Blood pressure drug recall: FDA investigates foreign plants that made drugs with cancer-causing impurities

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FDA inspections of factories in China and India that made carcinogen-tainted ingredients that forced dozens of recalls of blood pressure drugs in recent months show a history of problems.

Drug companies recalled dozens of lots of the front-line blood pressure and heart medications valsartan, losartan and irbesartan – alone or in combination with other drugs – after testing revealed the drugs had cancer-causing impurities in trace amounts.

The Food and Drug Administration is investigating the underlying causes of the impurities. The federal agency hasn't completed its inquiry, but inspection reports reveal problems at both factories – Zhejiang Huahai Pharmaceutical in China and Hetero Labs in India – before the carcinogen-tainted drugs were discovered.

More: More blood pressure medication recalled over carcinogen concerns – this time, losartan (/story/news/health/2019/01/07/high-blood-pressure-drug-medication-recall-torrents-losartan-tablets-fda/2500692002/)

More: Three more blood pressure drugs recalled over cancer concern: Here's what you need to know (/story/news/health/2018/12/06/mylan-pharmaceuticals-blood-pressure-medicine-recall-valsartan-amlodipine-hydrochlorothiazide-fda/2230721002/)

More: FDA recalls another blood pressure drug for possible cancer risk (/story/money/nation-now/2018/11/13/fda-losartan-recall-cancer-risk-tied-blood-pressure-drug/1985858002/)

The recalled products are part of a large class of drugs called angiotensin II receptor blockers, or ARBs, which work by blocking the effects of a hormone that narrows blood vessels. Many of these commonly prescribed drugs are not part of the recall. Consumers can check the FDA's website (https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm) for a full list of recalled drugs.

Drug companies generally advise affected patients to check with their doctor or pharmacist before they stop taking their medications. Discontinuing a recalled drug could cause more immediate harm than staying on the medication.

The recalls underscore the FDA's enormous challenge in overseeing a global pharmaceutical supply chain in which about 80 percent of drug ingredients and 40 percent of finished drugs sold in the USA are made or handled at more than 3,000 plants overseas.

The FDA has worked through a backlog of unchecked foreign drug plants that has grown over the past decade as the pharmaceutical industry accelerated production overseas. The FDA scrapped its policy of checking all foreign and domestic plants at least once every two years, instead prioritizing checks at facilities based on potential risk to U.S. consumers.

Since 2015, the agency has conducted more inspections overseas than at domestic factories.

Even when inspectors identify issues, it's not always enough to prevent tainted drugs from reaching the USA, where they are prescribed by doctors and taken by patients.

Analysts said the agency struggles to keep pace with a global industry.

"As we see when there are widespread recalls and widespread quality questions, there is a tremendous price from a public health standpoint," said Michael Carome, director of the health research group at Public Citizen.

Though the FDA works to ensure the quality and safety of the drugs sold in the USA, Carome said, it's under pressure to reduce drug shortages.

"There is always that pressure to not cease manufacturing to add to the drug-shortage list," Carome said. "I think we have a federal agency that is overwhelmed in trying to keep up."

FDA hires inspectors, assigns staff overseas

Congressional investigators found in 2017 that the FDA was making strides in overseas inspections this decade, but about 1,000 plants had never been inspected (https://www.gao.gov/products/GAO-17-143) as of mid-2016.

The Government Accountability Office, the nonpartisan investigative arm of Congress, reported that 46 percent of the FDA's offshore inspector jobs were unfilled.

In response to the GAO report, the FDA said it hired more inspectors, developed a workforce recruitment and retention plan, offered incentive pay to retain foreign staff and temporarily assigned domestic staff to short-term stints overseas.

Only 15 percent of inspector jobs were unfilled as of July 2018.

The FDA prioritized domestic and overseas inspections based on potential risk, evaluating factors such as a factory's compliance, recall history, date of last inspection and the risk of the drug.

Stepping up inspections and producing detailed findings don't guarantee that drug companies will correct or prevent manufacturing problems that can lead to recalls.

"They aren't running the plant," Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, told USA TODAY. "People say you should go back and inspect all of the time. Really, a lot of responsibility is on the people who manufacture and offer these drugs for sale."

Since 2013, nearly 300 products have been recalled by 65 drug plants within one year of an FDA inspection, according to Kaiser Health News.

Inspectors typically review a factory's detailed records and cleanliness and evaluate whether workers follow written procedures.

Fraying gaskets, rusted screws, shredded documents

FDA inspectors who visited the Zhejiang Huahai Pharmaceutical factory in Linhai, China, found that workers repeatedly failed to investigate testing anomalies in drug batches. The FDA did not include the names of the drugs with anomalies in its report.

Inspectors at the factory, the source of the bulk of blood pressure drug recalls, discovered equipment had fraying gaskets, rusted screws and missing pieces. (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM616397.pdf)

Despite these findings, factory operations continued uninterrupted. It was not until another company tested the Zhejiang factory's drug ingredients last June and discovered unacceptable levels of the carcinogen nitrosodimethylamine, or NDMA. The FDA investigated and announced a recall in July.

Follow-up testing revealed a second carcinogen, nitrosodiethylamine, or NDEA, in batches of valsartan.

The FDA issued an import alert in September to block products made at the plant from entering the USA. The FDA issued a warning letter (https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm628009.htm)in November about challenges including impurity control, change control and contamination from one manufacturing process line to another.

The FDA said the Zhejiang factory inadequately investigated the initial report of NDMA.

It's unclear how long the factory had been making the tainted pharmaceutical ingredients first detected by a customer last June.

In November 2011, Zhejiang factory workers changed how they made valsartan to produce more product at lower cost. The factory failed to assess the possibility of forming toxic impurities such as NDMA, the FDA said in a warning letter.

The India plant also had signs of trouble.

In 2016, employees at the Hetero Labs plant in Jadcherla were found shredding documents (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM537060.pdf) before inspectors were scheduled to arrive, according to the FDA. The lab failed to keep a log of the documents that were shredded.

One customer complained that a finasteride tablet was twice as thick as others in the bottle, FDA inspectors said in a report. Hetero failed to recall the defective lot, as required, until inspectors pointed it out.

The FDA issued a warning letter to Hetero Labs in August 2017 saying the drugmaker failed to investigate discrepancies found in drug batches and did not regularly clean, sanitize or sterilize equipment to prevent contamination of drug ingredients. The FDA recommended the lab hire a consultant to ensure it followed good manufacturing practices.

The FDA did not issue an import alert against Hetero, as it did for the Zhejiang factory.

Representatives of the Zheijiang factory have issued several statements about the recall through its U.S. subsidiary, Huahai US.

The company noted that the FDA closed inspections in 2016 and 2017 without finding any impurities in valsartan batches. When the factory confirmed the impurities in June, the company said, it notified regulators and initiated a recall.

Hetero Labs representatives shared recall notices with customers and generally advised customers to check with their pharmacists. The company did not respond to USA TODAY about the FDA's inspections.

'A lot of people are rightfully concerned'

It's unclear how many people on valsartan and the other blood pressure drugs have been affected by the recall.

About 103 million U.S. adults had high blood pressure in 2017, the American College of Cardiology, the American Heart Association and other groups said in a report.

The groups based the number on new, more aggressive guidelines for treating hypertension. They estimated that 36 percent of adults should be treated with medication.

ARBs and another class of drugs called angiotensin converting-enzyme inhibitors, or ACE inhibitors, are often the first drugs doctors recommend to lower a patient's blood pressure.

Philadelphia attorney David Stanoch represents patients in multiple lawsuits against the China and India drug plants and their U.S. subsidiaries.

Patients usually stay on these drugs for long periods of time,he said, and many worry about the health implications over time of taking medication with small amounts of carcinogens.

"This was a maintenance drug, and a lot of folks were taking this to control their blood pressure for quite some time," Stanoch said. "The last thing thing you'd expect when you are taking a drug of this nature is, 'I may have been exposing myself to a carcinogen for years.' "

The FDA maintains an adverse event database to track side effects and problems reported by patients, doctors, pharmacists, drugmakers or others.

Patients on valsartan reported 2,695 "adverse events" through the first nine months of 2018. That's the most adverse events for valsartan in the more than two decades included in the FDA database and nearly double the 1,382 reports for all of 2017.

The FDA, which evaluates the reports to monitor patient safety, warned that several factors can affect their reliability. The data might include duplicate reports or harms that are not caused by the drug. Negative publicity about a drug, such as a recall, can cause a surge of reports.

Given the challenges of global oversight, some people work to bolster domestic drug manufacturing.

Deborah Drew is founder and CEO of Drew Quality, a Massachusetts nonprofit group attempting to bolster generic drug manufacturing in the USA.

She said encouraging domestic manufacturing is critical to improving quality and safety and addressing drug shortages.

She said generic drugmakers operating on thin profit margins skimp on quality and safety. When these companies are the only source of a drug used worldwide, she said, safety and quality challenges become more problematic.

"If there is not someone else to go to who can supply the United States market, you can't just turn it off," Drew said. "This is where the FDA's hands are tied."

Drew said she works to warn decisionmakers of the risks of overseas manufacturing, particularly for drugs that have a limited number of sources.

"We are going against a very large, very powerful economic sector," Drew said. "We are talking about changing their business model."

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