Drug Batch Tainted? Just Hit Delete and Ship It to the U.S.

BLOOMBERG ARTICLE QUOTES ANDREW BEATO, "THERE'S A PATTERN OF CONDUCT AT OTHER COMPANIES THAT ARE SIMILAR, IF NOT IDENTICAL, TO THE RANBAXY PROBLEMS"
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In a lab in an Indian village during the height of monsoon season in 2011, a technician hit a delete button - keystroke that would have consequences three years later.

The quality-control employee of Sun Pharmaceutical Industries Ltd. had run high-powered chemical analyses on a drug sample to check for impurities that day. A certain level of impurity means the whole batch is supposed to be thrown out.

That's not what happened. Instead, the results of the failed tests were deleted, according to a previously undisclosed account detailed in a November 2013 FDA document obtained by Bloomberg News. The following day, workers used a sample from the same batch that passed the test. That result got entered, and the entire batch was declared clean and ready to ship abroad, eventually to be used by patients in the U.S. The FDA's computer forensics experts eventually found 5,301 additional deleted results from chromatography tests at the facility.

Generic Drugs: As Imports Rise, Regulators Struggle

"Our review found that analysts regularly delete undesirable chromatographic results, and products are retested without initiating an investigation as required," inspectors wrote in the document. The incident "raises concerns about the integrity of all data generated by your firm," the FDA wrote in a separate warning letter to Sun in May. Two months earlier, the agency had banned imports from the plant, near the western city of Vadodara.

The name of the drug or ingredient that the company was testing was redacted in documents Bloomberg obtained from the FDA under a Freedom of Information Act request. Frederick Castro, a spokesman for Sun Pharma, declined to comment.

Not Isolated

The incident wasn't isolated to Sun. A review of FDA documents by Bloomberg News found that similar actions on quality tests have happened at dozens of other companies' plants across India that make drug ingredients and pills for export to the U.S. While not as visible as the dead frogs and flies

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inspectors have found in other Indian labs, the pattern of data integrity breaches worries doctors in the U.S. and elsewhere. They say they fear prescribing generic drugs that may not do what they're supposed to.

"If they make multiple batches, does it come out the same, with the same amount of drug in it? And when you give it to a patient, can you assume it will work consistently?" said Harry Lever, a cardiologist at the Cleveland Clinic.

Reporting Failures

A review of inspection documents and warning letters shows that at least 12 drug companies with Indian facilities banned from sending pharmaceutical products to the U.S. since last year -- many of which supplied Americans' most vital medicines -- are accused of failing to report data from tests that were supposed to confirm the drugs were safe and would work.

India is the second-largest drug exporter to the U.S., and companies there mainly produce generic drugs and active ingredients for medicine. The top 10 pharmaceutical companies based in the country generate $15 billion in annual sales, according to data compiled by Bloomberg.

The U.S. doesn't require tests of imported drugs as they cross the border. The FDA relies on factories themselves to conduct quality tests and report accurate results, only performing its own studies if it gets enough complaints about a medicine.

The agency has about a dozen staff members in India to police about 600 factories registered there with the U.S. This year, the FDA had conducted 97 inspections of drug manufacturers as of the end of October, said Tara Goodin, an agency spokeswoman.

Antibiotic Recall

Sun Pharma has 25 manufacturing facilities worldwide, including 11 in India and seven in the U.S. The plant near Vadodara was approved to make generic cephalosporin, a class of a popular antibiotic. Three years after the incident highlighted by the FDA, Sun's Caraco Pharmaceutical Laboratories Ltd. in Detroit recalled 450,000 bottles of cephalexin, a type of cephalosporin. The active ingredient made by Sun wasn't produced using good manufacturing practices, the FDA said in an enforcement report in August, without providing details. It's unclear whether the Detroit plant and the India plant processed the same products.

About 22 million prescriptions of cephalexin, which is made by several generic companies, are written each year in the U.S., according to data compiled by Bloomberg. Caraco representatives didn't return phone messages.

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Exacting Process

The FDA told Bloomberg it could only handle requests for four inspection documents, known as Form 483s, at a time without making the process lengthier and more complicated. With about 600 FDA-registered factories in India, that makes it difficult to get a snapshot of data integrity across the entire industry.

Warning letters are public and don't require a Freedom of Information Act request. However, not every red flag in an inspection results in a warning letter, meaning the full extent of violations may not be publicly available.

Sometimes there's a lag between an FDA inspection and an export prohibition. A banned Ranbaxy Laboratories Ltd. plant in Toansa was inspected Jan. 5 to 11, and the FDA stopped allowing its product into the U.S. about two weeks later.

Sun's plant was banned four months after its inspection. A senior quality control officer told FDA investigators lab employees there frequently pre-tested samples before recording a final result, according to the agency's warning letter to Sun. The practice is unacceptable, the FDA said. The missing results were in an obscure "default" folder in a software program called Empower, according to a Form 483.

Staying Compliant

The maker of Empower, Waters Corp., said the chromatography data system, or CDS, software is designed to help labs comply with government regulations.

"One of the goals of compliant CDS software is that controls are in place so data cannot be deleted, either accidentally or maliciously, and that the data is always maintained," Jeff Tarmy, a spokesman for the Milford, Massachusetts-based company, said in an e-mail. He said he couldn't comment on a specific investigation or client.

The data-integrity incidents detected at Indian plants are the subject of stepped-up scrutiny from regulators. Guragon, India-based Ranbaxy pleaded guilty last year to felony charges for similar violations and paid $500 million in fines. In a statement last year, Ranbaxy Chief Executive Officer Arun Sawhney said the company was "disappointed by the conduct of the past" and is "pleased to continue bringing safe, effective and quality medicines to market."

A spokesman for Ranbaxy, which is being acquired by Sun, declined to comment.

Pattern of Conduct

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"There's a pattern of conduct at other companies that are similar, if not identical, to the Ranbaxy problems," said Andrew Beato, the Washington-based lawyer who helped a whistle-blower expose Ranbaxy.

Reporting on product safety and effectiveness is only valuable "when it is reliable, truthful and accurate," Goodin, the FDA spokeswoman, said in an e-mail. When it's not, "those manufacturers' practices raise questions about the accuracy, reliability, and truthfulness of all the data and information they collect and report," she said.

Asked whether felony prosecutions were possible for any of the 12 companies with plants in India on the banned list, Goodin said: "Firms unable to demonstrate control over their processes and testing may not be producing safe, high-quality products and therefore may be subject to enforcement action."

Data-integrity breaches weren't just limited to plants in India that are banned from exporting to the U.S. They also happened in places that haven't been prohibited thus far, according to FDA observation reports and warning letters.

Missing Papers

At a plant in India run by Lake Forest, Illinois-based Hospira Inc., the FDA said in a December 2013 document that workers didn't make available records on drug production. Then investigators saw two boxes of what appeared to be paper records locked in a janitor room, they said in their report. Key in hand an hour later, investigators found one of the boxes removed, and when it was returned from the "waste area," the papers were missing, according to the Form 483. The document didn't say how investigators first spotted the boxes in the locked room.

The Hospira plant had already received a warning letter in May 2013 following an October 2012 inspection. It's not clear if any new action resulted from the December 2013 inspection. Hospira representatives didn't return phone messages.

International Expectations

While the Indian government has had good manufacturing practices for drugmakers to follow for years, it hasn't had strict guidelines for testing laboratories, said India Drugs Controller General G.N. Singh, the pharmaceutical industry's top regulator in the country. The government introduced laboratory guidelines to manufacturers in 2012 and made it a requirement last year to comply, he said. Over time, the new rules will help Indian companies avoid the lapses cited by the FDA, he said.

"It normally takes a few years to catch on, get adopted fully, and the training the industry gives to the analysts takes some time," he said. "Now the results will start coming, as per the international expectations."

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Many of the companies in India on the FDA's banned list supplied vital therapies or ingredients. For example, India-based Smruthi Organics Ltd. supplied the active ingredient in the antibiotic Noroxin to Merck & Co., the second-largest drugmaker in the U.S., according to the U.S. National Library of Medicine.

A Smruthi plant was banned from sending its product to the U.S. in June 2013. The company was formally warned by the FDA in March on its facility, where the agency said workers blended failed batches of active ingredients with passing ones and destroyed any related documentation. FDA staff also observed pooled urine in bathrooms that lacked drainage and no soap for hand washing in two bathrooms.

FDA Testing

Merck confirmed it "no longer sources" ingredients from Smruthi, and the company discontinued Noroxin in April. Mylan Inc., the largest generic drugmaker in the U.S., also suspended a relationship with Smruthi, which supplied ingredients for 12 Mylan products -- all of which Mylan recalled. The plant remains closed. Neither Merck nor Mylan were found to be in violation of FDA rules.

Eaga Purushotham, managing director of Smruthi Organics, didn't respond to e-mails and calls seeking comment. Smruthi "is making every attempt to resolve regulatory issues," which contributed to a loss in the quarter that ended in September, the company said in a filing last month.

FDA Commissioner Margaret Hamburg traveled to India in February and vowed to step up efforts to help companies there overcome hurdles on compliance. She also pledged to increase the FDA's personnel in India to 19, though staffing remained at 12 as of the end of October.

'Similar Culture'

Meetings with the FDA have helped Indian regulators make progress on meeting international standards, said Singh, the drugs controller.

India's national drug regulator, the Central Drugs Standard Control Organisation, has 400 staff, aided by about 1,500 additional personnel in the offices of individual state regulators. Singh said he aims to raise the total number to 10,000 to 12,000 in the next three to five years.

"We want to have a similar culture as what the other regulators are expecting," he said.

FDA-Banned Factories and Their Owners' Responses

Besides Sun, Ranbaxy and Smruthi, these nine companies own factories whose exports were prohibited by the FDA. They are listed with their comments or with Bloomberg's attempts to reach them via phone and e-mail.

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Amsal Chem Pvt. Ltd. -- The company has sent a response to the FDA and is awaiting its feedback, Director Subhash Majithia said in an e-mail. The company has "a continuous process of upgrading in all areas," Majithia said. **Apotex Inc.** -- "We are actively working with the agency and independent consultants to implement measures that will enhance our quality assurance protocol," Apotex said in a statement. "We stand fully behind the safety and efficacy of our products and are staunchly dedicated to further enhancing our global quality systems." **Canton Laboratories Pvt. Ltd.** -- No response. **Amanta Healthcare Ltd.** -- No response. **Micro Labs Ltd.** -- No response. **RPG Life Sciences Ltd.** -- No response. **Sentiss Pharma Pvt. Ltd.** -- "We received the import alert from FDA and since then have been working diligently to comply with all requirements of FDA," the company said in a statement. "Accordingly, necessary responses have been sent to FDA for their consideration and approval. We have also hired the services of a reputed GMP consultant from USA who have been assisting us in our efforts. We strongly believe in complying with all requirements of regulatory agencies of the countries that we work in." **J.B. Chemicals & Pharmaceuticals Ltd.** -- The company closed down its Unique Chemicals facility in Rabale, India, in 2010, said Secretary Mayur Mehta. The company hasn't received communication from the FDA about an import alert for the facility, Mehta said. The FDA said its inspection in 2013 was to verify that the facility was no longer operating, and the agency put the plant on import alert to make sure its previously manufactured products weren't exported to the U.S. **Wockhardt Ltd.** -- No response.

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