

Katherine Eban
Investigative journalist and *New York Times* bestselling author,
Bottle of Lies: The Inside Story of the Generic Drug Boom
Testimony before the U.S.-China Economic and Security Review Commission
“A Healthy Relationship? Assessing the Risks and Opportunities of China’s Medicine and Health
Development.”
July 31, 2019

Introduction

I spent a decade investigating the overseas manufacturing plants that are the principal suppliers of generic drugs to the U.S. market. That effort culminated in the recent publication of my *New York Times* bestselling book, *Bottle of Lies: The Inside Story of the Generic Drug Boom* (Ecco/Harper Collins May, 2019).

The book takes readers into the overseas manufacturing plants where the majority of our low-cost generic medicine is made. It reveals endemic fraud and dire conditions in an industry where companies routinely falsify data and circumvent principles of safe manufacturing to minimize cost and maximize profit. To report the book, I traveled to four continents, interviewed hundreds of sources and obtained over 20,000 pages of confidential FDA documents.

The U.S. drug supply is 90 percent generic, with a majority of those drugs coming from overseas, principally India and China. As well, 80 percent of the active ingredients in all our drugs, whether brand or generic, come from overseas, the bulk of those from China and India.

It is crucial to the health and safety of the American public that these drug products are effectively regulated. No substandard drug product should be permitted to enter the U.S. market. And yet China has been a continuing source of adulterated drug products, most recently of active ingredients for the generic blood pressure medicines valsartan, that was found to contain a carcinogen previously used in the production of liquid rocket fuel. As well, FDA investigators have found widespread fraud and manipulation of quality data in Chinese manufacturing plants.

After extensive reporting on this topic, it is my conclusion that: the FDA is not effectively regulating the overseas manufacturing plants, including in China, that export to the U.S. market; FDA officials are allowing substandard drug products to enter the U.S. market. They are making exceptions for reasons that include concern over drug shortages and confusion about their own authority. The FDA’s investigators are spread too thin, with a depleted staff in China, and a relatively small cadre of U.S.-based investigators willing to perform inspections overseas.

In conclusion, I believe the FDA must overhaul its foreign inspection system, and more strictly enforce its own regulations, to ensure the safety of the American public.

1. Chinese drug plants systematically engage in deceptive practices

One FDA investigator, Peter Baker, who I feature in my book, inspected 48 plants in China from 2014 to 2016, and found evidence of serious data integrity violations in 38 of them. As well, additional evidence supports the view that fraud and manipulation of quality data is endemic in Chinese drug plants.

In February 2015, Baker arrived in Beijing, where he became the FDA's sole drug investigator stationed in China, responsible for inspecting over four hundred factories approved to export drugs or drug ingredients to the United States.

Within a month, he arrived at the massive Zhejiang Hisun plant in Taizhou, two hundred miles south of Shanghai. The plant was the site of a joint venture with Pfizer, started in 2012, to create high-quality, low-cost medicine under the umbrella of Hisun-Pfizer Pharmaceuticals. The company seemed like a safe bet: it was already China's largest exporter of drug ingredients to the United States.

The FDA's investigators had been at the Zhejiang Hisun plant over a dozen times and had found little to concern them. But Peter Baker had a different inspection style. Instead of requesting documentation, as other FDA investigators do, he looked directly in the computer systems of the plants he inspected, as was his right. At the Zhejiang Hisun plant, he went to the quality control laboratory. Using the rudimentary Mandarin that he learned in college, he hunted through the forest of Chinese symbols in the computer audit trails for the words "trial injection" and "experimental sample."

Despite Pfizer's three-year head start, it took Baker about a day to figure out that the plant was running an alternate and hidden laboratory operation. The plant was secretly pretesting its drug samples and then masking the results, in part by turning off audit trails to leave no evidence of the tests. In one instance, Baker found that technicians had turned off the audit trail on February 6, 2014, at 9:09 a.m., then proceeded to run eighty secret tests. The audit trail was turned back on two days later at 8:54 a.m., and the tests— now rigged and with the outcomes assured— were repeated.

Baker found the telltale evidence in the software's metadata. By the third day of inspection, the plant managers and analysts were well aware of how devastating his inspection might be. When Baker returned from a lunch break to the quality control laboratory, he saw an analyst quickly remove a thumb drive from one of the HPLC machines and slip it into his lab coat. Baker demanded that he hand over the thumb drive, but the man "began running and fled the laboratory premises," he documented in his inspection report.¹ Fifteen minutes later, a manager returned to offer him the thumb drive, but Baker had no idea whether it was the same

¹ FDA, "Form 483: Inspectional Observations," Zhejiang Hisun Pharmaceutical Co., Taizhou, China, March 2–7, 2015, 7.

one. He noted the incident as a refusal to share records— which was serious enough to get the plant’s drug ingredients blocked from the United States.²

The prevailing attitude in the Chinese drug industry has long been, “we can always fool a foreigner,” as one Western drug executive put it. Baker’s inspections cast a harsh light not just on Chinese drug manufacturing, where fraud was endemic, but also on the FDA’s foreign inspection program. Four-fifths of the plants he inspected in China were engaging in some sort of data manipulation or deceit to conceal regulatory violations or substandard drug products from FDA regulators. “Every time he puts a foot in a company, he’s finding more problems,” as one senior FDA official said of Baker. “What does that say about an inspectional force that’s not finding this?”

Six weeks after the Zhejiang Hisun inspection, Baker went to Dalian in the Liaodong Peninsula and inspected another plant; this one, owned and operated by Pfizer, was making finished doses for the U.S. market. There, too, he found manipulated tests, unreported results, and loose batch records that showed the plant using expired materials. One stack of documents disappeared entirely during his inspection; he found them later on an upper floor, tucked inside a wooden crate.³

Most of the FDA’s investigators who are sent to China do not speak the language. They can’t read the manufacturing records. The FDA does not always provide independent translators. Instead, the companies provide translators who, more often than not, are company salesmen. Sometimes, FDA investigators simply give plants a pass, deeming them to be No Action Indicated because they have no way to tell otherwise.

The investigators also can’t read street signs, which make them vulnerable to wild manipulations. Companies steer them to phony “show” plants, where everything looks compliant, but the companies aren’t manufacturing there. Sometimes a group of companies pool their resources and invest in the same “show” factory, so that different FDA inspectors return to the same plant at different times, each one thinking they are inspecting a different facility.

2. Data shows that a large number of Chinese manufacturing plants are engaged in deceptive practices

Data fraud is endemic in Chinese drug plants. In 2016, an investigation by China’s own State Food and Drug Administration (SFDA) found that 80 percent of clinical trial data submitted by Chinese companies to regulators to gain approval for new drugs was fabricated.⁴

² FDA, “Warning Letter” to Zhejiang Hisun Pharmaceutical Co., Taizhou, China, December 31, 2015.

³ FDA, “Form 483: Inspectional Observations,” Pfizer Pharmaceuticals Ltd., Dalian, China, April 13–17, 2015.

⁴ Fiona Macdonald, “80% of Data in Chinese Clinical Trials Have Been Fabricated,” Science Alert, October 1, 2016, <https://www.sciencealert.com/80-of-the-data-in-chinese-clinical-trial-is-fabricated> (accessed September 30, 2018).

A just-published analysis⁵ by an auditing expert on current good manufacturing practices (cGMP), Barbara Unger, shows that drug plants in China get the most warning letters focused on data integrity, from the U.S. FDA. Of the 85 warning letters the FDA issued to drug plants in 2018, 42 of those dealt with the problem of data integrity. Of those, China received the most, with fifteen warning letters. It has also received the most data-integrity warning letters over the last decade.

With her permission, I have included three tables from Ms. Unger's data here.

Table 2: Number of Data Integrity Associated Warning Letters by Country, CY2008–CY2018

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | TOTAL |
|--------------------|----------|----------|----------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|------------|
| China | 1 | 1 | 3 | 1 | | | 2 | 2 | 14 | 19 | 15 | 58 |
| U.S. | 1 | 2 | 1 | 1 | 1 | | | 0 | 7 | 15 | 8 | 36 |
| India | 1 | 1 | | 2 | | 6 | 7 | 10 | 9 | 12 | 6 | 54 |
| Europe | | 1 | | | | | 1 | 2 | 6 | 3 | 1 | 14 |
| Brazil | | | | | | | | | 3 | | | 3 |
| Japan | 1 | | | | | | | | 2 | 1 | 3 | 7 |
| Thailand | | | | | | | | 1 | | | | 1 |
| Canada | | | 1 | | 1 | | | | | 2 | 1 | 5 |
| Mexico | | | | | 2 | | | | | 1 | 1 | 4 |
| UAE | | | | | 1 | | | | | | | 1 |
| Jamaica | | | | | 1 | | | | | | | 1 |
| South Korea | | | | | | | | | | 2 | 4 | 6 |
| Singapore | | | | | | | | | | 1 | | 1 |
| Australia | | | | | | | | | | | 1 | 1 |
| Taiwan | | | | | | | | | | | 1 | 1 |
| Dominican Republic | | | | | | | | | | | 1 | 1 |
| TOTAL | 4 | 5 | 5 | 4 | 6 | 6 | 10 | 15 | 41 | 56 | 42 | 194 |

⁵ Unger, Barbara. "An Analysis Of 2018 FDA Warning Letters Citing Data Integrity Failures." Outsourced Pharma. June 12, 2019. Accessed July 19, 2019. <https://bit.ly/2JH9Ftx>.

Figure 1

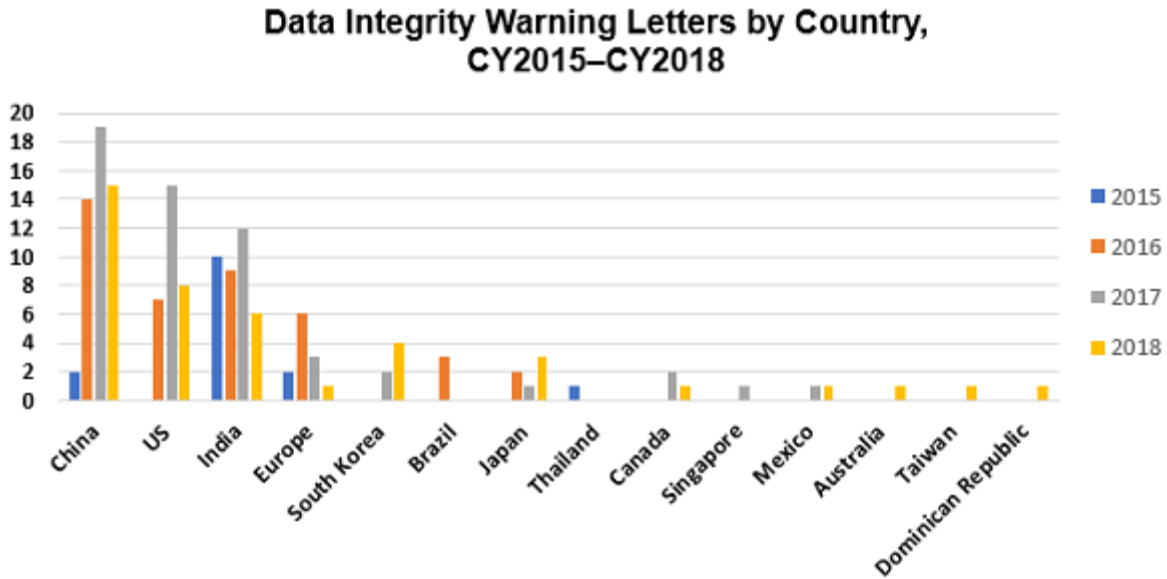


Table 3: Geographic Totals and Percentage, 2015–2018 and 2008–2018

| Country | Total Number, 2015-2018 | % of Total, 2015-2018 | Total Number, 2008-2018 | % of Total, 2008-2018 |
|---------------|-------------------------|-----------------------|-------------------------|-----------------------|
| China | 50 | 32% | 58 | 30% |
| India | 37 | 24% | 54 | 28% |
| United States | 30 | 19% | 36 | 19% |
| Europe | 12 | 8% | 14 | 7% |
| Rest of World | 25 | 16% | 32 | 16% |

In both raw numbers and percentages, Chinese drug plants have received the most warning letters related to data integrity. These numbers are especially significant, in light of key differences in U.S. and overseas inspections.

In the United States, in order to inspect drug plants, FDA investigators simply show up unannounced and stay as long as is needed. But for overseas inspections—due to the complex logistics of getting visas and ensuring access to the plant – the FDA has chosen to announce its inspections in advance. Overseas drug plants typically “invite” the FDA to inspect and the agency accepts. Plant officials serve as hosts to the visiting FDA investigators, who become their guests. It is not unusual for manufacturing plants to arrange local travel for FDA investigators. This system has allowed manufacturing plants to “stage” inspections, as one FDA investigator put it, and conceal evidence of data fabrication.

Despite this favorable system, which works to the advantage of foreign manufacturing plants, the violations in China's plants are evident. But a major question remains: what does the FDA do with the problems that it finds?

3. How the FDA Responds to Findings

The FDA has been irresolute in cracking down on Chinese drug plants when its inspectors find problems. Below are several examples.

In May 2017, in Linhai, China, an FDA investigator inspected Zhejiang Huahai Pharmaceuticals, the world's largest manufacturer of the active ingredient for valsartan, a generic version of the blood pressure drug Diovan. He found evidence at the plant that the company was failing to investigate potential impurities in its own drugs, which showed up as aberrant peaks in its test results. The investigator recommended the inspection be categorized as Official Action Indicated, which would have required the manufacturing plant to urgently make changes or face further sanctions.

But in a September 7, 2017 memo, the agency downgraded the recommended classification to Voluntary Action Indicated, which allowed the company to make non-urgent corrections. The memo⁶ concluded:

“The firm's response is mostly adequate including as it concerned the observation pertaining to their investigation of aberrant peaks on HPLC chromatograms. The firm provided data and information to demonstrate the peaks did not impact product and timeframes for improving their method and revising their investigation procedure.”

In fact, the peaks were a clue to a compromised product. Less than a year later, the company wound up in the middle of a worldwide quality scandal. In July 2018, European regulators announced a harrowing discovery: the active ingredient made by Zhejiang Huahai contained a cancer-causing toxin known as NDMA.

In the United States, over a dozen drug manufacturers, all of which used the Chinese ingredient, recalled their products, as did dozens more manufacturers around the world. The Chinese company tried to defend itself by explaining that it had altered its production process in 2012 to increase yields of the drug, a change that had been approved by regulators. In short, the change had been made to maximize profit. But some patients had been consuming the toxin daily for six years. As the FDA tried to reassure consumers that the risk of developing cancer, even from daily exposure to the toxin, was extremely low, a second cancer-causing impurity was detected in the ingredients.

⁶ Tamara Felton Clark, Branch Chief, Global Compliance Branch 4, “Reclassification of Surveillance Inspection: VAI as Inspection Classification,” CMS File—Work Activity 161861, Zhejiang Huahai Pharmaceutical

The FDA's decision to overrule its own investigator and downgrade the Zhejiang Huahai inspection was not unique. According to the FDA's own data, which I obtained, from 2013 to 2018, out of 864 inspections in China that FDA investigators recommended as Official Action Indicated, FDA officials downgraded 78 of those. By contrast, in the same time period, out of 11,642 inspections that FDA investigators conducted in the U.S. and recommended as Official Action Indicated, only one inspection was downgraded in that time. This reflects the FDA's willingness to give foreign plants, particularly in China, an opportunity to reform without sanctions.

Two months before downgrading the sanctions against Zhejiang Huahai, an even more troubling incident unfolded during an FDA inspection in China. In July 2017, an FDA investigator and her translator arrived at Bangli Medical Products in Zhejiang province. The plant manufactures lidocaine and capsaicin skin patches for treating pain. There, as the FDA inspector moved through the plant – requesting documents and taking photographs – the company's general manager grew increasingly upset. When the FDA employees returned to the conference room, he accused them of not actually being with the U.S. government, announced they could not leave the conference room, demanded that they destroy their photographs of the plant and called the local police.

In holding the FDA investigator hostage in a conference room, it seemed clear to the FDA's staff in China that the company had refused an inspection and its drugs needed to be blocked from import into the United States. An FDA supervisor wrote back to officials at the agency's Maryland headquarters: "Needless to say, they first refused the inspections and refused to recognize our investigator's authority to inspect the premises. We need to immediately put this firm on import alert."⁷ An import alert would have prevented the company's products from coming into the U.S.

But an official at FDA headquarters quickly sounded a note of caution about "declaring that we have 'authority' in the foreign arena." Another official weighed in, stating that it didn't appear the plant manager who'd imprisoned the FDA's investigator "was making a specified refusal."

In China, the Bangli inspection underscored the confusion and difficulty that surrounds the FDA's "authority" in the overseas arena. As one FDA assistant commissioner emailed colleagues:

"...section 704(a)(1) of the Act gives an authorized employee the authority to enter and inspect at reasonable times but it only applies in the domestic arena. This provision, if

⁷ The incident is documented in an internal FDA email: Kelli Giannattasio, "Re: For Cause Inspection of Bangli Medical Products," email to Susan F. Laska and Sherry Bous, July 27, 2016.

the inspection is declined/refused, allows for a warrant to be pursued. In the foreign arena, since we don't issue notices of inspection (482), the firm must give permission for us to enter and inspect. To result in an Import Alert as suggested below, we have historically asked and documented the refusal by the firm to allow FDA to enter and conduct its inspection, and we have explained how this refusal could be evaluated and potentially result in an import alert. Before an IA gets recommended, we may need to fully document this refusal which may have related to concerns about if these were actually FDA employees. Once that is established, we should determine if the firm is actually refusing the inspection and document the discussion with the firm's senior management.

The FDA did send a different investigator back the following month. He discovered that the plant was not actually testing any of its products or ingredients to ensure their purity or strength and had no cleaning procedures for its manufacturing equipment. The plant was then placed on an import alert, restricting its products from entering the United States.

In some instances, manufacturing plants have figured out how to keep selling their drug products to the United States, even after the imposition of strict regulatory sanctions. After Peter Baker's inspection at the Pfizer-affiliated Zhejiang Hisun plant, the FDA restricted the import of thirty of the plant's drug products. But fifteen of the drug ingredients were in short supply in the United States, so the agency lifted the restriction on about half of the drugs, including a crucial chemotherapy drug for treating leukemia and breast and ovarian cancers.⁸

To Baker, that decision made no sense. According to regulations, the drugs had no place in the U.S. supply. They weren't good or safe enough. Shortages didn't change that fact.

The FDA's investigators believe that companies committing fraud purposefully make drugs in short supply, as a way to protect their bottom line. Those will not be restricted, whether made with dubious methods or not, and can serve as a steady source of business, even if companies are caught making unsafe drugs. "There are no consequences for companies that are shipping substandard product," Baker observed to a colleague. "It's a win-lose situation— and [patients] are the losers."

4. Suggested reforms to better safeguard drug products from China

- The FDA needs to overhaul its foreign drug inspection program

⁸ E. J. Lane, "U.S. FDA Ingredient Exceptions from Banned Zhejiang Hisun Plant Draw Scrutiny," FiercePharma, July 25, 2016, <https://www.fiercepharma.com/pharma-asia/u-s-fda-ingredient-exceptions-from-banned-zhejiang-hisun-plant-draw-scrutiny> (accessed June 9, 2018).

The FDA's overseas offices are poorly staffed, and its cadre of U.S.-based investigators willing to perform inspections overseas is relatively small and demoralized. The FDA needs a specialized and highly trained workforce that can make a years-long commitment to serve overseas and become a "go to" group for emergency assignments. This would remedy the problem behind the FDA's anemic recruitment to foreign posts: a lack of clear career progression and promotion opportunities. Right now, those who serve overseas often return to the FDA's U.S. headquarters without a guaranteed job, and sometimes have to accept demotions. Instead, superior training, pay, and a clear professional pathway, similar to that for State Department officers, would help cultivate more elite investigators. The U.S. government should demand that more of its investigators be given visas for work in China.

- The FDA should perform short-notice or no-notice inspections in China

The FDA's current regimen of pre-announced overseas inspections is counter-productive and ineffective. It allows Chinese manufacturing plants to stage-manage inspections. If the U.S. government actually wanted to get tough with China, it could insist that U.S. FDA investigators be allowed to inspect on short notice, or no notice. The model for this would be a highly successful FDA pilot program that ran for 18 months in India, from January 2014 on. Under that program of short and no-notice inspections, the FDA's investigators exposed widespread malfeasance that had previously been hidden.

By showing up unannounced, the investigators uncovered an entire machinery that had existed for years: one dedicated not to producing perfect drugs but to producing perfect results. The inspections led to an almost 60 percent increase in findings of Official Action Indicated. As a result of the pilot program, drugs from 41 plants in India were restricted from the U.S. market.

- Downgrades should be rare

Too often, FDA officials at the agency's headquarters in Maryland overrule the judgment of investigators in the field, and downgrade recommended findings.

In the course of my reporting, an FDA spokesperson justified these downgrades as follows:

"The FDA can and does change assessments of a plant's compliance. After the initial data gathered by the investigator is reviewed by both the Office of Regulatory Affairs and the Center for Drug Evaluation, additional information can be taken into account. Oftentimes, a firm is not able to provide paperwork at the time of an inspection but can produce documents later on that provide more insight into the matter. Assessments can also change based on how willing a firm is to cooperate and fix issues that are found."

However, the problem with this system is that it allows manufacturing plants to fabricate documents and generate excuses for submission to the FDA. It has also allowed substandard

drug products to enter the market, as was the case with the Zhejiang Huahai plant.
Downgrades should be rare.