STATE OF THE NATION 2024

GUEST CONTRIBUTION

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

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FDA FOCUSES ON QUALITY MANAGEMENT MATURITY AS PHARMACEUTICAL RECALLS AND SHORTAGES SPIKE

It is FDA's mission to ensure medicines meet high standards for safety, effectiveness, and quality at every link in the global supply chain. This means oversight of suppliers, manufacturers, hospitals, and providers until the drug reaches patients. Supply chains have become more diverse at the same time as medicines have become more complex. This means regulatory environments must keep pace and become more exacting. This trend has contributed to an increase in U.S. pharmaceutical recalls, as seen in 2023 which had the most recall events in more than ten years.

Recall Trends in 2023

Recalls are an important mechanism for removing potentially hazardous products from the market. Most recalls are voluntarily initiated by the manufacturer, who should be able to identify and investigate emerging quality issues and, when appropriate, initiate and manage recall events. Effective recall strategies can help companies minimize the risk of subsequent FDA enforcement action.

The primary drivers of pharmaceutical recalls in the U.S. are deviations from current good manufacturing practices (CGMPs), followed by lack of sterility assurance and failed impurities/degradation specifications. For example, a series of high-profile eye drop recalls in 2023 were initiated after an FDA inspection of an Indian manufacturing facility found unsanitary conditions and contamination risks for products supplied to several U.S. retailers and distributors.

The agency has also intensified its push for more stringent supplier oversight and quality management of excipients, the inactive ingredients in drugs. For instance, FDA has issued alerts about serious adverse events associated with a specific emulsion used in cough syrups and other products. The agency discovered that the excipient contained diethylene glycol (DEG), a toxin formed during the manufacturing process. After recent reports from several other countries of DEG and ethylene glycol (EG) contamination outbreaks linked to children's cough syrups, FDA has heightened its focus on DEG/EG testing and excipient controls more generally. Specifically, FDA has issued guidance for industry on DEG/EG testing, alerts about serious adverse events associated with DEG and EG contamination, and multiple Warning Letters to drug manufacturers making products containing high risk excipients.

Benzene contamination is another ongoing concern. There has been an increase in recalls and warning letters associated with products containing benzene, a known human carcinogen that is linked to leukemia and other blood disorders. The enforcement actions have largely been for spray-on personal care products such as deodorant and sunscreen.

Recall Readiness

Preparation is critical for effective recall management and risk mitigation. In 2022, the FDA issued a final guidance that lays out the agency's expectations and recommendations to help companies ensure recall readiness at all stages in a product's distribution chain. The recommendations include establishing and maintaining written procedures to identify potential events from quality investigations, product quality compliance, and other sources; assigning recall responsibilities to appropriate personnel; conducting mock recalls; complying with FDA reporting requirements, including field alert and biological product deviation reports; communicating with customers and/or the public if a recall is appropriate; and maintaining distribution records.

In addition, companies should conduct a health hazard evaluation (HHE) of the potential health risks of the product being considered for recall as part of an underlying quality investigation during a recall. While a recall decision does not depend solely on the health risk associated with the recalled product, the evaluation helps guide the manufacturer's recall strategy. In addition, HHE findings help inform the FDA of potential risks to the public and guide appropriate actions for the company and the agency.

As part of the HHE, manufacturers should engage qualified personnel, including medical professionals or a multi-disciplinary team with subject-matter expertise, who can assess a range of factors such as whether any disease or injuries have already occurred from the use of the product. The conclusion must be supported by scientific documentation and/or state that it is the opinion of the individual(s) making the health hazard determination.

Further, HHEs should evaluate the hazard to various segments of the population who are expected to be exposed to the product with particular attention paid to individuals who may be at greatest risk, such as children. Manufacturers should also assess the seriousness of the health hazard to which populations would be exposed, the likelihood of occurrence of the hazard, and both the immediate and long-term consequences of the potential health hazard.

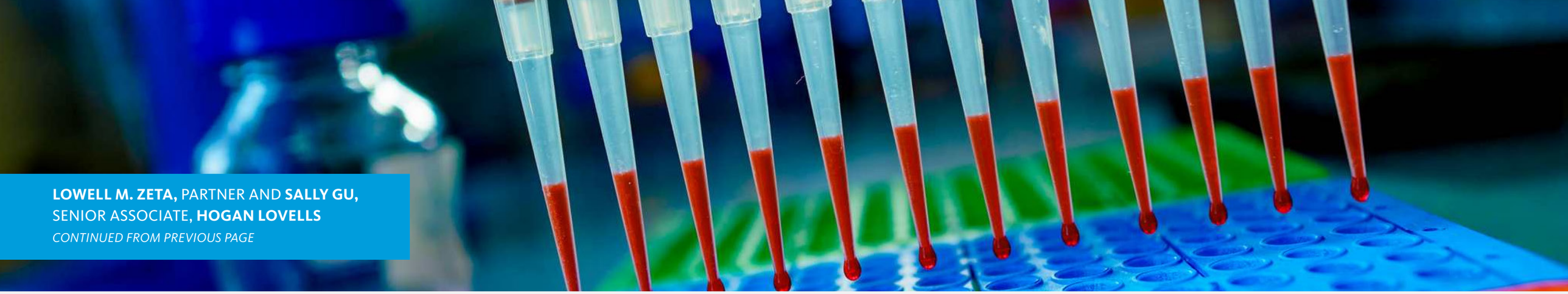
Persistent Drug Shortage Crises

When determining if a drug needs to be recalled, the FDA considers whether a recall could result in a shortage of a critical medicine. Manufacturers of medically-necessary drugs who believe they may have a product that needs to be recalled should immediately notify the FDA's Drug Shortage Staff (DSS) so the Agency and manufacturer can work to avoid a shortage.

Drug shortages not only introduce significant risks to the health of patients and consumers but also disrupt hospitals, health systems, and pharmacies, and have potential national security implications. Supply disruptions persist despite the FDA's reform and prioritization to ensure the availability of drugs, as evidenced by the growing number of drug shortages and instances that require the FDA to exercise regulatory flexibilities to prevent supply disruptions. In February 2024, the FDA listed more than 120 drugs currently in shortage on the agency's Drug Shortage List, and trends from the past year indicate that ongoing and active shortages have risen to their highest levels since 2014. Recent and current shortages include critical drugs used to provide parenteral nutrition, address serious medical conditions, and treat cancer, infections, respiratory illnesses, heart failures, and psychiatric conditions. Children's acetaminophen and ibuprofen are among the medications in scarce supply due in part to an increase in respiratory illnesses.

Although the FDA's critical drug supply challenges pre-date the COVID-19 pandemic, many Americans became acutely aware of national drug shortages during the pandemic. Drug supply challenges are multi-factorial, including manufacturing quality issues, increasing complexity for manufacturing advanced medicines, over-reliance on foreign manufacturing capacities, rigidity of the global supply chain ecosystem, and surging demand. There are also U.S. and global production capacity shortfalls for some critical medical products, particularly sterile injectable drugs.

The FDA's authority has expanded in response to recent shortages. The agency has more visibility into global supply chains through increased manufacturer reporting requirements and an enhanced ability to expedite the review of selected products or procedures. For example, FDA temporarily authorized the importation of drugs produced by non-FDA-approved Chinese manufacturers to alleviate a national shortage of a critical cancer drug



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after the manufacturer of the critical cancer drug was temporarily shut down after an FDA inspection found quality issues. However, there are limitations to FDA's role in addressing drug shortages. It cannot require a manufacturer to produce certain drugs and is not involved in pricing or coverage decisions.

The regulatory discretion to allow products from non-approved facilities is similar to another increasingly used tool within the FDA's toolbox—allowing drug manufacturing facilities with serious compliance problems to continue manufacturing medically-necessary products while they address the issues noted by the FDA. The agency has also tried to improve access by allowing a manufacturer to implement additional safety controls such as increased testing and third-party oversight to provide greater quality assurance.

According to FDA officials within the Center for Drug Evaluation and Research (CDER) presenting at an industry conference, the percentage of FDA drug inspections classified as Official Action Indicated (OAI) for which the agency exercises regulatory discretion is unusually high. The OAI classification is used for facilities deemed to be in an unacceptable state of compliance. To prevent or mitigate shortages for critically-needed drugs, the FDA may decide not to issue a warning letter, request a

regulatory meeting, impose an import alert, or to initiate more serious enforcement even if the facility is designated as OAI if the action would disrupt supplies. In FY 2023, October 1, 2022 – September 30, 2023, there were more than 285 FDA CGMP inspections of drug manufacturing facilities with OAI classifications. Of that total, approximately 66 sites received warning letters; 62 sites resulted in regulatory meetings; 75 sites were placed on import alert; and 80 sites benefited from FDA's regulatory discretion, which means no enforcement action was taken.

According to the data, many of these OAI facilities were producing critical medicines, including COVID-related medical products. The drug supply chain has not fully recovered from shutdowns and delays during the pandemic, so the FDA granted some leniency. As the industry moves back into pre-pandemic operational and drug supply levels, the FDA is likely to use regulatory discretion less frequently. In addition, the agency may be looking to tighten the reigns because it is under increased public attention for its perceived role in drug shortages and supply chain challenges. Committees and members of Congress are looking more closely at the agency following the lack of access to several high-profile drugs, including mental health medications, medicines for diabetes and weight loss, and Respiratory Syncytial Virus (RSV) vaccine supplies for infants.

Addressing the Root Cause of Drug Shortages: Quality Maturity

As the number of pharmaceutical recalls and shortages continue to rise to record levels, the FDA is stepping up its efforts to address quality management maturity (QMM), widely considered to be one of the primary root causes of the issues.

QMM is achieved by implementing quality management practices that go beyond minimum CGMP requirements to manage continuous improvement. QMM improvements result in sustainable compliance, reliable supply chains, and confidence in the quality and accessibility of critical medicines. Investments by drug manufacturers in QMM practices mitigate the likelihood of issues associated with poor drug quality. They can also lead to greater operational performance, improved relationships with regulators and customers, and higher revenues.

The FDA proposed a QMM program in 2019 that created a rating system to inform purchasing and contracting decisions. However, the pharmaceutical industry was not convinced the program would alleviate shortages, especially when there were no clear regulatory incentives.

More recently, the agency has renewed its efforts to develop a QMM program and has run pilot programs, published multiple white papers, convened an advisory committee workshop, and solicited comments from the industry. While the exact timing and components of a formal QMM program remain unclear, the FDA appears to be applying QMM principles to its existing compliance programs. For instance, a 2022 annual report released by CDER's Office of Pharmaceutical Quality (OPQ) showed that the data for site inspection scores suggest a correlation between low scores and potential drug recalls. The FDA also revised its drug compliance programs for pre-approval inspections and drug manufacturing inspections to make key changes aligned with underlying QMM principles for a holistic approach to quality and compliance.

Additionally, FDA added a new primary objective, "Commitment to Quality in Pharmaceutical Development," to the agency's pre-approval inspection compliance program. The data companies provide to show they meet this primary objective will be used by the FDA for data analysis or internal trending, not as the basis for a potential enforcement action. The information may also assist in the identification of risk factors for future pre-approval inspection decisions.

According to the agency, mature quality practices that exceed CGMP requirements are indicative of a modern, risk-based pharmaceutical quality system (PQS). In turn, this approach leads to sustainable compliance and reliable production of high-quality drug products without extensive regulatory oversight. The FDA will assess pharmaceutical manufacturers' ability to develop and manufacture drugs of consistent quality.

Advice for Manufacturers

The agency's revised compliance policies suggest a higher threshold for quality systems for drug manufacturers. During inspections, the FDA has increasingly cited companies for ineffective quality systems. Specifically, it has mandated a comprehensive assessment of a company's global manufacturing operations and support from executive leadership to proactively address emerging issues and to assure a continuing state of control.

An increasing focus on proactive and continuous improvement and an effective quality risk management approach are critical to ensure the quality of the drug on the market. It also demonstrates to the FDA that the manufacturer is able to address potential risks and avert problems. In turn, this assurance could lead to more flexible approaches to oversight to support regulatory decisions.

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