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In generic drug plants in China and India, data falsification is still a problem

By Katherine Eban *and* Sony Salzman

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A pharmacist works in a lab where medicines are being made on the outskirts of Mumbai, India. *Rafiq Maqbool/AP*

As the generic drug industry faces allegations of data manipulation, headlines about carcinogen-tainted[2] blood pressure medicine, and an intensifying probe by the House Energy and Commerce Committee, whose health subcommittee is holding a hearing on Wednesday[3] on safeguarding our global drug supply, generic drug industry lobbyists are fighting back.

They claim[4] that low-cost drug makers operating overseas — where the majority of our generic drugs are made — follow the same intricate rules as U.S.-based drug makers. They argue[5] that instances of manufacturing fraud or negligent practices are a thing of the past, having ended largely in 2013 when India's largest drug company, Ranbaxy, pleaded guilty in the United States[6] to seven felonies related to falsifying manufacturing data.

The Food and Drug Administration, also on the defensive, has been quick to reassure consumers and Congress[7] that its regulatory system of data review and inspections is effective regardless of where drugs for the United States are made.

But our analysis of the FDA's own records reveals that violations of data integrity are not only persistent and ongoing in overseas drug manufacturing plants, but are happening with greater frequency than in U.S. plants. With the help of FDAzilla[8], a leading data analytics company, we analyzed 5 1/2 years of FDA inspection records, from 2014 to the present, for four major markets: China, India, Europe, and the United States.

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The data show significantly greater falsification or manipulation of manufacturing data in Indian and Chinese drug plants. "Egregious data integrity violations are alive and well, especially in China and India," said Michael de la Torre, chief executive officer of FDAzilla's parent company, Govzilla. "While the U.S. and Europe are not immune to serious data integrity violations, China and India are at least twice as likely to have these issues."

Out of more than 12,000 FDA inspections of drug plants in the United States, about 15% uncovered violations of the FDA's data integrity rules. These

stipulate that all manufacturing data must be preserved — unaltered — and made available to regulators. In India, about 25% of the plants inspected committed some sort of data violation, while in China, that figure hovers just above 32%.

Country	Number of inspections	Number (percentage) of violation forms (Form 483[10]) issued	Percentage of Form 483s that cite data integrity violations	Percentage of Form 483s that cite data manipulation
China	916	617 (67.4%)	32.4%	48.1%
India	1,693	976 (57.6%)	25.3%	44.0%
Europe	2,969	1,445 (48.7%)	17.3%	35.6%
USA	12,000	6,794 (56.6%)	14.7%	25.9%

While this analysis reflects a serious problem, it likely understates the severity. The FDA is failing to detect a significant amount of fraud in overseas plants because of the way it conducts those inspections. In the United States, FDA investigators show up unannounced for inspections. But abroad, the agency has chosen to pre-announce its inspections, a system that gives plants time to clean up any evidence of unsanitary conditions, wrongdoing, or data manipulation.

In 2014, when the FDA attempted a short-lived experiment of giving Indian drug plants only short or no advance notice of inspections, the serious violations uncovered by its investigators rose by almost 60%[11].

The glaring shortcomings of the FDA's decision to pre-announce overseas inspections, exposed in "Bottle of Lies: the Inside Story of the Generic Drug Boom,"[12] which one of us (K.E.) authored with help from the other (S.S.). These inspections are now under review by the House Energy and Commerce Committee's oversight and investigations subcommittee.

But these numbers tell only part of the story. We also wanted to understand if there is a difference not only in the *rate* of data violations but in the *nature* of the wrongdoing. Some practices, like multiple lab technicians using the same log-in information, suggest unprotected computer systems. That might amount

to negligence. But other practices, like lab technicians deleting irregular test results or discarding raw data, suggest fraud. Here, too, our analysis shows that data integrity violations in India and China are more egregious than they are in the United States and Europe.

To distinguish negligent practices from egregious ones, we worked with FDAzilla to identify key words in the FDA's inspection reports, such as falsification, destruction, and backdating. By comparing inspection reports, we discovered that in the United States about 28% of plants cited for data integrity problems exhibited truly deceptive behavior. In India, that number rose to 55%, and in China, to 65%.

For example, a January 2019 FDA inspection at Indoco Remedies in Goa, India, uncovered that the manufacturing plant had faked the data in its batch production records[15] to justify the release to market of its diabetes drug glimepiride. By contrast, the raw testing data showed that the drug did not meet quality standards and therefore should not have been released to patients.

While data integrity violations may sound minor and technical, for patients they can mean the difference between a safe, effective generic drug that functions just like the brand and a drug that is not equivalent to the brand, or that may contain toxic impurities or foreign particulate matter. In short, a difference between life and death.

At the Cleveland Clinic, as "Bottle of Lies" chronicles, heart transplant patients whose anti-rejection medication was working fine ended up suffering organ rejection after taking an ineffective Indian-made immunosuppressant.

At the manufacturing plants themselves, data integrity violations can mean profound deceit: tearing up records of failing drug tests and smuggling them from the plant; or inventing data to indicate that a plant is sterile, without actually doing the required microbial testing of the surfaces, air, and water.

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The FDA recently announced[17] what appeared to be great news: It had approved 1,171 new generic drug products for fiscal year 2019, a new record. But this week, as congressional leaders hold yet another hearing on the safety of our drug supply and the adequacy of the FDA's regulatory system, they need to consider an unpleasant truth: The overseas manufacturers that are ostensibly saving us from runaway drug prices are actually exposing us to growing risk of getting drugs with undetected impurities or faked results.

There is no question that Americans need more affordable medicines. But to ensure high quality, the FDA needs to overhaul its overseas inspection program — and it should start by ending the practice of the advance-notice inspections for which plants prepare. In March, for example, an FDA investigator inspecting the NingBo Huize Commodity Co., in Zhejiang, China, found that the plant had falsified all sorts of documents[18]: cleaning validation reports, batch records, and annual reports. Under questioning, the plant's general manager confessed that the documents had been faked "for the purpose of this inspection," according to an August warning letter.

In today's interconnected, global drug supply chain, the FDA's regulatory honor system — which relies on company-submitted data and pre-announced inspections and does not systematically test drugs to verify their contents — is no longer adequate. Americans should demand that the FDA and its investigators police overseas manufacturing plants and their drug products with the same rigor — and using the same standards — as they do domestic ones.

Katherine Eban is an investigative journalist and the author of "Bottle of Lies: The Inside Story of the Generic Drug Boom"[12] (HarperCollins, 2019). Sony Salzman is a freelance science and medical journalist who worked as a researcher on "Bottle of Lies."

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