Case Studies: How Unsafe Drugs Can Reach Patients

The following case studies illustrate breaches in the pharmaceutical supply chain—the route a drug travels from its raw-material origins to the delivery of a finished medicine. These examples, many of which are summarized in the Pew report *After Heparin: Protecting Consumers From the Risks of Substandard and Counterfeit Drugs*, demonstrate the different ways that contaminated, fake, or otherwise unsafe medicine can reach patients. They also underscore the need for reform.

Eighty percent of the active and bulk chemical ingredients in U.S. drugs originate overseas, according to estimates by the Food and Drug Administration (FDA).[1] The increasingly global and outsourced production of drugs creates vulnerabilities in the pharmaceutical supply system, which, without sufficient oversight by industry and regulators, can put patients' lives at risk.

Once a finished drug enters distribution, it can pass through many hands before reaching a pharmacy, thereby creating opportunities for criminals to insert illegitimate products into the supply chain. Stolen and counterfeit medicines have made it onto pharmacy shelves or reached patients numerous times over the past decade.

Previously dispensed drugs, held under unknown conditions, were illegally resold to patients at U.S. pharmacies, costing the New York Medicaid program $500 million.

In 2012, the U.S. attorney for southern New York uncovered a massive criminal ring of drug diversion and relabeling that cost the state Medicaid program more than $500 million and put unknown numbers of patients at risk from compromised medicines.[2]

"Collectors" purchased the drugs from patients and sold the medicines back into distribution through pharmaceutical wholesalers, allowing them to eventually reach pharmacies. The unsuspecting patients who received these recycled drugs were exposed to medicines that may have expired or been contaminated.[3]

The practice of diverting and reintroducing pharmaceutical products for profit is not new. Similar schemes in other states are well documented. In 2013, for example, three people were indicted in Tennessee for allegedly buying medicines that had been collected from patients and then reselling the drugs to pharmacies as legitimate products.[4]

Counterfeit cancer medicines were distributed in the United States.

Twice in 2012 and once in 2013, FDA announced that counterfeit cancer medicines had been found in the United States. The fake drugs contained none of the active ingredient necessary to treat the disease.[5]

According to FDA, the counterfeit drugs came from foreign suppliers that were providing medicines to U.S. medical practices using illegal channels that were approved for use in other countries such as Turkey, but not the United States.[6] FDA notified more than 100 doctors in 33 states that they had purchased illegal prescription drugs from foreign or unlicensed suppliers.[7]

An adulterated blood thinner harmed patients in the United States.

In early 2008, the U.S. Centers for Disease Control and Prevention began investigating an outbreak of allergic-type reactions in patients undergoing dialysis. Most of these patients had received intravenous heparin, a widely used blood thinner manufactured by Baxter Healthcare.[8] Further investigation revealed that an adulterant with toxic effects, oversulfated chondroitin sulfate (OSCS), had been introduced during heparin's manufacture in China.[9] The chemical structure of OSCS so closely mimicked heparin that it passed standard tests.[10]

Dozens of Americans suffered adverse reactions, including death.[11] Investigations into this tragedy have revealed a number of systemic failures, including inadequate oversight and supply chain management by both regulators and industry. Heparin's complex production chain was left vulnerable to abuse by perpetrators who have not been identified.

Manufacturing quality and safety problems at an India-based generics company led FDA to ban imports of more than 30 drugs produced there.

Ranbaxy is one of the largest worldwide producers of generic medicines. Its products filled 52 million U.S. prescriptions in 2007.[12]

In 2008, in-depth plant inspections by FDA resulted in allegations of numerous safety and quality issues.[13] According to the agency, Ranbaxy exposed products to potential cross-contamination by penicillin and failed to adequately investigate sterility failures.[14] A Department of Justice subpoena motion stated that Ranbaxy also used active pharmaceutical ingredients made at sites not approved by FDA.[15]

In 2008, the agency suspended importation of more than 30 Ranbaxy products, including drugs for epilepsy, diabetes, and allergies.[16] It again suspended importation of products made at a Ranbaxy plant in 2014. FDA believes that increasing its on-the-ground presence in countries such as India could strengthen its oversight of imported drugs.[17]

A pharmaceutical broker falsely labeled medicines imported into the United States to conceal unapproved manufacturing plants.

In the late 1980s and early 1990s, drug broker Flavine International Inc. bought cheap materials from Chinese plants that were not approved by FDA. Flavine falsely labeled the products as active ingredients from Long March Pharmaceutical, an FDA-approved facility.[18] The drugs, which included bulk shipments of the antibiotic gentamicin, were sold to U.S. manufacturers, which eventually recalled gentamicin products from the market.[19] In 1997, Flavine was fined, and its owner was sentenced to two years in prison.[20]

This case underscores the importance of manufacturer scrutiny of brokers and suppliers to verify that all drug production is actually occurring at the declared sites and that sufficient quality assurance systems are in place.

A major foreign manufacturer of antibiotics for the U.S. market admitted that it did not follow approved manufacturing standards.

In the 1990s, the Italian pharmaceutical manufacturer Biochimica Opos, then a wholly owned subsidiary of the French drug company Roussel-Uclaf, falsified records to conceal its use of undisclosed manufacturing sites in Italy, France, and Romania to produce the antibiotic cefaclor. The company ultimately recalled this and other products and withdrew its approved marketing applications.[21]

In 2001, Roussel-Uclaf's successor, Aventis Pharma AG, pleaded guilty to multiple felony charges and was ordered to forfeit $10 million in proceeds and pay a $23 million criminal fine to the U.S. government. The case represented the first time a foreign corporation making a drug product entirely outside the United States received a criminal punishment for defrauding FDA.[22] As drug manufacturing becomes increasingly globalized, such international collaboration is essential for improving oversight and identifying wrongdoing.

Cough medicine in Panama was mixed with an industrial solvent falsely labeled as sweetener.

In Panama, 78 people died in 2006 after taking a cough medicine that the government had unknowingly mixed with toxic syrup originating in China. Diethylene glycol (DEG), an industrial solvent often used in antifreeze formulations, had been labeled as glycerin, which is commonly used to make syrup formulations of medicines.[23] The material passed through brokers in China and Europe, receiving new labels along the way, before finally reaching Panama.[24] Product testing by the brokers was either insufficient or nonexistent. The Panamanian government ultimately distributed 60,000 units of medicine mixed with DEG to patients.[25]

False labeling masked the source of the problem from officials; as a result, the cause of patient deaths was not identified for more than a month after initial distribution of the adulterated medicine.[26]

Insulin known to be stolen was discovered on pharmacy shelves.

In 2009, thieves in North Carolina stole a truck containing more than 120,000 vials of Levemir insulin made by Novo Nordisk.[27] According to an FDA affidavit, the temperature-sensitive medicine was illicitly sold back into distribution through wholesalers and eventually reached medical centers in Texas, Georgia, and Kentucky.[28] Diabetic patients received the stolen goods, and some reported poor blood sugar control.[29] In this case, according to the same affidavit, wholesaler documentation of the insulin's origins (the drug's "pedigree") indicated it was purchased from a national distribution company Feb. 7, 2009, a day after the medicine was reported stolen.[30]

State requirements for drug pedigrees and drug wholesaler licensure vary. Most pedigrees are paper and thus easily falsified. A national system to track and authenticate drugs would improve distribution security.

A counterfeit injectable anemia drug was sold into legitimate distribution in the United States, resulting in subtherapeutic dosing and severe side effects for patients.

In 2002, criminals in Florida relabeled up to 110,000 bottles of low-dose Epogen, an anemia drug, to create counterfeit high-dose Epogen and Procrit.[31] The counterfeit drugs passed through several registered and unregistered intermediaries before a portion was allegedly sold to a national wholesaler.[32] As a result, patients received insufficient levels of life-preserving therapy and suffered painful side effects.[33]

The relabeling of low-dose Epogen to resemble a stronger product yielded an estimated $46 million in profits. FDA recovered less than 10 percent of the counterfeit medicine; more than 90,000 vials may have reached patients. This illustrates the potential for counterfeit drugs from domestic sources to enter the U.S. supply chain.[34]

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Contact: Sarah Carroll, communications
Email: scarroll@pewtrusts.org
Project website: pewhealth.org/drugsafety