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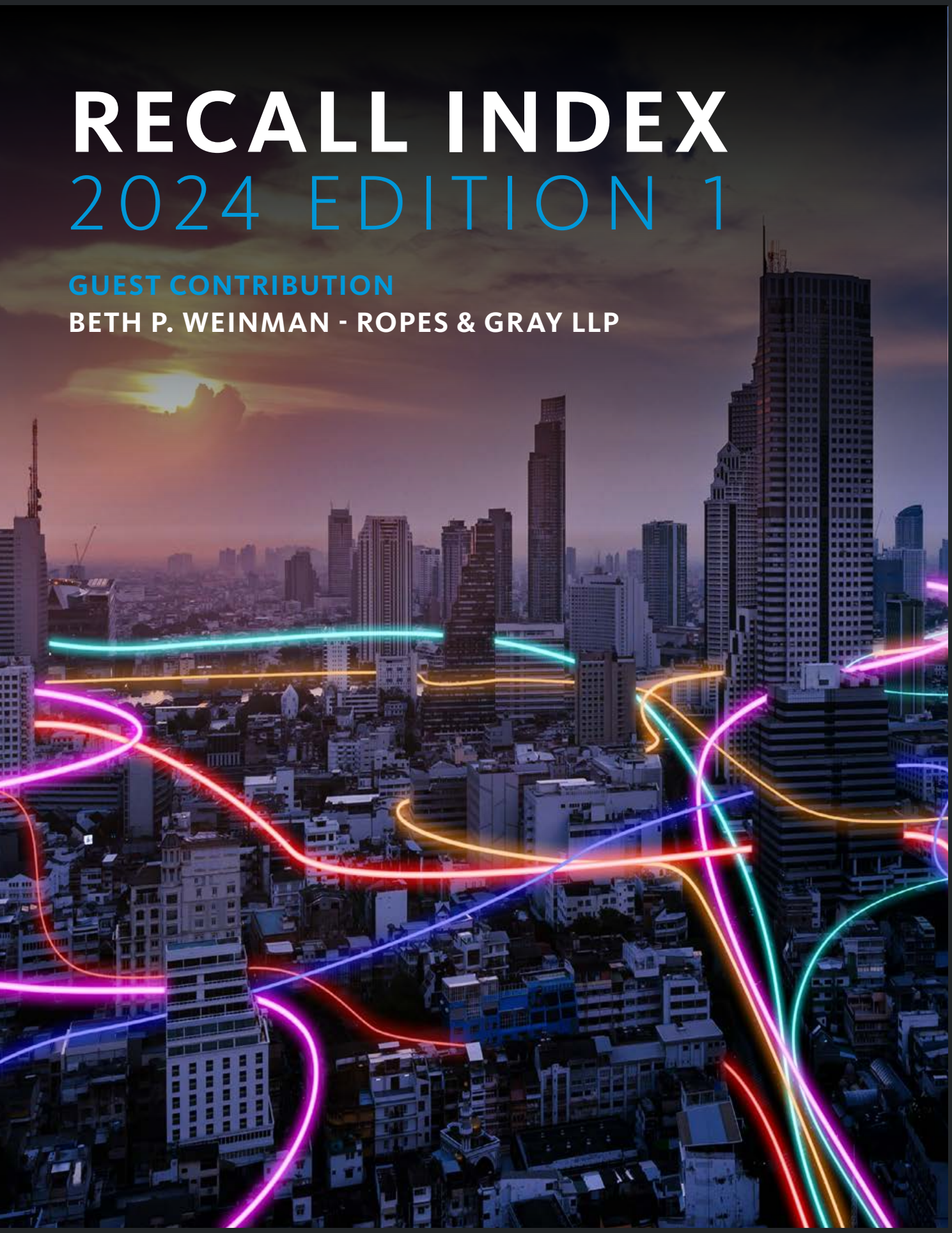

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ENHANCING QUALITY SYSTEM MATURITY TO REDUCE DRUG SHORTAGES

The Food and Drug Administration (FDA) reported 112 pharmaceutical recalls in Q1 2024 and the agency issued more than 40 drug-related warning letters. However, no new safety trend or specific concern is clearly reflected in these actions.

There are, however, lingering concerns about contaminants like benzene, diethylene glycol (DEG), and ethylene glycol (EG) and the presence of methanol in hand sanitizer. One hand sanitizer manufacturer recalled its product due to the presence of methanol and an anti-fungal spray was recalled due to the presence of benzene. The recalls this quarter were driven by several concerns including particulates in drug products, drugs with microbial and other contaminants, the presence of undeclared drug ingredients, and the potential distribution of superpotent drugs.

The warning letters posted in Q1 2024 reflect a few targeted areas of concern. These include unapproved pain-relieving topical creams, smelling salt products intended as stimulants, and contaminated eye drops, which has been an issue in previous quarters. There are a variety of failures noted by the FDA in its warning letters for current good manufacturing practice (cGMP) violations including problems with component identity testing and batch release testing.

In addition to the health risks described by recalls and warning letters, manufacturing quality concerns can also lead to product shortages. The U.S. continues to battle supply issues and the risks they pose. The FDA recently announced its intent to test a protocol for assessing quality system maturity as it seeks a way to reward high quality manufacturing in an effort to combat shortages.

Drug safety challenges and risks

The U.S. is widely understood to be the global leader in pharmaceutical innovation and is the largest producer of medicines in the world. Yet, drug shortages persist and FDA has recognized that many shortages are largely due to manufacturing quality issues. As pressure to reduce the price of prescription drugs has intensified in recent years, so have concerns about a race to the bottom in drug quality, especially in connection with imported, cheaper foreign-made drugs. The issue of ensuring a steady supply of high quality drugs may be the drug safety challenge of our generation.

There are currently 114 drugs on FDA's drug shortage list. The medications range from cancer treatment medications, the critical antibiotic amoxicillin powder used to create suspension formulations for those who cannot take pills, nitroglycerin injections needed to control congestive heart failure in patients who have had a heart attack, epinephrine injections needed to treat allergic reactions and reverse cardiac arrest. The list also includes active ingredients like those in commonly used ADHD medications and in a widely popular glucagon-like peptide 1 (GLP-1) weight-loss medication that is also used to treat Type 2 diabetes.

The lack of readily available critical medicines poses a major risk for patients. Shortages of drugs can lead to a flood of compounded versions of the product that may raise quality concerns of their own. This is being widely seen with the GLP-1 weight-loss drug.

Immature and under-resourced quality systems in drug manufacturing plants are a factor in some of the drug shortages. The FDA has been working on ways to incentivize greater investment in quality. The agency's 2019 drug shortage report recommended the creation of a ratings system to measure and rate the quality management maturity (QMM) of manufacturing facilities based on specific objective factors. Facilities that achieve a high degree of QMM would be rewarded for their robust quality systems by being able to charge higher prices for their higher quality products.

The report noted that "a rating system could be used to inform purchasers, group purchasing organizations (GPOs), and even consumers about the state of, and commitment to, the quality management system maturity of the facility making the drugs they are buying." The agency said this would introduce transparency in the market with respect to quality.

In the last quarter of 2023, the FDA solicited comments on a new Center for Drug Evaluation and Research (CDER) Quality Management Maturity program. On January 25, 2024, the agency published an announcement in the Federal Register for a limited number of manufacturing establishments to participate in a voluntary QMM Prototype Assessment Protocol Evaluation Program. The initiative would "encourage drug manufacturers to implement quality management practices that go beyond current good manufacturing practice (cGMP) requirements."

This program follows two pilot programs that took place between October 2020 and March 2022 to assess QMM. The learnings from those programs contributed to the development of the prototype that will be applied and tested in the newly announced program.

How can companies prepare?

The FDA and many other government players are laser focused on resolving shortages. Driving improvements in manufacturing quality appears to be a continuing priority of these efforts. Manufacturing facilities that have held off making necessary investments in quality should move ahead with those plans quickly.

New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) holders will need to choose their active pharmaceutical ingredient (API) manufacturers and any contract manufacturers extremely carefully. The FDA assessments of QMM that enable greater transparency could ultimately help in that regard, but it will take time for the program to expand enough to be a useful tool for selecting vendors.

Even when those assessments are available to help with vendor selection, they are no replacement for comprehensive quality agreements, robust auditing rights, and serious attention to quality trending reports, root cause investigations, and effective corrective and preventive actions (CAPAs).

With the FDA also pushing companies to significantly reduce the presence of impurities in drugs that may form during manufacturing, like nitrosamines and nitrosamine drug substance-related impurities, this may not be an easy time for manufacturers to make additional investments in quality systems. However, compliance budgets are always tight, and making systemic upgrades in the short term may reduce long-term costs.

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Predictions for the future

It remains to be seen whether FDA's new QMM prototype assessment protocol program will ultimately lead to a "ratings" program that can facilitate higher prices for products produced in facilities with a higher level of QMM. It is unclear whether the market will bear higher prices. However, the FDA's report, "Lessons Learned from CDER's Quality Management Maturity Pilot Programs," cites research suggesting that good quality often leads to lower costs in the longer term. It may be that investments in quality are able to pay for themselves at some point.

Regardless, it appears increasingly likely that the FDA will eventually settle on a number of factors and assessment tools to measure a firm's QMM and that firms with higher levels of QMM will be able to use these measurements to their advantage. For example, firms may be able to market their high QMM to consumers and payors.

In addition, firms with positive assessments of QMM are likely to see fewer inspections as the agency applies its monitoring resources to higher risk firms. The opposite is also true, however. Firms that have not been assessed with high levels of quality management maturity may ultimately find themselves a higher inspection priority in a risk-based inspection surveillance environment. That means they will be more likely targets for agency enforcement action if quality practices are found to be lacking.

It will also be interesting to see if the FDA's efforts to find ways to better assess quality management maturity will lead to more specific and stricter manufacturing practice obligations applicable to all firms.

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