PRESCRIPTION

FOR PRODUCT SAFETY

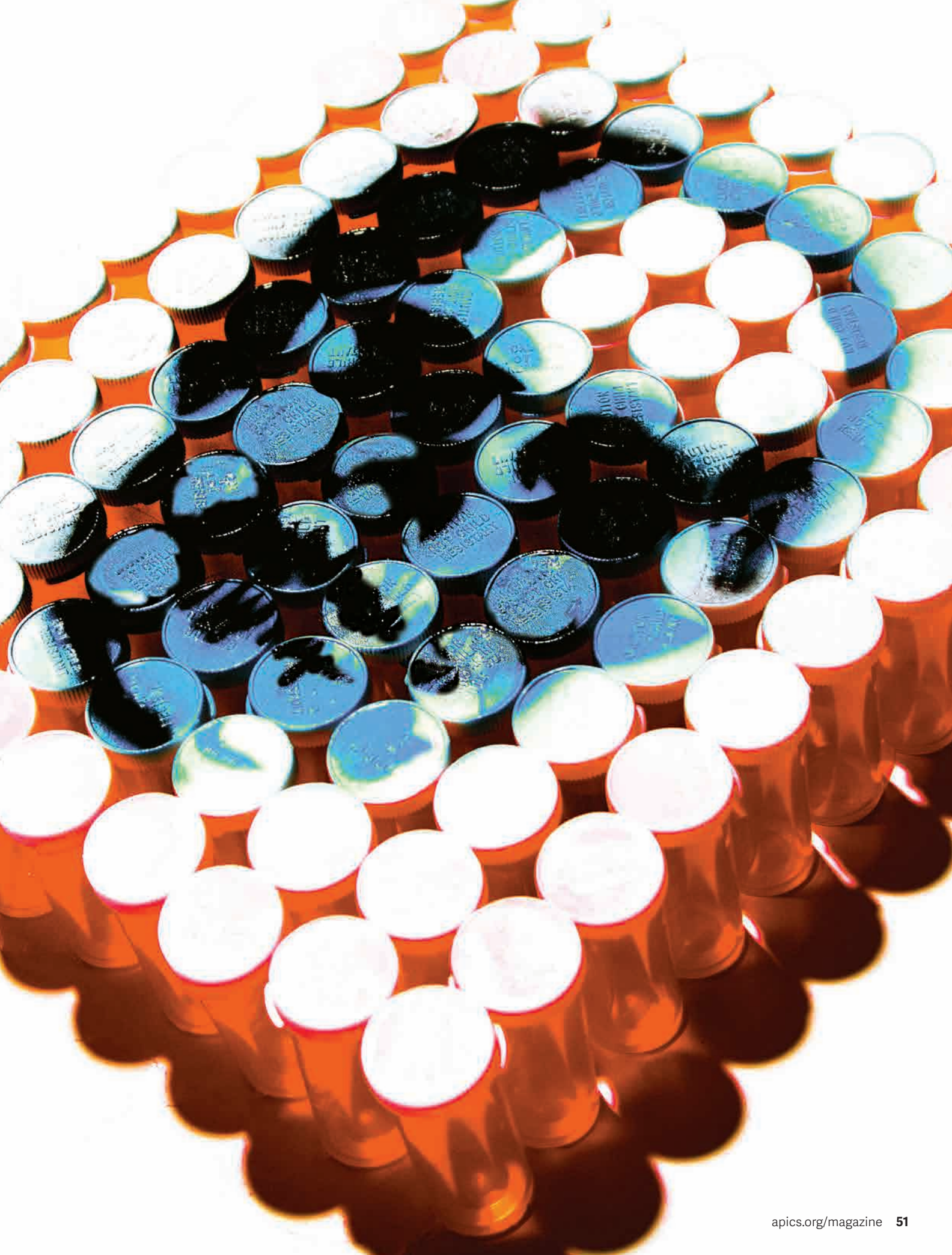
Filling dangerous cracks in the pharmaceutical supply chain

The pharmaceutical supply chain stretches around the world like a rubber band wrapped around a ball. The smallest fault in any segment of that rubber band challenges the integrity of the whole and could lead to catastrophic failure of the entire system.

When such a crack causes product standards to slip, consumers are the first ones who are hurt. In 2007, at least 100 Panama residents, many of them children, died from consuming cough syrup that was tainted with poisonous diethylene glycol, a chemical commonly used in antifreeze as a substitute for glycerin. Investigators found that this particular diethylene glycol product originally had a Chinese label correctly designating it as a substitute for glycerin, according to a US Food and Drug Administration (FDA) public meeting report. However, in the translation process, the substitution note was dropped from the paperwork, and the product was assumed to be glycerin, which is non-toxic and commonly used in pharmaceuticals and as a sweetener. This paperwork mistake ultimately became a life-or-death issue.

In other cases, patients have been hurt because a medicine contained too much or too little of a necessary ingredient, Liam O'Riordan notes in his whitepaper "Serialization in Life Science: 'A business perspective.'" For example, in 2009, a drug that was used to lower blood sugar in diabetic patients contained six times the normal dosage of a key ingredient. As a result, two people in China died, and several others there were hospitalized. In 2012, 19 US medical practices were affected by batches of Avastin, a drug used in cancer treatment, that lacked the necessary active ingredient.

BY REGINALDO MONTAGUE



Counterfeiting is just one of the many threats to the global pharmaceutical supply chain.

If any players in these examples acted knowingly, their actions would be considered counterfeiting, which *The American Journal of Tropical Medicine and Hygiene* defines as the deliberate and fraudulent mislabeling of a medicine with respect to its identity or its sources to make it appear to be a genuine product. However, counterfeiting is just one of the many threats to the global pharmaceutical supply chain. Others include intentional adulteration—when the product is deliberately diluted or includes substitute ingredients—theft and illicit sale of products, and the unsanctioned movement of products from the intended market to another, according to supply chain consortium Rx-360's "Rx-360 Supply Chain Security White Paper: A comprehensive supply chain security management system."

A 2015 study by Tim K. Mackey, Bryan A. Liang, Peter York, and Thomas Kubic analyzed 1,510 counterfeit incidents reported to the Pharmaceutical Security Institute between 2009 and 2011. Of those, 95 percent were either unspecified incidents—in which the exact cause was not known or verifiable—or counterfeit products and packaging. (See Figure 1.)

It is difficult to determine the prevalence of counterfeit drugs in the global supply chain, but McKinsey & Company estimates a 2–10 percent global counterfeit drug average with rates as low as 1 percent or less in developed countries and as high as 30 percent in developing countries. The Pharmaceutical Security Institute states that the number of incidents reported to its counterfeit incident system grew exponentially between 2002 and 2014 to 2,177 incidents.

Many counterfeit medicine reports come from Latin America and parts of Asia, as these regions have less robust regulatory frameworks. However, because of the global nature of the pharmaceutical supply chain, counterfeit products are not localized issues. According to The Pew Charitable Trusts' presentation "Implementation of Drug Supply Chain Provisions of Title VII of FDASIA," 80 percent of the active pharmaceutical ingredients (APIs) and chemicals in US drugs originate from outside the United States, and more and more are coming from emerging economies where robust regulatory frameworks are not yet established. This increases risk for the global supply chain.

According to the *American Journal of Health-System Pharmacy*, drug shortages are a primary driver of today's counterfeit drug rates. Drug shortages "disrupt the pharmacy supply chain, leading to further fragmentation of care, price gouging, and trafficking in counterfeit and diverted drug products of questionable quality through gray-market distributors, which ultimately result in adverse patient outcomes and increased health care costs."

The counterfeit drug market also steals revenue from legitimate pharmaceutical firms and supports organized crime. Economics researchers Joseph P. Fuhr Jr., PhD; Erwin A. Blackstone, PhD; and Steve Pociask estimate that counterfeit drugs produce $75 billion in revenue for illegal operations. The existence of counterfeit products and product ingredients also create litigation and recall costs for pharmaceutical companies.

To overcome these threats, the US FDA is working to better regulate the global supply chain in the following ways.

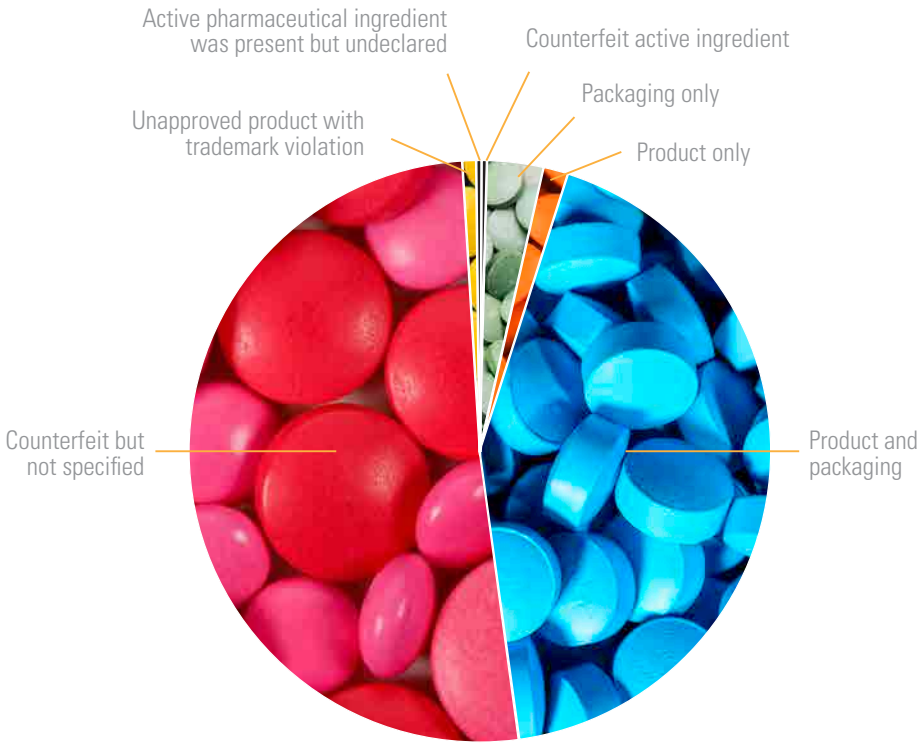


Figure 1: Counterfeit medicine incidents by type

Source: Mackey, Tim, et al. 2015. "Counterfeit Drug Penetration into Global Legitimate Medicine Supply Chains: A global assessment." *The American Journal of Tropical Medicine and Hygiene* 92, no. 6: 59-67.

INCREASING SCOPE

Three decades ago, the drug supply chain was more localized and far less complex, and the US FDA operated on a national scale. However, now that APIs are sourced from multiple global organizations, which provide varying quality and produce with varying regulatory frameworks, the global pharmaceutical supply chain contains a wide range of risk profiles. To better manage this fragmented and vulnerable network, the US FDA added to its arsenal the FDA Safety and Innovation Act (FDASIA), which was signed into law July 9, 2012. FDASIA authorizes the US FDA to "protect the integrity of the drug supply chain" by overseeing non-domestic manufacturing facilities and enhances the FDA's tool kit for overseeing the global manufacturing environment.

Specifically, Title VII, which contains the supply chain provisions of FDASIA, updates the regulation of everything in the pharmaceutical supply chain, from ingredients to finished products. The section is designed to facilitate the flow of information between the US FDA and its peers, keep track of drug manufacturers, and increase the traceability of drugs and their raw materials as they move around the world. These provisions are already working. Prior to the FDASIA manufacturer registration requirement, the US FDA did not know how many firms globally were making APIs and formulating drugs for export to the United States. By fiscal year 2014, the US FDA registered 12,949 drug establishments, 3,619 of which were foreign companies.

With more information about the players in the drug supply chain, the US FDA has been able to shift to a risk-based approach to inspection to better distribute its limited resources to facilities that require attention. In addition, the US FDA has been collaborating with the Chinese government and the European Medicines Agency to conduct joint inspections and increase global drug safety. During fiscal year 2014, the US FDA conducted 5,554 good manufacturing practice inspections of registered foreign and domestic establishments. Although this total represents an 8 percent decrease from 2013, 1,379 of these inspections were of non-US facilities—a 17 percent increase in international inspections. (See Figure 2.)

The regulation also enables the US FDA to obtain records in advance of inspections and provides incentives for cooperation. This means the FDA can detain and destroy products and pursue prison terms as long as 20 years or fines as high as $1 million for intentional alteration of drugs. These and other FDASIA rules can be enforced both inside and outside the United States. Together, these provisions should enable the US FDA to better address the flow of unsafe drugs entering the pharmaceutical supply chain.

SUPPLY CHAIN SUPPORT

Pharmaceutical manufacturers, suppliers, auditors, and associations have joined forces to help with this effort. The pharmaceutical industry formed Rx-360, a supply chain consortium for sharing alerts about threats to the supply chain, audit information, and other important notices. Rx-360 membership comprises 27 manufacturers, such as AbbVie, AstraZeneca, Bayer, Johnson & Johnson, Pfizer, Procter & Gamble, and Takeda Pharmaceuticals, and 30 suppliers, including BASF, DSM Nutritional Products, GE

Figure 2: FDA good manufacturing practices inspections of registered domestic and foreign drug and device establishments

	2013	Percent	2014	Percent	2013-2014 Change	Percent
Domestic	4,858	81%	4,175	75%	-683	-16%
Foreign	1,138	19%	1,379	25%	241	17%
Total	5,996	100%	5,554	100%	-442	-8%

Source: US FDA. 2015. "2015 Annual Report on Inspections of Establishments in FY 2014." *FDA.gov.* http://www.fda.gov/

Healthcare, and Merck. Fourteen auditors and 26 associations round out the group.

Together, these members have created an operating framework that complements FDASIA and addresses threats to the supply chain. The group's 2012 whitepaper "Rx-360 Supply Chain Security White Paper: A Comprehensive Supply Chain Security Management System" offers guidance about implementing a comprehensive supply chain security management system and includes information about preventing, detecting, and responding to incidents that could adversely affect patient safety during the source, make, and market steps of the production and distribution process. The major program characteristics include incorporating security principles in agreements, supplier selection, risk assessments, incident management, improvement in tracking and traceability, continuous improvement, training, education, collaboration with law enforcement, inspections, audits and other operations.

Rx-360's Joint Audit program, for example, employs third-party auditors and uses a standardized audit approach during supplier audits. Through the Joint Audit approach, member firms reduce the number of audits they have to perform and can instead purchase the audit reports.

The *American Journal of Health-System Pharmacists* states that the pharmaceutical industry also is calling for enhanced track-and-trace systems, including investments in infrastructure and technology. In response, solutions are emerging and being implemented to increase traceability. For example, a serialization technique uses serial numbers at the unit level. Under this model, a tamper-evident medicine package would be equipped with a code of random numbers that helps trace the item throughout the supply chain. Aggregation is a packaging hierarchy for a pallet of items. Each is linked electronically to its parent packaging, shipper case, and pallet. In this way, the product can be tracked throughout the supply chain at the unit level, and a history of transactions can provide traceability.

IN THE WORKFLOW QUEUE

Although these frameworks and technologies are filling some of the cracks in the global supply chain, there are administrative challenges that also need to be addressed in the coming years.

For example, some governments do not welcome the US FDA's inspectors. Angelo Depalma notes in a *Pharmaceutical Manufacturing* article that the US FDA's authority abroad has not yet been challenged in court, and experts wonder whether the agency would even win such cases. In addition, many FDA inspectors have less than two years of experience, so more training could be needed there.

Variability in regulatory structures around the world also creates detection gaps. Each producing country may have its own rules that differ from US FDA regulations. On the extreme end of the spectrum, some countries might only have immature regulatory frameworks that provide ineffective detection. The aforementioned 2015 study by Mackey, Liang, York, and Kubic found no evidence of Pharmaceutical Security Institute Counterfeit Incident System counterfeit reporting in 127 out of 196 countries. This does not mean that no reporting is taking place, but it indicates that many nations have an insufficient regulatory framework in place to detect emerging risks.

Supply chain participants—including the pharmaceutical firms, distributors, retailers, regulators, and consumers—all play a role in safeguarding the supply chain. Although new regulations are a welcome step in the right direction to increase security, challenges and vulnerabilities remain. To protect supply chain integrity and the lives of patients, the US FDA, Rx-360, and other players must continue working together toward a secure global pharmaceutical network.

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