understanding of these impurities, there may be challenges for setting and receiving FDA-concurrence with NDSRI AI limits.

SCOTT KAPLAN, PARTNER; **JAY JARIWALA,** SENIOR DIRECTOR OF REGULATORY COMPLIANCE; AND **KELLY CHO,** MANAGING ASSOCIATE, WITH **SIDLEY AUSTIN LLP**

CONTINUED FROM PREVIOUS PAGE

Diethylene Glycol and Ethylene Glycol

The FDA released a new guidance in May 2023, which expands on its previous 2007 guidance on testing of glycerin for Diethylene Glycol (DEG). The new guidance was issued in the wake of more than 300 deaths abroad from Diethylene Glycol and Ethylene Glycol (DEG/EG) contamination in drug products in 2022 and 2023, mostly in children under the age of five. Under the new guidance, liquid drug manufacturers should test glycerin as well as at least four other excipients—propylene glycol, maltitol solution, hydrogenated starch hydrolysate, and sorbitol solution—for both DEG and EG.

The previous guidance had described three common sources of DEG/EG contamination. These remained unchanged in the new guidance: (1) failure to perform full identity testing on the glycerin raw material, (2) reliance on the certificate of analysis (COA) provided by the supplier, and (3) reliance on COAs that do not clearly provide the origin of the glycerin and/or chain of custody. At a high level, the guidance reminds manufacturers that their products must meet cGMP requirements, which include "oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished products."

More specifically, the guidance states that manufacturers should perform full identity testing and comply with compendial identity standards and any specified DEG/EG limits for drugs or drug components recognized in the United States Pharmacopeia and the National Formulary (USP-NF), among others. Any tests to detect and quantify DEG/EG should use a safety limit of no more than 0.10%, and if the concentration in the distributed drug products exceeds this safety limit, manufacturers should submit a Field Alert Report (FAR).

Recently, the FDA has taken an aggressive approach to controlling DEG/EG. The agency has issued as many as 30 warning letters this year to foreign and domestic firms for non-compliance with GMP requirements relating to DEG/EG testing. Cited violations include failure to demonstrate adequate identity testing of incoming glycerin, failure to validate and establish the reliability of a component supplier's test analyses at appropriate intervals, and failure to determine whether each component conformed with all appropriate written specifications for purity, strength, and quality before using them. The FDA has also placed a number of companies on import alerts, which highlights the agency's focus on preventing contaminated products from entering the U.S.

Steps for manufacturers

Despite continuous efforts by the agency and the pharmaceutical industry to protect drug products from contaminants, these risks persist. The FDA's recent activity demonstrates that controlling contaminants remains an area of focus.

It will be important for drug manufacturers to be recall ready so that they can act quickly and effectively execute recalls when contaminants are detected. This includes developing and establishing the procedures and systems necessary for a recall, such as a comprehensive recall readiness plan.

Recalls can become further complicated if they lead to drug shortages. For example, the FDA's recent nitrosamine guidance instructs manufacturers to "immediately" contact a specific agency email address if manufacturing changes or recalls are likely to lead to a disruption in the drug supply.

Lastly, responding to and addressing FDA enforcement actions, such as warning letters or import alerts, can also be extremely labor-intensive. FDA enforcement actions will require significant internal and possibly external company resources to resolve and are often accompanied with tight deadlines. Drug manufacturers should do everything they can to ensure compliance so that they aren't faced with enforcement actions and the impact they have on the company's resources and reputation.

sedgwick

RECALL INDEX: EDITION 3, 2023

DOWNLOAD THE FULL EDITION HERE

Website: sedgwick.com/brandprotection
Telephone: 1.888.732.3901
Email: brand.protection@sedgwick.com

sedgwick | brand protection