Canadians kept in dark about defective drugs

U.S. inspections of Canadian drug companies reveal systemic problems that have put Canadian patients at risk.

Apotex's Bangalore facility in India was criticized by the U.S. Food and Drug Administration for not reporting unfavourable drug quality test results.

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North American patients have been put at risk by prescription drugs that Canadian pharmaceutical companies sold with knowledge that their products were defective, a Star investigation has found.

Using records obtained through U.S. freedom of information laws, the Star also found other Canadian companies have:

- Hidden, altered and in some cases destroyed test data that showed their products were tainted or potentially unsafe.
- Not reported evidence of side-effects suffered by consumers taking their drugs.

Since 2008, more than 40 Canadian drug companies, including Toronto-based generic giant Apotex have been cited for serious manufacturing violations.

All of these violations are detailed in inspection reports provided to the Star not by Health Canada but the American Food and Drug Administration (FDA), which also inspects Canadian facilities.

The Star investigation found that while the FDA strictly and transparently enforces drug manufacturing laws, Health Canada leaves Canadians in the dark by keeping secret details of problems its inspectors find.

Meanwhile, drugs and drug ingredients banned from the U.S. market have been allowed by Health Canada into Canadian pharmacies.

The inspection documents obtained by the Star reveal:

- In June, at a facility in Bangalore, India, that makes drugs destined for North America, Apotex employees did not report undesirable test results and doctored bacterial growth test records.
- Generic drug maker Taro Pharmaceuticals of Brampton kept drugs on the market despite company tests showing batches of the medications deteriorated before the expiry date listed on the label.
- Cangene Corp., a Winnipeg drug manufacturer, failed to tell authorities of blood clots, fever and other side-effects associated with their products.

The U.S. FDA inspects facilities in Canada and around the world where drug and drug ingredients bound for the U.S. market are made. The regulator may ban drugs from the U.S. market or prevent a company from introducing new products until the manufacturing and safety problems are fixed.

The FDA reports do not specify all the countries where drugs made by the inspected companies were shipped. The Star found many of these same drugs are also made for Canadian consumers, and the factories are subject to Health Canada inspections as well.

There have been at least 19 Apotex inspections by the FDA since 2008, 16 of them resulting in findings termed "objectionable" or noted as "repeated deficiencies." In one case, the FDA said the company failed to uphold "its legal obligation."

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DINESH THAKUR
FORMER RANBAXY EXECUTIVE

"If there truly is an efficacy or safety issue then you're putting out a product that could potentially harm a consumer."

TAMIKA CATHEY
FORMER INSPECTOR FOR THE FDA

"Health Canada is claiming the drugs are medically necessary but won't tell us which drugs they are. That is the height of stupidity and obstruction."

AMIR ATTARAN
UNIVERSITY OF OTTAWA
LAW PROFESSOR

During an interview at one of Apotex's Toronto factories, and in email correspondence, company president and CEO Dr. Jeremy Desai and another manager did not challenge the FDA's findings and told the Star that the firm is fixing the problems and its products are safe.

Desai told the Star "compliance is a journey" and his company has addressed what he calls the "procedural lapses" identified by the FDA and has invested in improved data collection and staff training programs.

The Star found details of the inspections because the FDA makes inspection dates and results available to the public on its website. The U.S. regulator has posted online dozens of warning letters to Canadian companies, many of which detail egregious conditions in drug manufacturing facilities.

A 2010 letter to Apotex revealed details of earlier inspections of its Toronto facilities where U.S. inspectors found the company distributed antihistamine and diabetes tablets made with contaminated ingredients. Apotex recalled more than 600 batches of drugs made at its GTA facilities from Canadian and U.S. markets.

In contrast, Health Canada does not tell the public the number of times it has inspected individual facilities at Apotex or other major drug companies.

The regulator only says when it last inspected a facility and gives only sparse details, in rare cases, about conditions that have been imposed.

It has posted its inspection findings of just one Canadian manufacturer, and that only came after a Star article exposed Health Canada was keeping the records secret despite a public FDA warning letter detailing problems at the same facility.

Otherwise, Health Canada does not give any details of the problems, if any, that it finds during individual inspections. The Canadian regulator does not even make public the names of the 20-plus companies that have been cited since 2012 for severe manufacturing violations.

"Health Canada is giving the least amount of information that they can," said Alan Cassels, a drug policy researcher with the University of Victoria. "Instead of actually increasing people's confidence in the system, this kind of secrecy is degrading it. What's the reason for all the secrecy?"

In response to a series of questions, Health Canada spokesman Gary Holub emailed the Star saying, "Health Canada does not allow drug products to be sold, including those imported for sale, in Canada unless there is satisfactory evidence that (good manufacturing practices) standards are being met in the facility where the product is made." Holub said the Canadian regulator also monitors drugs on the market to "identify and act on safety risks to patients should they emerge."

If an FDA inspection of a drug company turns up violations, the American regulator hands the company what is known as a form 483, which former FDA inspector Tamika Cathey calls a "wake-up call" to fix serious problems.

Cathey, an inspector for the FDA from 2008 to 2012 who now works for EAS Consulting Group, told the Star that the FDA inspections are critical in exposing problems that could "put consumers at risk."

"If there truly is an efficacy or safety issue," she said, "then you're putting out a product that could potentially harm a consumer."

Since 2008, the FDA has conducted at least 110 inspections of Canadian facilities or foreign factories owned by Canadian firms that have resulted in objectionable findings.

Under U.S. freedom of information legislation, the Star quickly obtained additional records for more than 30 of these FDA inspections north of the border. Health Canada said it will take months to decide whether it will release similar information.

In several cases, the Canadian regulator said it will first need to consult with the inspected Canadian drug companies before publicly disclosing the information, a practice Cassels called "absolutely absurd."

Drug companies are increasingly moving production overseas where labour is cheap. As much as 20 per cent of the drugs Canadian consume are made in countries such as India and China.

While FDA data shows it inspected nearly 150 international facilities last year alone, Health Canada, on average, annually visits only 10 foreign sites that make products destined for Canadian pharmacies.

Health Canada mainly relies on reports prepared by other health regulators that physically inspect the factories.

Earlier this year, during one of those rare visits outside the country, Health Canada inspectors went in February to an Apotex facility in Bangalore that produces finished drug products. (Health Canada records say Apotex has three factories in Bangalore, all in the same industrial park — one that makes drug ingredients and two that make finished drugs.)

The regulator provided the Star little detail of its visit but a spokesperson said Health Canada gave a thumbs-up to Apotex for its manufacturing of tablets and capsules.

Seven months before this inspection, and again four months after, the FDA went to the same site in India. The U.S. inspectors uncovered blatant and repeat problems at the plant.

The American inspectors watched as an Apotex quality control microbiologist wrote over documents detailing a bacterial contamination test "using a black marker in order to make it appear that the growth promotion testing had been performed" on an earlier date.

Inspectors found that 500 power outages over one year could have affected quality tests of drugs.

Meanwhile, employees continued to retest drug products when the first test yielded "unknown impurities" and then did not bother to report the undesirable results. They did so despite the fact that this same kind of data rigging had been flagged during an FDA inspection a year earlier, in July 2013.

The FDA's enforcement activities in India have resulted in sweeping import bans on drugs made by two large generic companies: Apotex and India-based Ranbaxy, which also distributes its products throughout North America.

The Star has found that these same drugs and drug ingredients, deemed potentially unsafe for U.S. patients, have been available in Canada.

"The crux is this: India is supplying Canada with medicines that the United States knows are adulterated. These are available in your pharmacies today for you," said Amir Attaran, a University of Ottawa law professor who has studied drug regulations.

In April, the FDA barred the importation of all but one product from another of the Apotex facilities in Bangalore. Inspectors found the plant, which makes chemical drug ingredients, had manipulated data, retested samples until it got favourable results and destroyed records.

Though Health Canada reviewed the FDA's findings and agreed the plant was "non-compliant," the regulator chose to allow the products into Canada "due to the medically necessary nature of the drug products," according to a April 25 internal memo prepared for a senior Health Canada official and obtained by the Star through access to information legislation.

Apotex told Health Canada it would test all the ingredients upon their arrival in Canada before using them to manufacture any drugs at its domestic facilities.

Health Canada and Apotex did not provide the Star a list of products sold in Canada that use ingredients made in Bangalore.

"Health Canada is claiming the drugs are medically necessary but won't tell us which drugs they are. That is the height of stupidity and obstruction," Attaran said. "If the Americans are taking a precautionary approach, what does it signal but that Canadian lives are worth less than Americans?"

The Star found that this was not the only example of the differing regulatory approaches of the U.S. and Canada.

In 2008, following scathing FDA inspections, the U.S. government barred imports from two Ranbaxy facilities in India, which also supply drugs to the Canadian market. Last year, the company's U.S. subsidiary paid $500 million in criminal fines and settlements after admitting it made "false, fictitious and fraudulent statements to the FDA" about drug data and distributed "adulterated" medications.

Meanwhile, Health Canada has allowed drugs made at the Ranbaxy plants into the market as long as they first undergo additional quality tests.

"The (Ranbaxy) formulations that were sold in Canada were typically the same strength as those sold in the United States. . . . I feel confident there were problems with drugs that were sold in Canada, as well," said Dinesh Thakur, a former Ranbaxy executive, in an interview with the Star.

Thakur was a whistleblower who helped American investigators expose his company's marketing of adulterated drugs.

Thakur told the Star that Health Canada has never contacted him for information about Ranbaxy's operations and how they may have impacted Canadian consumers.

Health Canada said it has assessed side-effect data and not found any health risks associated with Ranbaxy drugs coming from India, adding it "has not requested a recall of any Ranbaxy products."

When asked by the Star, both Ranbaxy spokesman Chuck Caprariello and Health Canada refused to itemize a list of his firm's drugs that are banned in the U.S. but for still for sale in Canada.

Ranbaxy "has taken significant steps to ensure all products sold in the Canadian health-care system are of the highest quality," Caprariello said, adding that all of Ranbaxy's facilities have been deemed compliant by Health Canada.

The Star's analysis of FDA inspections show a troubling range of violations found at Canadian drug facilities:

- At least five firms knowingly shipped defective drugs for sale or kept them on the market after quality control tests revealed problems. At Cangene Corp. in Winnipeg, where the FDA also found side-effect information was not reported to the regulator, products that employees flagged as defective were nevertheless distributed to

consumers. The American company that now owns Cangene told the Star that the Winnipeg facility moved quickly to address the problems and said that "ensuring patient safety, developing safe and effective products, and complying with relevant quality standards are top priorities at our company."

At the time of the FDA inspections, Apotex owned 61 per cent of Cangene.

Staff at Taro Pharmaceuticals in Brampton did not respond to six Star requests to talk about the FDA inspections that found the firm kept drugs on the market despite company tests showing batches of the medications failed a quality test or deteriorated before the expiry date listed on the label.

- At the Quebec plant of Macco Organiques, after charred, black particles spoiled a batch of a pharmaceutical ingredient, the firm shipped it to the customer anyway. Inspectors saw dead insects and live ones buzzing around production material and areas of the factory covered in "dust and debris." Company president Robert Briscoe told the Star that no consumers were harmed by the problems found in the FDA inspection. He also said the FDA inspectors were rigorous. "They were extremely difficult. It made us a better company," he said, adding that Macco spent $1 million in improvements after the inspection.
- Dirty facilities risked contaminating vaccines and other drugs made by at least four companies. A 2012 FDA inspection of Sanofi Pasteur's Steeles Ave. facility found "no less than 58 documented non-conformances relating to the isolation of mold" in less than two years in the sterile area used to make a tuberculosis vaccine and bladder cancer treatment. The company recalled batches of the vaccine, suspended production of a bladder cancer drug, renovated the Toronto facility and, a company spokeswoman said, "worked closely with the FDA" and Health Canada to improve the manufacturing and testing process.
- Apotex has destroyed records, manipulated data and allowed "adulterated" and defective drugs on the market.

Inspectors have also found the firm — with facilities in Toronto, Richmond Hill and India — has failed to file timely warnings of defective drug batches to the FDA and did not properly follow up on customer complaints.

During the 2009 inspection of the Toronto facilities, then company president Jack Kay told the FDA inspectors that some of the problems reflected "unacceptable sloppiness." And after the inspection, which led to a U.S. ban on products that lasted two years, the firm pledged a "global" overhaul to bring all production into compliance and outside consultants were hired.

Apotex executives were also bristling, though, and in 2012 complained before an international trade tribunal that the U.S. government was unfairly punishing the Canadian firm and that its actions had cost Apotex hundreds of millions of dollars and "decimated" its U.S. sales. The firm sought up to $1.5 billion in damages.

Meanwhile, the manufacturing problems did not stop.

American inspectors have over and again found serious problems at Apotex. The regulator has on several occasions noted that the firm has failed to address violations found during previous inspections.

A January 2014 India inspection turned up serious violations that inspectors found during previous visits in 2010 and 2006.

After that same inspection, the firm promised the FDA that it would hire a "third-party auditor" to help fix the problems.

It also followed up on the FDA's warning letter with a claim that the problems found by inspectors had "no effect" on patient safety. But the FDA said the firm's analysis was incomplete, as "undesired records appear to be excluded."

The FDA instructed Apotex to investigate whether middle and top management were involved in “data manipulation.”

Apotex president Jeremy Desai told the Star: “We continue to manufacture our products for all our markets, and (are) confident that the product that is being sold to . . . the public, is safe, efficacious and manufactured to a high quality.”

He also said that under U.S. President Barack Obama the FDA has “increased the level of scrutiny on all pharmaceutical companies.”

In late August, the trade tribunal unanimously rejected Apotex’s claim against the FDA and ordered it to pay all of the U.S. government’s legal costs.