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Drug Recalls Put Spotlight on Drug Supply Chains

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Nov. 19, 2018 -- Since the 1990s, American drug companies, and the patients they serve, have leaned heavily on a supply chain that starts in factories on the other side of the globe.

Nearly 8 out of 10 medications Americans take have some component made abroad, largely in developing industrial powers China and India. Globalization has helped keep the costs of those drugs down, but it's also created a supply chain that's difficult to police.

That leaves pharmaceutical companies vulnerable to embarrassing recalls that may dampen the benefits of lower costs, says Robert Handfield, director of the Supply Chain Resource Cooperative at North Carolina State University.

"As pharmaceutical companies have started to offshore, they're getting more quality issues, more product recalls," Handfield says. "It's definitely a trend we're seeing."

Problems Began in Summer

For many patients, a series of recalls of blood pressure drugs from China and India has taken that question from the realm of abstract policy straight into their medicine cabinets. Since this summer, several batches of three generic drugs used to treat high blood pressure have been recalled because they were tainted with chemicals listed as probable human carcinogens -- first N-nitrosodimethylamine, or NDMA, and later N-nitrosodiethylamine, or NDEA.

Drug Recalls

The problem began in July when the first batch of valsartan blood pressure medications were recalled.

- In July, the FDA announced a recall of the blood pressure drug valsartan after pills made by Chinese manufacturer Zhejiang Huahai Pharmaceuticals were found to have been contaminated by NDMA and NDEA. The drugs were sold in the United States by more than a dozen companies, and the list eventually covered more than half the valsartan products on the U.S. market.
- In late October, Indian pharmaceutical manufacturer Aurobindo recalled 22 batches of the blood-pressure drug irbesartan, which also is used to treat kidney disease in diabetes patients with high blood pressure. Aurobindo reported it had found the drug was contaminated by NDEA.
- And in early November, Sandoz had to pull back a similar medication, losartan potassium-hydrochlorothiazide, after discovering NDEA in it. Losartan, the active ingredient in the pills, was also made by Zhejiang Huahai.

All three of the recalled blood pressure medications are known as angiotensin II receptor blockers, or ARBs, which prevent blood vessels from narrowing.

The FDA is urging patients to keep taking their drugs until they can be replaced.

“Patients should expect safe and high-quality drugs,” FDA Commissioner Scott Gottlieb, MD, said in a September statement. “And the manufacturers who develop and ship these products should expect a secure supply chain that guarantees the custody of these medicines. That means accountability throughout the supply chain.”

FDA spokesman Jeremy Kahn says the agency is still investigating the cause of the contamination, but inspectors suspect the compounds were the unintended byproduct of chemicals being mixed.

Consumer Impact

The recalls are already raising concerns among consumers -- and in the case of valsartan, making the drug harder to find, says Craig Beavers, PharmD, cardiovascular clinical pharmacy coordinator at the University of Kentucky Medical Center.

“Not only is there a potential to be harmed from the product that has been recalled, the secondary problem is there’s not enough of the products that haven’t been recalled out there,” Beavers says. “So people have to change their drug product because we don’t have enough drug product to switch them over. They have to either change therapy, or -- and this is the sad part -- some of the prices of those non-recalled products have increased. So either way, the patient gets punished for this.”

About 40% of finished medications are made overseas, according to the Government Accountability Office, the investigative arm of Congress. So are about 80% of active pharmaceutical ingredients, which are made into pills at other plants.

“You really want to make sure, as a provider, that you’re giving the best options, the best treatment. And on top of that you want it to be safe, not just [effective],” Beavers says. “So when you have these issues that come up and question the purity and safety of the product, you really do start to question the source it’s coming from and the company you trust.”

A 'High-Risk Issue'

The GAO calls offshore manufacturing of drugs a “high-risk issue,” one that imposes far-reaching responsibilities and increasing demand on the FDA. Congressional investigators have been keeping tabs on the issue since 1998 and especially since 2008, when contamination of the blood-thinning medication heparin from a Chinese plant caused a worldwide recall.

“We’ve seen a lot of progress over that period of time,” says Geraldine Redican-Bigott, the GAO’s assistant director for health care.

In 2008, the FDA conducted 267 drug quality inspections, according to an agency database. In 2017, there were more than 1,500 inspections.

The FDA has opened offices in China, India, Europe, and Latin America, and it now conducts more inspections overseas than within the U.S. It’s also changed how it decides which plants get inspected, based on the potential risk of problems with the process -- the result of a 2012 change in federal law.

“They have started to do many more inspections of foreign establishments, and they’ve been able to show some improvement,” Redican-Bigott says. It’s also reached agreements with other drug-importing nations that allow U.S. regulators to rely on inspections by countries like Britain, France, and Sweden.

Handfield, of N.C. State, who has advised pharmaceutical companies on safety and testified as an expert witness in court, says more quality problems have emerged as companies move offshore. Outsourcing can lead to communication problems between the consumer-facing company and its manufacturer, “and you kind of get what you pay for.” The problems may happen at “a very small percentage” of plants -- but he adds, “Once you lose control of a process, all bets are off.”

“You really don’t have control over what’s going on, particularly when you go to low-cost countries like China and India,” says Handfield, who has advised companies involved in earlier drug recalls. “You get high turnover in some of these factories. You get people who aren’t trained in the procedures, or they take shortcuts, or they don’t follow all of the steps, and you get impurities introduced through chemical reactions and so forth.”

Pharmaceutical Research and Manufacturers of America (PhRMA), the drug industry’s leading trade association, says it’s confident the FDA has the tools to do its job.

Regardless of where they are made, medicines (and their active pharmaceutical ingredients) marketed in the U.S. “must be manufactured according to the FDA’s current good manufacturing practice regulations,” PhRMA spokesman Andrew Powaleny tells WebMD. “Before a medicine can ever reach patients in the U.S., it must meet individual product specifications approved by the FDA, which represents the gold standard for protecting public health.”

The FDA eventually will discover the cause of the immediate problem, Handfield predicts.

Not the First Time

In 2014, contaminated drugs made by the Indian pharmaceutical company Ranbaxy -- acne and epilepsy medications, and the antibiotic ciprofloxacin -- led to felony charges and $500 million in fines and settlements for the company, as well as import bans on products made in two of its factories.

But if the FDA’s suspicion about the cause of this year’s blood pressure drug recalls is correct, the agency would not have caught the problem in advance, Kahn says. The FDA approves the manufacturing process when it first agrees to allow the company to make drugs for the U.S. market, he says. After that, inspectors focus on how closely the company sticks to that protocol but don’t necessarily test the drugs themselves.

The FDA inspects pharmaceutical plants based on the risk of the drug being made, the plant’s history of compliance and recalls, and how recently it’s been inspected, either by the FDA or its counterparts from other governments, Kahn says.

“Mostly they’re looking for things like clean rooms that aren’t specifically up to par where there could be contaminants, or items that shouldn’t be in a clean room ... whether the equipment in the facilities may have something wrong, or maybe the procedure the folks on the factory line are doing is incorrect,” he says.

In 2017, an FDA inspector criticized Zhejiang Huahai Pharmaceuticals -- the Chinese plant where the tainted valsartan was made -- for poorly maintained equipment, failing to investigate problems in equipment used in quality controls, and dismissing questionable test results.

After the valsartan recalls started, the FDA cited 11 problems with the same plant, including changes to manufacturing processes without adequate study, inadequate quality assurance, and poor record-keeping and sampling plans.

“Product deviations are not always reported and evaluated and critical deviations are not always investigated and the conclusions recorded,” it noted.

But Kahn says contamination of a raw material, as the FDA suspects happened in this year’s recalls, “is not something that would be caught in quality inspections.”

Zhejiang Huahai was the first overseas manufacturer the FDA approved to produce medication for the U.S. market. In a corporate statement in August, the company said it promptly notified regulators of the problems with valsartan after discovering them in June and took steps to keep any contaminated product from reaching consumers. But the FDA slapped an import ban on the company’s products in September after the contamination problems continued.

A 2013 federal law, the Drug Supply Chain Security Act, requires manufacturers to start adding labels to their products to help regulators trace them through the supply chain. The FDA has given companies until late November to start doing so after a 1-year delay. In September, the agency issued updated guidance to manufacturers that Gottlieb said would “bring us towards a more secure supply chain to help avoid these types of issues going forward.”

Adam Garber, of the consumer watchdog Public Interest Research Group, says drug manufacturing moved overseas to reduce costs with little public discussion about safety. While efforts to beef up inspections are good, he says the companies on the consumer end of the supply chain may need closer scrutiny from regulators.

“They have an obligation to ensure the product they’re delivering to customers is safe,” Garber says. “So the government and we need to establish policies that will ultimately put part of the responsibility on them so they can be held liable in the case of these contamination cases. Historically, when that’s happened, companies do a better job of monitoring these supply chains versus passing it off as a problem with an offshore manufacturer.”