Executive Summary

Thirty years ago, most medicines consumed in rich nations were made there. Today most of the ingredients and nearly half the finished products come from India and China. India and China have low costs, which have driven the three-decade change. Both nations have capable chemists and businesses that can make high-quality products, but they also have a lot of slipshod producers (not unlike the West of the mid-20th century).

Western regulators’ difficulties in overseeing these plants, domestic regulators’ lack of interest in overseeing them, and generic companies being unable to differentiate their products (due to prescribing practices, limits on advertising, and so forth), amid the fiction that all generics are equal, mean that quality, which should be more assured, is more hit-and-miss today than before. This is not a problem limited to a single group, company, or country. However, in this paper I primarily address India.

The rapid rise of India’s pharma industry has not been matched by a sufficient capacity to regulate legal medicine production. India is far from unique in exhibiting this problem, but it is the worst protected of the major exporting nations. Like other nations, policing medicine counterfeiting is at least attempted in principle, but unfortunately in India it is almost nonexistent in practice. Additionally, widespread corruption enables all sorts of bad actors to endanger patients by exposing them to a wide variety of inferior-quality medicines. Most worrying is increasing evidence that not all, or even the majority, of legal Indian manufacturers are operating to acceptable standards.

Any manufacturer, even well-known Western companies, makes mistakes. But in countries with robust rule of law and effectual regulation, infractions are noticed and remedies made, either by the federal government or through the threat of private litigation. Manufacturers know that repeated negligence will lead to plant closures, massive fines, civil damages, and even bankruptcy, and so they happen rarely.

This was certainly not the case historically. For much of the 20th century, manufacturers in the US and Europe operated with little oversight, and in response, reputable companies differentiated their brands by ensuring quality or purity, which nurtured trust, reputation, and brand loyalty. Rigorous regulation slowly followed, and an iterative process of quality production and stricter regulation has evolved. Undoubtedly this process has improved quality in the West.

India is, in many ways, in a similar situation to the West of 60 to 70 years ago. India currently lacks regulatory oversight and exhibits legal weaknesses that encourage substandard drug producers to flourish, often crowding out better producers, which cannot compete on price with those cutting corners. While Europe and America faced this problem in the mid-20th century, at that time it was easier to differentiate products based on branding and advertising, whereas today, all “generic” products are assumed to be interchangeable, and advertising is often illegal. This means companies can often distinguish themselves only on lower price and reliable delivery.

Additionally, the plethora of substandard products is worsened by the Indian government’s price-control policy, which drives low prices for government contracts to supply pharmaceuticals—prices so low, some manufacturers simply cannot make good-quality medicines and cover costs.

Furthermore, some Indian producers seem to be consistently and intentionally making poorer-quality products for certain domestic and foreign markets where quality control and consumer discernment are perceived to be weak. But companies sometimes send poor-quality medicines to markets with good oversight, too, and occasionally get caught as a result.
Increasingly, Western regulatory agencies are identifying failing Indian companies and sanctioning them—most infamously, the pharmaceutical company Ranbaxy paid a $500 million settlement in 2013, as the company admitted to fraud and supplying substandard medicines. Since then, dozens of other Indian companies have been reprimanded or fined by the US Food and Drug Association (FDA) or limited in their ability to export their products to the US. But the Indian government continues to deny it has a problem, to the chagrin of foreign regulators and drug producers and of increasing concern to some American physicians and patients. Perhaps most striking, India’s regulators never even bothered to investigate Ranbaxy following the US case.

As a result, Indian regulators are increasingly isolated from the rest of the world. Indian producers may also be isolated in the future; US congressional committees are investigating drug quality, and President Donald Trump is pushing for more production in the US. But at the same time, the president wants cheaper drugs, and no producers can beat India on price.

We may be approaching a crossroads for Indian medicines. If India does not shape up, resulting in tragedy to US patients, a US boycott of Indian drugs could devastate India’s pharmaceutical industry—the good with the bad. It may also double the price of medicines in the US and lead to shortages. It is in nearly everyone’s interest that India sort out its medicine business.

This paper explains the problems with Indian medicines, while acknowledging the vital role they play, and then discusses some of the methods by which quality can be improved, using a mixture of carrots and sticks.

Several options are available to fix the lack of consistent quality. The simplest is to be open about quality differences and allow the market to adapt. Allowing generic manufacturers with spotless records to advertise this fact, pointing out how their products are more reliable than their competitors, would probably drive demand by patients for those products and drive drug wholesalers and pharmacists to deliver demanded products based on such differentiation. The knock-on effects would be significant: If Indian or Chinese companies are exposed as making shoddy products, they would lose business, and some, maybe most, would change practices as a result.

A more likely political approach would be for the US to enact legislation that prevents all Indian and Chinese products from being imported, unless they are certified to the highest standards. This means not just passing an initial FDA inspection, but passing ongoing private-sector audit requirements, with stringent penalties such as marketing prohibition if a producer fails in these audits.

Price increases and shortages would be an inevitable result of such an approach, but whatever path is taken, there are only imperfect real-world policies with trade-offs that affect patients and entrenched interests. It is ironic that an overreliance on the cheapest sources of chemicals and finished products is caused by the near impossibility of differentiating products based on quality.
India’s Dodgy Pharmacy

Roger Bate

The pharmaceutical industry is one of the most heavily regulated in the world, yet medicine manufacturing is often opaque, even to the very regulators charged with protecting consumers from ineffective and potentially dangerous products. Furthermore, patients and even physicians are often ignorant of the products they take or prescribe every day.

Regulation is slow to change, often for good reasons, since business dislikes uncertainty and invests more when the rules of the game are set. But as industry has changed, its practices, notably its procurement practices, have changed so radically in the past three decades that the regulatory environment is no longer capable of overseeing consistent product quality. With no effective regulations and with opaqueness from most of the supply and distribution system, quality problems were almost inevitably going to arise.

A key change has been geographic. India has developed a reputation of producing cheap generic drugs, making it the pharmacy to the world. It is a well-deserved reputation since Indian drugs dominate pharmacy sales in every part of the developing world and increasingly in the West.

Price Is King, Quality an Afterthought

As a British colony until independence in 1948, India had, in principle, a developed-world system of medicine oversight. K. A. Hamied founded Cipla in 1935 to promote domestic production, following the self-sufficiency mantra of revered leader Mahatma Gandhi. K. A. Hamied’s son, Yusuf, worked with the Indira Gandhi administration to abolish product patents on pharmaceutical products in 1970. This allowed domestic firms, led by Cipla, to imitate and adapt foreign therapeutic inventions. More than 2,000 licensed drug manufacturers existed in 1970, but within 25 years the number was more than 16,000.

India’s drug industry was a commercial success and became a net exporter of pharmaceutical products. Unsurprisingly, the market share of foreign multinational corporations dropped from more than 80 percent to 40 percent over the same period. Domestic employment in the sector was more than half a million people by the turn of the century. Today the domestic market is totally dominated by domestically produced medicines.

From the beginning the Indian government supported the Indian drug industry and its aims. The desire was for an export-driven industry that generated wealth, paid taxes, employed a lot of people, and improved the image of India internationally. While the health benefit of cheaper medicines was not ignored rhetorically, health was not a government priority. Even today the amount spent on health is low.

The Indian government spent only $23 per capita on health in dollar terms in 2014 ($80 in purchasing power parity terms). Total health spending per capita
was $75, which means that government expenditure is less than a third of the total. Meanwhile China spent more than $234 per head in 2014.\textsuperscript{2} India’s neighbors are actually worse than India—Pakistan and Bangladesh spend even less—but neither of these nations claims to be a leading light in health delivery.

Sanitation is also not a priority, which means cheap drugs are often a substitute when insanitary conditions lead to sickness, and this has major ramifications for drug resistance. Furthermore, improving the architecture under which medicines were made was never a priority. For instance, colonial-era laws still exist, significantly amended to be sure, but never truly updated.

India’s drug regulation is murky and outdated. The Drugs and Cosmetics Act is a legal relic from 1940, which does not even require that the regulator ensure a drug’s safety or effectiveness before approving it. This requirement, standard almost everywhere else in the world, was an afterthought added to the law just over a decade ago in subordinate rules, and altogether inadequately at that.

One alarming aspect of the rules is that under section 122, “new drugs,” including new dosage forms (but not vaccines), are only effectively regulated by India’s national government for four years at the longest. After four years, they become old drugs, and it is no longer within the national government’s authority to approve their manufacturing for sale. At best, this means that India’s states—some of which, like Haryana and Uttar Pradesh, are havens for counterfeiters and corruption at every governmental level—are in charge of invigilating manufacturing standards. At worst, it means that even if the national government later discovers that it inappropriately or even illegally approved a drug, it can never claw back that mistaken decision once four years have passed, and the drug will go on being manufactured for sale. India’s own parliament summarizes the rules this way:

As per Rules, a New Drug is deemed to be a New Drug for four years. After four years, the State Drug Authorities have the powers to issue manufacturing licenses without reference to DCGI [the Drug Controller General of India]. Therefore, if initial approval is given unlawfully by the DCGI, the doors open for other manufacturers to market the drug after four years.\textsuperscript{3}

India is quite possibly the only country where drug regulation has a statutory time limit, which is shorter than the drug’s marketing life. The potential for risk is obvious, and even if the national government does the best possible regulatory job for the first four years, there is great uncertainty thereafter when the states take over, at least in theory.

**Public Health and the Role of the Regulator.**

India’s equivalent of the Food and Drug Administration (FDA) is called the Central Drugs Standard Control Organization (CDSCO). Some of its staff were found to be corrupt and colluding with local companies, according to India’s own Parliamentary Committee on Health.\textsuperscript{4} The committee found faked endorsement letters from doctors to secure marketing authorizations, that products were approved without conducting clinical trials, and that companies were paying bribes to get fast approval of products. The report also noted that while scrutinizing 39 drugs, the committee found that 13 were banned for sale in major developed countries, and 25 lacked the opinion of experts before being granted approval. India’s own Central Bureau of Investigation caught a deputy controller of the CDSCO red-handed accepting bribes to renew a blood bank’s operating license.

The CDSCO’s data on near-universal good drug quality in India are also suspect, as will be discussed below. Overall, the regulator is underfunded and weakly and politically staffed, rather than staffed by professionals whose priority is patient safety.

It is somewhat embarrassing to Indian officials and companies that the FDA deems it necessary to inspect its plants. It is apparent to most independent observers that the FDA does not want to inspect manufacturing plants in India; it is not doing so to expand its turf or at the behest of American businesses keen to limit Indian exports, as some Indian commentators claim. The FDA is being forced to inspect in India because of noted distrust of Indian manufacturing, which rightly ought to be the purview of the national regulator.
But with a toothless regulator, India lacks legal reminders from the government of why quality control matters. And while practical skills are certainly present in the industry, the inevitable result was inconsistent-quality medicines, from at least some, arguably all, manufacturers. As Indian companies succeeded in winning more business (both final product bids and intermediate product deals with Western companies), it has become more obvious that quality has not always been perfectly sustained.

India’s Central Bureau of Investigation caught a deputy controller of the CDSCO red-handed accepting bribes to renew a blood bank’s operating license.

Part of the solution for India is a strong and incorruptible national regulator, but that is not likely anytime soon. So what has the Indian industry delivered?

Cheap Drugs and Intellectual Property Concerns. Since 2007 my colleagues and I have sampled medicines from emerging markets, and nearly half were made in India. It was the stated aim of Indian policy to make the cheapest generic medicines in the world; therefore, I compared the prices of the Indian products my research team and I bought with the prices of those made elsewhere to determine whether this was accurate. Stripping out known fake products, we procured more than 11,000 generic medicines of the same therapeutic categories, which were manufactured in myriad locations. After India, the top locations for production of these medicines were Belgium, China, Kenya, and Nigeria, although the latter two were only for products bought in Africa, which were not available elsewhere.

Most of these products were bought outside of India. (Indian products made up 97 percent of our procurement from the Indian market.) Therefore, the most important test of drug price is a generic product comparison outside of India. Of the Indian products bought outside of India, the average price in Africa was $2.34, and in other emerging markets (notably Brazil, China, Russia, Thailand, and Turkey), the average price was $6.49. Compare that with the non-Indian-made identical products (to treat the same diseases) bought in Africa (average price $3.42) and elsewhere (average price $9.78). So for generic products, Indian export products are undoubtedly cheaper, roughly a third cheaper in both markets than comparable products made by African, Chinese, or European generics producers sold in those markets. And in the directly comparable product category of antibiotics (notably Cipro) bought in all markets, Indian-made products procured in India are at least 50 percent cheaper than antibiotics sold elsewhere. (Indian domestic competition has probably driven the prices even lower than is seen in the export market.)

In other words, the widely held assumption that Indian generics are the cheapest in the world is strongly supported from our own procurements. The fact that so many more people will be able to afford their medications as a result should always be borne in mind whenever discussing the problems of Indian drug quality.

It is also important to recognize that to a certain extent, Western industry has driven Indian production. Western industry wanted to take advantage of the low costs offered in India (and China), so it moved production to such locations and bought ingredients from local companies. In essence they trusted their own quality controls and believed or at least hoped that they would spot any flaws in the ingredients or even finished products they procured. Not only did this process drive the current flaws in quality (as well as lower costs and higher profits for these companies), but it also provides the crucial reason why Western companies have not been out front and center in criticizing quality in these markets—after all
they are bound to them in trade and manufacturing, and hence a broad critique could undermine their own reputations.

But the lack of focus on Indian quality from Western companies is also because the latter’s prime concern is the weak enforcement of intellectual property (IP) rights in India. As a result IP has been the major area of confrontation between Western companies and India, and it has sucked all the air out of the room for discussions of quality.

To gain access to the global market enabled by the World Trade Organization (WTO), India had to ratify the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the most influential treaty on global IP. Doing so included introducing full product patents on pharmaceutical innovations, extending all patents from 5–14 years to 20 years, and accepting limitations on compulsory licensing. The government agreed against its wishes to TRIPS for the additional benefits of WTO membership. Under TRIPS regulations, patenting has accelerated in India, but its enforcement has been spotty.

Legal But Deadly: A Substandard Pharmacy to the World. I claimed that Indian medicines are at best of inconsistent quality. But what does the Indian government report? In 2015 the CDSCO published the largest and arguably most comprehensive study of medicine quality any country has ever undertaken. The report shows that more than 3 percent of the samples tested fail basic quality control. Yet many questions remain, such as whether the medicines most likely to fail were even tested.

Mind you, this latest report is superior to its 2009 Report on Countrywide Survey for Spurious Drugs, which largely denied a problem existed. It found only 11 fakes from a sample exceeding 24,000 (and under 1 percent substandard). But the Indian government’s own yearly assessments through the 1990s and 2000s found failure rates of 5–10 percent. So if the CDSCO is to be believed, India’s drug-quality problems suddenly vanished in 2009–10 and reappeared in lessor form last year.

Vijay Karan, a former chief of police in Delhi who made combating dangerous drugs a priority, explains the discrepancy: Pharmacists had apparently been warned in advance, so they knew to offer only the best when the inspectors arrived in 2009.7 The methodology followed in the latest samplings is rather opaque, but it may have been subject to the same problems.

In May 2013, the Indian Parliamentary Standing Committee on Health and Family Welfare published a report candidly admitting that at least 7 percent of medicines in India are substandard, some of which “can harm patients,” and others of which were never lawfully approved at all, and that India’s drug regulator was guilty of myriad acts of “corruption.”

There are no other detailed and comprehensive reports of Indian drug quality. But there are smaller studies and valuable anecdotal reports that Indian companies produce inferior-quality medicines. I turn to those now.

The Story of Ghana and the USP. The most damning evidence comes from Ghana. In February 2013, the Ghana Food and Drugs Authority (GFDA) and the United States Pharmacopeial Convention (USP), supported by the US Agency for International Development, published a study on maternal health products sold in Ghana.9 The GFDA and the USP procured samples of oxytocin and ergometrine, used to treat potentially lethal postpartum hemorrhage. While such products are used routinely in Western hospitals to speed the contraction of the uterus after birth and lower risk of hemorrhage, Anna Adjoa, an obstetric nurse in Accra, explained to me that she uses them “mainly in emergency situations.” She says that if these drugs do not work, the chances are “far higher” of the new mother bleeding out in the delivery room.10

Of the 303 samples procured, the study found that most were not registered in Ghana—and all of those that were not registered failed basic quality tests, making them unfit for patient use. Roughly 95 percent of the 80 samples that were subjected to all methods of quality and sterility tests failed. The companies that registered the products they sold (a legal requirement ignored by all but three of the 16 companies) performed better, but most of their products failed, too.
Some of these products may have been falsified—made by criminal outfits pretending their products were made by a legitimate company. But the USP, which has a history of detailed product analysis, suggests only a few of the samples were fakes, with the vast majority made by the companies that appeared on the packaging. Possibly, some of the products were made well but then degraded in the supply chain due to poor storage. However, the samples made by the one Swiss manufacturer, passing through the same distribution chain, all passed quality control. And the conditions I saw in major clinics were reasonable for product storage—in other words, Ghanaians were unlikely to blame for the problems with the products.

Roughly 95 percent of the 80 samples that were subjected to all methods of quality and sterility tests failed.

The overwhelming conclusion is that all the manufacturers made some or all of their products badly. Most of the products procured were made by companies from India or China. None of them are large producers like Ranbaxy, but at least three of the Indian companies claim to have World Health Organization (WHO) good manufacturing production (GMP) certificates, and at least one is verifiable from publicly available WHO data.

Stephen Opuni, chief executive of the Food and Drugs Authority in Accra, told me that some of these companies had actually registered the products with his agency—providing the dossiers for their medicines, along with samples to test—but, “eventually, after they got their marketing authorization from the Food and Drugs Authority, they intentionally put substandard, and some of them, fake medicines on our market.”

Opuni recalled the dangerous products and asked the police to pursue those thought to be “involved in criminal acts.” Such action is certainly appropriate, and lives will be saved as a result. But with insufficient resources to combat poor-quality drug manufacturing, and with little regulatory harmonization across African countries, it is likely that sellers of the suspect products will easily find receptive markets elsewhere.

I covered the USP/GFDA report in the media, but Western journalists were slow to pick up on it. In January 2014, I pulled up the USP website and downloaded the report to show one journalist and noted the report had changed. The original page 4 and 5 had disappeared; these pages had contained the names of the Chinese and Indian companies.

On January 24 I emailed a senior scientist at the USP involved with the relevant programs undertaking the study, and he was unaware of the redacted version. In subsequent emails he copied a scientist at the GFDA who was also unaware. I am still waiting for the real reason for the redacted copy.

I am also worried that the USP, perhaps unknowing to its scientists, has come under pressure to redact the names and meekly did so. This would not be the first time that exposing substandard medicine has led to threats. Evidence for this supposition is supported by the USP Press Office’s response to my questioning about the reports on the website: “We did not circulate a version with manufacturers’ information because it is confidential pending regulatory action from the Ghana regulatory authority. Once action is taken I believe the information will be made public.”

This is an interesting response. It is also inaccurate; one might even call it a lie. From the internet archive’s snapshots, we can see that the un-redacted report was on the USP website on May 2, 2013. And on the June 4, 2013, snapshot, one can see the redacted version. But the original was still on the site in August 2013 when I downloaded it. Also the idea that releasing the names of the pharmaceutical companies is prohibited is, at best, disingenuous, given that the GFDA already named four of the companies (three Chinese and one Indian) in public in August 2013.

The USP is a good organization with an important mission, including to combat substandard medicines.
But if it folds under pressure from Indian companies, then it makes the jobs of those trying to improve quality and regulation in India harder still, and that puts lives at risk.

The Sun Pharma Story. A more recent issue arose in Panama. In an effort to maintain access to the richest market in the world, some Indian companies have established plants in the US. Using their own ingredients and US manufacturing staff and allowing greater oversight by the FDA, they win generic drug approval.

One such company is Sun Pharma, which has fallen afoul of US regulators with its Halol plant in particular. But it has established a plant in New Jersey to make a range of products to sell into the US market. One such product is imatinib, which treats chronic myeloid leukemia (CML).

Getting FDA approval and sustaining it is quite difficult, and it is a badge of honor for companies to achieve the status. Other nations know this, so any products approved by the FDA are most likely to be approved rapidly in emerging markets.

Panama approved Sun Pharma’s imatinib largely because the FDA approved it. But according to local experts, Sun Pharma has been selling the imatinib made at the Halol plant in India, not the product made in New Jersey. And the FDA has not approved the product made at Halol.

CML is a horrible disease. To suffer from it is bad enough, but to be taking a possibly substandard medicine is totally unacceptable. This alleged sleight of hand might seem small, but how many nations are like Panama and approve products based on FDA approval?

In the nations where my team has sampled medicines, we found 16 examples of the practice in five nations, in six different categories of medicine, including cancer, heart, and analgesic medicines, as well as antibiotics. It is not possible to be entirely certain that in every case domestic approval was expedited because of FDA approval, but it appears likely.

Local experts told me that the Panamanian authorities were aware of Sun Pharma’s sleight of hand but so far have done nothing to punish the firm or, more importantly, ensure good-quality medicines reach patients.

What is so depressing about this issue is that the FDA only approves companies that can make medicines to the highest standards. Yet the same companies choose to sell drugs from plants deemed inappropriate. Maybe the drugs they sell are fine, but should we assume that lying to regulators about quality has no costs to patients?

To suffer from CML is bad enough, but to be taking a possibly substandard medicine is totally unacceptable.

The Ranbaxy Story. While not as significant in terms of risk to patients, the Ranbaxy saga is the most famous and worrying insight into large and previously respectable Indian pharma.

In the summer and fall of 2004, the team overseeing portfolio management for Ranbaxy, a billion-dollar Indian generic firm, discovered a widespread system of fabricated data and data manipulation undertaken across myriad products and plants to win contracts from agencies and buyers, including the US government and the United Nations. While the team’s initial focus was on antiretroviral drugs purchased by these agencies for distribution in Africa, as the investigation proceeded, the team learned that many products sold worldwide by Ranbaxy were approved by regulators based on fraudulent data submitted by the company seeking their market authorization. What the team, and notably Dinesh Thakur, found would lead Ranbaxy into a multiyear regulatory battle with the FDA and into the crosshairs of a Justice Department investigation that, nearly nine years later, was finally resolved.

Ranbaxy’s corporate culture encouraged management to dictate the results it wanted and for those beneath to bend the process to achieve it. Thakur described how Ranbaxy deliberately took its greatest
liberties in markets where regulation was weakest and the risk of discovery was lowest. His investigation found that there were no data supporting some of Ranbaxy’s drug applications in those regions and that management was fully aware of this.

This was a case of outright fraud, in which the company knowingly sold substandard drugs around the world—including in the US—while working to deceive regulators. The impact on patients will never be known. But clearly millions of people worldwide ingested medicine of dubious quality from Ranbaxy.

On May 13, 2013, Ranbaxy pleaded guilty to seven federal criminal counts of selling adulterated drugs with intent to defraud, failing to report that its drugs did not meet specifications, and making intentionally false statements to the government. Ranbaxy agreed to pay $500 million in fines, forfeitures, and penalties—the most ever levied against a generic-drug company. (No current or former Ranbaxy executives were charged with crimes.) In addition, the company became signatory to a cumbersome consent decree that forced Ranbaxy to withdraw three first-to-file applications pending with the FDA, citing data-integrity issues. As Fortune said of the saga:

What occurred inside Ranbaxy and how the FDA responded to it raises serious questions about whether our government can effectively safeguard a drug supply that last year was 84% generic, according to the IMS Institute for Healthcare Informatics, much of that manufactured in distant places. More than 80% of active pharmaceutical ingredients for all U.S. drugs now come from overseas, as do 40% of finished pills and capsules. As the Ranbaxy story makes vividly clear, generic-drug makers intent on breaking the rules—especially those operating abroad—can easily do so.

The immediate concern over Ranbaxy’s mendacity quickly turned into a round of questioning, notably whether the FDA acted appropriately and timely in its dealings with Ranbaxy. (It should be noted that despite all the criticism of the FDA, no other national regulatory agency has acted with such vigor against Ranbaxy.)

Firstly, should the FDA have acted faster? It received information in August 2005 and did not prevent Ranbaxy from exporting products to the US until three years later.

Also, the FDA allowed Ranbaxy to become the only supplier of atorvastatin in the market in 2011, many years after it knew of the company’s dubious practices, only to force a massive recall of this drug six months after launch for manufacturing deficiencies. Should the agency have restricted Ranbaxy’s ability to win generic exclusivity and limited its exports sooner?

More importantly, the agency advised patients to continue taking their medications while implementing its Application Integrity Policy against Ranbaxy, which banned 30 products manufactured in India from entering the US market. This begs the question: What, if any, clinical data does the FDA have when it implements such punitive actions as import alerts? Are adverse event data from multisourced products (generic drugs) enough to determine the quality and therapeutic benefit of these drugs? Does the agency have the good clinical data required during the application-approval process to make informed decisions on therapeutic effectiveness such as Certificates of Analyses?

The reaction at the agency appears to have been to conduct more inspections, and since the resolution of the Ranbaxy case more than four years ago, it has documented similar data-integrity issues at other large Indian generic manufacturers—namely, Wockhardt and Sun Pharma, both of which supply a substantial portfolio of generic drugs to the US market.

Following the Ranbaxy scandal, the FDA and the UK’s Medicines and Healthcare Products Regulatory Agency have identified similar behavior in other Indian companies. Most of their focus has been on the lack of data integrity. In the past few years, at least 12 pharmaceutical companies with facilities in India have been banned from shipping products to America. A far from exhaustive list of regulatory findings by both regulators is below:

- In June 2010, an intravenous antibiotic manufactured by Claris Lifesciences Limited in India, with three manufacturing plants in
Ahmedabad was discovered to be non-sterile and to contain floating white particles, identified in at least one case as mold. Three of the manufacturer’s products were recalled, and in November 2010, the FDA placed Claris Life-sciences under import alert, preventing its products from entering the United States.

- Sun Pharma, an Indian manufacturer with plants in Dadra, Halol, Jammu, Sikkim, and Silvassa, was found in November 2010 to have failed to disclose information in a timely fashion about problems with its distributed batches of promethazine hydrochloride, an antihistamine.

- Zydus Cadila, based in Ahmedabad, Baddi, Goa, and Sikkim, and Aurobindo Pharma, based in Haryana and Hyderabad, both falsely reported that no microbiological contaminants existed in their quality testing. These tests are done to ensure that employees do not contaminate the product. The detection of microbial contamination during multiple FDA inspections questions the validity of the data generated by these Indian firms.

- RPG Life Sciences, with its main facilities in Ankleshwar and Navi Mumbai, selectively reported test results, publicizing successful tests and deleting all initial data that might have been unfavorable.

- Fresenius Kabi, a global health care company, in a similar fashion as RPG, ignored results that were undesirable.

- In 2011, Sun Pharmaceutical Industries deleted more than 5,300 failed chromatography test results, according to FDA documents recently obtained by Bloomberg News. FDA inspectors concluded, “Our review found that analysts regularly delete undesirable chromatographic results, and products are retested without initiating an investigation as required.”

- Wockhardt, which has its biggest plant in Baddi, Himachal Pradesh, is a large exporter of medications to the US, including the recently withdrawn heart medication metoprolol. The company repeatedly delayed, denied, and then limited an FDA inspection in 2013. Products that failed to meet the in-process visual inspection were reported by Wockhardt employees as having met all specifications. Sample preparation data were also destroyed, making calculations and analysis impossible. In addition, the inspection documented more than 40 instances of incomplete training records for three staff members. In each case, the trainee and trainer names were left blank on the questionnaires but were pre-filled with the answers.

- Similarly, Canton Laboratories was placed under import alert by the FDA in 2014. Investigators concluded that there were “serious concerns regarding the integrity, reliability and accuracy of the data generated and available.”

All these companies are large and highly visible members of India’s pharmaceutical industry. There are also a number of import alerts on smaller Indian companies such as Amsal Chem, Fleming Laboratories, Kamud Drugs, Konduskar Laboratories, Nivedita Chemicals, Promed Exports, Posh Chemicals, Smruthi Organics, Stericon Pharma, Unique Chemicals, Ipca Laboratories, Apotex Pharmachem India, Aadvighnesh Chem, Aarti Drugs, Pan Drugs, Emcure Pharmaceuticals, Akorn India, Vignesh Life Science, Wintac, Yag Mag Labs, and Global Calcium. These do not often make news because of their small size. Currently, the number of Indian pharmaceutical companies under import alert by the FDA totals a whopping 35.

One would think that with dramatic stories such as that of Ranbaxy, there would be an outcry from the public health community. But one would be wrong—more on this later.

As part of the project to assess the problem with medicine quality, I established a research team and undertook a large selection and quality testing of those medicines. That is the subject of the next section.
Empirical Evidence of Indian Drug-Quality Concerns

As established above, strong anecdotal and study data point to inferior drug quality in transactions involving Indian producers, especially selling to those African nations that have the worst domestic quality controls.

In our tests, quality was measured using only one parameter (active ingredient), but even products with an adequate dosage of active ingredient could still be substandard due to inferior solubility, too many impurities, or a myriad of other possible problems. It suggests that if one is producing inferior medicines for certain markets, perhaps the bad products occasionally make their way into better regulated markets, perhaps by mistake, and perhaps because of inadequate inspections even in those better regulated markets.

Indian Drugs: Original Empirical Evidence.

Beginning with samplings of antimalarials a decade ago, my research team procured well over 11,000 medicines from emerging markets. Of these, more than half (nearly 7,000 medicines) had labels that indicated they were made in India. The vast majority of these medicines were to treat microbial infections (especially antimalarials, antibiotics, and antimycobacterials).

At least 138 (2 percent) of these medicines were fake (meaning they were not made by the manufacturer as stated on the packaging and in nearly every case had none of the active ingredient claimed on the package). Although the counterfeiters were Indian in some instances (the majority were made in China), these products are discarded from the analysis since they are fraudulently made and hence not subject to the kinds of issues central to this paper.

Several other caveats should be understood about these data. The ratios of types of products bought in the various locations are different. For example, there is no malaria, and moderate to low levels of tuberculosis, in most mid-income nations, so samples from these locations are more likely to be antibiotics than other categories. And while Africa does worse generally in terms of quality, antimalarials perform the best of all product categories in recent samplings due to efforts to improve quality among the malaria community, lowering failure rates overall. Also, some nations in a continent or region have been sampled more in some instances, due to convenience or other policy-related reason. The result is that drug types and locations are not consistent over time. These factors, and no doubt others, make comparisons more speculative across the data.

But I am fairly confident that the general conclusions drawn are accurate. The main reason is that the subsets of data that have been subject to greater scrutiny via the peer-review literature bear out similar results and hence conclusions. Given that samplings of medicines have now ceased, I include all samples in summary data form for the first time (even those that might not pass peer review due to “apples and oranges” types of arguments).

Finally, it is worth putting some things in context. The products made in Africa are on average twice as bad as those made in India (so African physicians and patients buying Indian imports is preferable to locally made medicines). The majority of products made in Organisation for Economic Co-operation and Development nations (especially Europe and the US) pass quality control far more often than Indian medicines, with few quality failures (well below 1 percent). In this respect, Indian products are, on average, inferior but far cheaper to Western medicines and better and cheaper than African medicines.

The data are split into three locations: India, Africa, and the rest of the world (ROW). Just over 5 percent of the sample of Indian-made drugs fail basic quality tests and hence should be considered substandard. But although the data are consistent within each region, they are quite different across the regions. First, under 2 percent of the products bought in ROW are substandard, whereas in India and Africa the figures are respectively 6 percent and just over 8 percent.

Figure 1 shows the percentage substandard medicines by location in the year sampled. This shows a consistent failure rate across time, with improvements in the latest samples in India and Africa and a worsening in ROW.
Bear in mind that this is a conservative estimate of substandard medicines. In a much smaller subset of medicines (about 12 percent of the total sample), subjected to more stringent tests, roughly 50 percent more products fail (10.5 percent as compared with 7.1 percent in the subset), indicating that Figure 1 underestimates the problem with substandard medicines.

So my data compare well with the other studies, including estimates by the Indian government committee overseeing the CDSCO. It is fair to conclude that at least 5 percent of Indian medicines in poorer nations, including India, are suspect.

If 5 percent of the medicines from a nation do not work, one would expect governments, or at least aid and health groups, to try and do something about it. But as we saw with the USP cover-up, many are more interested in preserving the cheap price of medicines than being sure that they work.

For example, one of the subsets of my medicine data was subjected to far more detailed analyses. And this subset includes medicines approved by WHO—in other words, the medicines were considered acceptable for donor procurement. Most of these medicines are made by large Indian companies.

In 2012 a few experts on my team wrote a paper analyzing these products. The results of the paper were not startling; however, the treatment of the original authors of the paper, even by people who have no direct connection to WHO, was.

In that study, 104 WHO-approved antimalarial medicines were procured from three West African nations—Ghana, Nigeria, and Togo. Eight (7.7 percent) of them were underdosed, the results published in a peer-reviewed scientific journal. Such a result is not surprising, as other papers with unapproved products showed far worse results (often 25–35 percent of...
the sample failing quality control).\(^{42}\) However, for WHO it was something of an embarrassment.

The detailed content analysis was done by Harparkash Kaur and her team at the London School of Hygiene and Tropical Medicine (LSHTM). Kaur was also part of a larger evaluation being undertaken by the LSHTM (and partner labs in other nations) on antimalarials. She was internally criticized by LSHTM management for assisting us, and pressure was applied by the WHO malaria department as well. In the end Kaur and the coauthors withdrew from the publication, and since the scientists who had done most of the analysis were no longer on the paper, the Associated Press, which had been due to cover the paper, declined to cover the results.\(^{43}\) WHO pressure therefore had worked to muzzle the findings.

Since our concern was potential threats to patients from poor-quality medicines, the authors sent the remaining samples from the failing batches to the WHO Prequalification of Medicines (PQ) Programme for analysis. WHO failed to confirm that they had analyzed the products we sent them. However, subsequently the WHO PQ Programme posted a statement on its website (since removed) to indicate that all batches of medicine were fine, after consulting with the companies that manufactured the medicines.

Of course WHO, and regulators like the FDA, must maintain relationships with manufacturers and seek clarifications when discussing their alleged quality problems. However, to rely on manufacturer veracity to identify problems of alleged substandard production at their facilities creates a conflict of interest to say the least. Fortune eloquently described the lengths of deception large companies can employ.\(^{44}\) Since WHO appears never to do postmarket surveillance, simply ignoring our work is risky for patients.

Frankly the WHO approval process is arguably valueless. In our research, products made by large Indian companies, those with annual revenues over $1 billion, failed approximately 2 percent of the time, whereas smaller companies failed over 9 percent of the time. Simply picking large companies would do much of what WHO claims to do in its assessments. In a subsequent analysis of more WHO-approved products, we found that, as expected, they performed better than unapproved products (made by smaller companies), but quality was not uniformly good.

Given that all the WHO-approved failing products contain at least 50 percent of active ingredients, they might work adequately in patients and cause no ill effect. However, there is also the chance that they would fail or increase population-level resistance. (Medicines with no active ingredients, such as falsified medicines, are far less likely to drive resistance.) As a result, occasional postmarket surveillance of products on the market and sanctioning of manufacturers breaking reporting rules is likely to keep them honest enough that clinical failure remains low and resistance pressure is limited.

Assuming our data are broadly accurate and WHO-approved products are far better than non-WHO-approved, locally registered products, which themselves are better than unregistered products, encouraging more patients to access WHO-approved medicines will on balance increase positive clinical outcomes and likely also lower resistance pressure.

However, there is a further caveat to this analysis. In 2013 Harvard Medical School scientist Preston Mason presented a study at a cardiology conference, which highlighted that many versions of the drug atorvastatin contained an impurity that undermined, either partially or totally, the cholesterol-lowering impact of the medicine.\(^{45}\) These medicines, widely considered to be generic medicines, were available in numerous countries, notably India and China, and several of them were made by firms that have either some or multiple PQ products. Are such impurities confined to atorvastatin, or could they apply to other medicines (some PQ) made by the same companies? We do not know.

Incidentally, none of the products approved by the FDA that Mason tested had any content or impurity problems. And to be clear, an impurity that prevents correct release of the drug may lead to the kinds of problems with underdosed medicines (clinical failure and resistance).

So while WHO approval of Indian medicines is likely beneficial for both clinical outcomes and limiting resistance, that may not always be true, and it may not be sustained over time. As shown by the
experiences of Ranbaxy’s whistle-blower and our own research team, where WHO entirely ignored evidence respectively of wrongdoing and poor quality, and Mason’s research finding of impurity flaws in WHO-approved medicines, under a worst-case scenario, WHO products might both fail patients and drive resistance. What is most worrying is that, presented with problems, WHO is not transparent and is loathe to criticize member states. So if the worst case were to happen, it is unlikely to be found by WHO. If WHO will not act, then what about the government of India?

Antibiotic Resistance

Complacency over Indian drug quality may manifest itself in antimicrobial drug resistance. Drug resistance is a natural phenomenon. Ever since the first penicillin was prescribed, bacteria have naturally selected for strains that resisted it. But natural resistance is aided by some especially poor practices.

The most egregious are prescribing antibiotics to those with viruses. Doctors often do not know for sure why a patient may be sick but suspect a virus. But they will prescribe antibiotics anyway—in some cases to get the patient out the door, in others to get kickbacks from drug sellers.

The second is patient noncompliance. The problem is the same the world over: A patient starts to feel better and stops taking the entire dose of the medicine. Dosing is designed to ensure the bacteria are flushed from our systems, and underdosing lowers the odds of all the bacteria being killed off.

But there is another type of underdosing, in which patient and doctor are not to blame—and that is the underdosing that results from poor medicine manufacture. It is important to understand why India is critically relevant in this practice.

The most obvious reason is that if antibiotics are cheap enough, they will be deployed against bacteria that thrive in unhygienic environments, which means that resistant strains are more likely to thrive and, crucially, pass plasmids between strains. A plasmid is a small DNA molecule that is physically separate from, and can replicate independently of, chromosomal DNA in a cell. Plasmids carry genes that may benefit the organism’s survival (e.g., antibiotic resistance) and can frequently be transmitted from one bacterium to another (even of another species) via horizontal gene transfer.

The New Delhi Drug Resistant Pneumonia.

New Delhi Metallo-beta-lactamase-1 (NDM-1) is an enzyme that makes bacteria resistant to beta-lactam antibiotics, such as carbapenems. Carbapenems are important antibiotics, and strains resistant to them are often called “superbugs.” They were developed to overcome beta-lactamase enzymes; however, NDM-1 is a carbapenamase beta-lactamase, carried by the blaNDM-1 gene. NDM-1 was first detected in a Swedish patient of Indian origin with Klebsiella pneumoniae in 2008 but was subsequently discovered in bacteria in India, Pakistan, the US, the UK, Japan, and Canada. The original patient was unsuccessfully treated in a New Delhi hospital, and the NDM-1 problem was discovered on the patient’s repatriation to Sweden. The authors of the original study concluded that the new resistant mechanism “clearly arose in India, but there are few data arising from India to suggest how widespread it is."

In the August 2010 issue of Lancet Infectious Diseases, a multinational team of researchers examined the emergence and spread of bacteria carrying the blaNDM-1 gene on plasmids. A total of 170 cases were found, of which most were in India. The following month, analysis of drinking water and seepage in Delhi found that just over a quarter of seepage samples (51 of 171) and 4 percent (continued on the next page)
**Does the Indian Government Care?** I am often asked why the Indian government does not act against its industry. Doesn’t the government care about these problems? I usually answer that the Indian government cares a lot about the Indian industry; it just does not care that much about health. As already noted, the government of India spends little on health, but it cares about the dollars earned by and reputation of its drug industry, one of India’s greatest exporters. The Indian government defends its industry—perhaps at any cost.

Three years ago my team analyzed a subset of 1,470 samples of antibiotics and tuberculosis medicines that were ostensibly “made in India,” as per the labeling on the package.\(^5\) We focused on these drugs because broad-spectrum antibiotics and specialized tuberculosis medicines in solid oral form are among the most commonly used in all developing countries. We found that more than 7 percent were substandard. Moreover, drugs purchased from Africa were more likely to fail than the same type of drugs sold in India or outside Africa.

We debated the causes of this effect at length, but the most likely explanation for the finding is that some Indian manufacturers intentionally export inferior products to Africa. This could happen because African countries are typically poorer, have a less educated population, and do not function well in regulating drug quality.\(^5\)

Our findings were published in a working paper by the National Bureau of Economic Research (NBER) in September 2014. We did not expect the Indian government or industry to be happy with our findings. And given that we launched the paper at the

(continued from the previous page)
of drinking-water samples (2 of 50) contained bacteria with the blaNDM-1 gene, according to *Lancet Infectious Diseases*."\(^4\)

This perfectly illustrates the problem for drug deployment in India. With a lot of the water in the region being contaminated and with 4 percent of the drinking-water samples able to spread resistance across myriad bacteria and millions of people, the chances of further resistance developing is not just inevitable but imminent.

And that is why the Indian government’s response was quintessentially disappointing. Rather than take head on the concerns, the Health Ministry spent most of its efforts claiming that calling NDM-1 after New Delhi was “unfair.” Other politicians went further, claiming that it was “malicious propaganda” and blaming multinational corporations.

At least an editorial in the March 2010 issue of the *Journal of Association of Physicians of India* blamed Indian health systems and said Indian doctors have “not yet taken the issue of antibiotic resistance seriously,” noting little control over the prescription of antibiotics by doctors and even pharmacists.\(^4\)

Unfortunately the Lancet’s editor, Richard Horton, furthered India’s cause by saying that naming NDM-1 after New Delhi was an error.\(^5\) This deflected action allows India politicians to ignore the problems, whatever the name of the superbug.

**Carbapenem Availability and Quality.** Watching this process move forward made me interested to see how available carbapenems were in Delhi pharmacies. Is access to the vital carbapenem antibiotic likely to be driving resistance?

My research team decided to assess what carbapenems were on sale in Indian pharmacies and then sample a subset of them for which we had good reference samples. The subset chosen was the popular meropenem group. The first meropenem was granted approval by the FDA in 1996 and was developed by Japanese pharma company Sumitomo Dainippon Pharma.

Whereas most antibiotics in India cost around $1–$2 per treatment pack, for meropenems it is at least an order of magnitude larger, median price being (roughly) $18–$20. Ciprofloxacin and erythromycin were always available without prescription in every pharmacy from which we sampled,
time of the visit of newly elected Indian Prime Minister Narendra Modi to Washington, DC, it was bound to cause some consternation. Yet the response from the Indian Commerce Department’s India Brand Equity Foundation (IBEF) was ludicrous. The IBEF published a press release demanding that the Indian government sue the authors of the NBER paper for defamation—for good measure they also wanted AEI (my employer) and possibly even the NBER to join the suit.53 SpicyIP, one of India’s leading legal blogs, weighed in, critiquing our paper and lambasting the Indian government for its threat to sue, since it has little standing, probably no jurisdiction, and absolutely no case.54

When we looked into the issue, we realized that criminal defamation prosecutions exist in India, carrying a two-year jail sentence. When Modi ran the state of Gujarat, his administration used criminal defamation prosecutions to silence political opponents, and in many cases they appear to have worked. But from all the media coverage in India, there was not a shred of self-reflection. Indeed, the obvious indig­nation of many well-educated Indians made me think that there could well be folks in the Indian government and even Indian industry that have absolutely no idea of the problems its industry has in drug production.

Now three years after the NBER paper was published, cooler heads have obviously prevailed, or at least the Indian officials have failed to find me and my coauthors to serve papers of the suit or prosecution against us. In reality the Indian government is really just hoping the embarrassment will disappear, which is the way Indian government handles most issues it does not like. As Mihir Sharma, an Indian policy expert, says, “most politicians have plumped for denial, ‘the one form of intellectual argument we have mastered.’”55

(continued from the previous page)

whereas more than half of the pharmacies asked for prescriptions for meropenems. The majority of these, though, actually provided the samples when prescriptions were not presented.

Of the 300 pharmacies approached, 220 had meropenems on sale. Of these, 44 percent (97 pharmacies) supplied the meropenems without asking for a prescription. Fifty-six percent (123 pharmacies) asked for prescriptions for meropenems, but when none was forthcoming, 62 percent of these pharmacies (76 pharmacies) supplied it. So in all, 173 of 220 pharmacies (78 percent) that had meropenems provided them.

All in all, we ended up with 163 samples of meropenems to test. Ten samples expired before they could be tested, which, given that they were tested within 60 days of procurement, is perhaps informative of the supply chain and how close some of these samples were to expiration when given to a potential patient.

Of the samples we tested, 158 passed basic assay test (97 percent), with one having only 45 percent of claimed ingredients, and three others being border­line at about 73, 75, and 77 percent of concentration, respectively. One sample had no active ingredient at all and was assumed to be a fake. That means four samples of 162, or 2.5 percent, were underdosed and hence could add to resistance.

The widespread inappropriate availability of meropenems is potentially worrisome. As affluence increases in India and existing antibiotics lose efficacy, demand for these second-line treatments, even at tenfold the cost of first-line therapies, will only increase.

And it is wishful thinking to hope that only 2.5 percent of the sample is of dubious quality. Without larger budgets, we could not conduct more detailed quality assessments. Tests for poor solubility, or impurities that undermine performance, were not conducted, and neither were any bioequivalence studies on patients. Our finding of 2.5 percent is very much a baseline figure.

Given anecdotal reports from three local doctors of inconsistent performance of some carbapenems, the overt problem of resistance is only the tip of the iceberg.
Win-Win Solutions in the Fight Against HIV.

While I have documented much bad behavior and doom and gloom in Indian medicine, one Western company has stood out in trying to overcome IP and quality issues by partnering with Indian companies. Its approach shows a way through the morass.

The rhetorical war over access to pharmaceuticals in poor countries admits to no middle ground. On one side are public health activists, health officials, and producers in developing countries, who see any attempt to price drugs significantly above their manufacturing costs as an outrage. WHO concurs: “In many countries, patents hamper the public’s access to life-saving medicines—in other words, profits are being put before public health.”56

While governments have failed to chart a way forward in high-profile negotiations, drug producers are recognizing that solutions that increase medical access without sacrificing IP protection really are possible. In fact, a pathbreaking deal between California-based Gilead Sciences and Indian generic drugmakers offers a model for how it can be done.

Debates over IP protection for drugs occur in many bodies worldwide, most of which have a dog in the fight. But since its inception in 1994, the WTO has been the primary battleground. The WTO’s founding charter details members’ responsibility to protect IP rights in TRIPS. Many WTO signatories, notably India, initially offered no pharmaceutical product patent protection, and so they negotiated a transition period until 2005 to establish product patents.57

Some health activists and developing country officials protested that TRIPS undermined nations’ ability to intervene in domestic health emergencies. This led to the 2001 Doha Declaration on TRIPS and Public Health, which “affirmed the sovereign right of governments to take measures to protect public health.”58 Two years later the WTO went a step further, allowing developing countries lacking manufacturing capability to bestow their emergency patent exemption on another country. Pharmaceutical companies in the designated country could then sell relevant drugs to the country in need.59 This resulted in quality and safety issues largely being removed from WTO discussions and separated from IP. Unfortunately, India blocks most efforts in other multilateral agencies, such as WHO, to combat substandard and fake pharmaceuticals. Until there is a real public health attempt to combat poor-quality medications, the WTO is right to continue to show an interest in how lack of IP protection and poor-quality products are linked.

Meanwhile, health activists, pharmaceutical companies, and governments shout the virtues of their positions past each other. Rather than addressing its own failure to enforce TRIPS, India (among other countries) focuses on the risks of strong IP rights enforcement. India’s patent office and courts have seemingly bowed to pressure from domestic producers to deny patent protection to several deserving oncology products, including Novartis’ Glivec and
Roche’s Tarceva, and HIV products, including Gilead’s Viread.60

While the bitterest fights between drug companies and activists have been over HIV drug access, it is also the arena in which recognizing the political realities has led to successful conflict resolution.

Back in 2010, Gilead’s Viread (generically, tenofovir disoproxil fumarate, or TDF) was arguably the best HIV drug available, but, as mentioned earlier, it was denied a patent in India in 2008. Nonetheless, Gilead continued to negotiate deals with Indian companies to make TDF. The model is simple: Gilead retains its patent rights in rich countries but provides technical assistance in making TDF to be sold in poorer countries in return for a 5 percent royalty. Gilead’s most successful Indian partner is Matrix Laboratories. Over the past six years, Matrix has sold far more TDF than Gilead, producing treatments for more than a million patients in more than 36 countries, mostly in Africa. Matrix does not need Gilead’s approval to make and sell TDF.61 Why, then, did it agree to pay royalties to the American company?

Gilead’s manufacturing know-how, plus assistance with quality control, allowed Matrix to get tentative approval from the US FDA to market TDF in just five months. And even after paying the modest royalty, its costs were lower than those of competitors who chose to go it alone on TDF. Matrix will also benefit from any future refinements of Gilead’s technology.

Gilead’s approach will not resolve all drug IP disputes between India and the West. But it certainly offers a path for Western companies to expand access to medicines without threatening their IP claims—which is the stated aim of many of these companies. There is even a little money in it for the companies, and there should be more as living standards rise in developing countries.

The only sticking point in deals like Gilead’s (and others that follow) is quality. As Gregg Alton, general counsel of Gilead, alluded to at a talk at AEI in 2013, the quality of the drugs made by the Indian generics companies is not identical, “just good enough.”62 But is it always?

Last month Gilead announced a new deal by submitting its new HIV medicine to a patent pool, where generic manufacturers can bargain for the right to produce drugs still under patent protection. That deal includes a production agreement with Sun Pharma.63 No doubt initial production will be done in good conditions, but one wonders whether the Halol plant will be used, given all the paper problems with this plant. Only time will tell. The decision by Gilead is still the correct one, but who will watch out for quality?

**Policy Options**

As established above, the rapid rise of pharmaceutical manufacturing in India was not matched by enhanced domestic laws and rules required for the modern drug-production environment. This error was compounded by limited oversight and funding of regulators. The result today is a flourishing of substandard drug producers, the only effective oversight coming in recent years from regulatory agencies in importing countries, such as the US FDA and European national and supranational agencies.

Yet problems persist because many Indians’ automatic reaction to criticism of quality standards is to dismiss it as a veiled attempt by foreigners to “keep India down.” This narrative is disappointingly adopted by most Western health advocates who almost never criticize quality problems, seemingly accepting failings in return for low prices. They do not want to be seen supporting brand-name drug giants—and they oppose big pharma on IP grounds and do not want confusing mixed messages to their supporters inside and outside politically active locations, especially US Congress.

Repeated infractions of quality control by Indian companies, including some serious enough to be successfully prosecuted as felonies in the United States, has led to increasing distrust of Indian products by patients and doctors in the US. Physicians such as Harry Lever, a senior cardiologist at the Cleveland Clinic in Ohio, have been reporting anecdotal evidence about the quality and batch-to-batch variability in generic drugs manufactured in India, routinely switching patients from Indian generics to other generics or brands to ensure proper therapeutic effect.64 Independent data back up Lever’s concerns.
Collaboration between Indian and US officials seems warranted, given the inferior quality of some Indian medicines and the likelihood that some are exported from India. Unfortunately, most recent public discussions about medicines between the two countries have revolved around India’s IP system and, as the US sees it, its lack of enforcement. With such heated debate, it has been tough for cool heads to prevail. So it was a good move by former FDA Commissioner Margert Hamburg to visit India in 2014. The results of the visit, however, were insignificant.

Public health is not a priority for the Indian government, which spends far less per capita than Brazil or China and vastly lower amounts than Western nations.

Indian officials asked that the US FDA provide advance notice and allow their inspectors to “shadow” the US FDA when inspecting manufacturing facilities in India, under the pretext of observing how the FDA conducts inspections and enforces its standards. FDA insiders tell me that they welcome strengthened communication between US and India. Increasing dialogue is certainly warranted, especially when a large majority of finished dosage forms and active ingredients for the US market are sourced from Indian manufacturers, but the main reason for the Indian generic industry’s problems is not lack of inspection competence of its regulator. There are more fundamental issues that need to be addressed.

Of course there probably are trustworthy folks at the CDSCO, but its track record makes me wonder if the FDA inspection playbook should be made freely available to its inspectors. After all, the FDA might end up giving a lesson on how to spot bad medicines and fraudulent manufacturing practices to those who may in turn pass this information on to the very companies that the FDA wants to inspect. FDA inspection plans would be worth huge sums of money to the pharmaceutical companies, which know only too well that coming out on the losing end of an FDA inspection is a lot more expensive than the average bribe paid to the CDSCO official.

India has to want to change. And the FDA has to realize that it is engaging with a highly politicized organization that does the bidding of powerful interests in the Indian pharma industry and where a culture of sensible, evenhanded regulation does not exist. Before helping the CDSCO, the FDA must ensure it has a commitment from the Indian government to take drug quality seriously.

What India needs is a culture change, so that sloppy manufacturing practices are not ignored from the top down. Public health is not a priority for the Indian government, which spends far less per capita than Brazil or China and vastly lower amounts than Western nations. Similarly, drug regulation is not taken seriously by India’s government and specifically India’s cabinet. It is seen as a lowly, unimportant portfolio and funded accordingly.

Changes Required at the CDSCO.\textsuperscript{65} The CDSCO needs to be run by a qualified, trained public health individual with impeccable credibility, not a political appointee, as is currently the case. It needs someone who had no part in the history of the Indian regulator, someone who can be hired from outside of India, like the governor of the Reserve Bank of India can. If the
UK can appoint a central banker from Canada, or Israel can pick a capable fellow from the US, then surely India can look for overseas talent to head the CDSCO.

The organization needs to have a free hand in implementing good public health policies away from vested commercial interests. As recent reports indicate, administrative officials (e.g., Keshav Desiraju) are routinely transferred at the whim and fancy of their political bosses and vested interests. How does one expect to implement a consistent policy if the system is prone to such influence?

The position of the head of the CDSCO needs to be at the ministerial level so that cabinet meetings on drug policy are not dominated by the Commerce department, which routinely ignores quality concerns and promotes Indian business regardless of publicly acknowledged quality-related issues. Despite high-profile prosecution of Indian companies by the US FDA and British authorities during this past year, there has been no visible accountability for these companies in India. Rather, most communication from the ministry decries Western oversight as Western propaganda aimed at hurting Indian pharmaceutical companies.

It is disappointing that, despite the largest settlement of its kind for a India-based pharma company, neither the CDSCO nor the Ministry of Health has found it important to contact the whistle-blower in the Ranbaxy case to better understand what led to the company pleading guilty to seven felony counts in a US court.

To demonstrate its seriousness about public health, the government of India should commission an audit by the comptroller and auditor general of the CDSCO (equivalent to the Office of the Inspector General in the US). The result of this time-bound audit needs to be publicly debated and its recommendations taken seriously by India’s cabinet. This will go a long way to remediate the image of the CDSCO as a corrupt and incompetent organization responsible for public health of more than a billion people in India.

What Should the FDA Do Differently? Before the FDA opens up its inspections dossiers, the CDSCO should show the US FDA how it inspects Indian facilities today and ensures quality medicines for Indian patients. Much has been said of the differing standards for good manufacturing practices between the two countries. “If I have to follow U.S. standards in inspecting facilities supplying to the Indian market,” G. N. Singh, India’s top drug regulator, said in an interview with an Indian newspaper, “we will have to shut almost all of those.”

Training is an investment that the US FDA can and should make, but it must first ensure that it has a trusted and honest partner that wants to be trained.

So it is important to see how the CDSCO enforces its own standards and what the outcome is when the inspectors from the US FDA tag along. If they did this for a year, trust could be built up before exposing what the FDA knows and does. Trust may not be easy to attain, since Singh went on to say: “We don’t recognize and are not bound by what the U.S. is doing and is inspecting. The FDA may regulate its country, but it can’t regulate India on how India has to behave or how to deliver.”

Even when the US FDA is ready to share inspection plans, the outcome of such inspections ought to be monitored closely to see if any undue influence or warnings were provided to the manufacturer that resulted in a more favorable outcome. These data ought to be provided publicly in the US FDA annual report.

Finally, there has to be an exit strategy in the proposed shadowing plan if the data demonstrate that the CDSCO has not changed its behavior and continues to collude with Indian drug companies. Maintaining
foreign operations is expensive. The US FDA now has 19 staff at its India office. An ongoing commitment to maintain an inspectorate and staff just to ensure standards of quality for medicines manufactured for the US market is a subsidy provided to India by US taxpayers. This should not be an open-ended proposition.

A good example of an effective approach to international enforcement is what the US Federal Aviation Authority did a couple of years ago when it found safety oversight lacking in the operations of India-based air carriers. It downgraded Indian aviation to category two, which limits the ability of India-based carriers to serve the US market.68 The onus to take corrective action is wholly on the Indian authorities, and the sooner they demonstrate their competence, the sooner their carriers get to expand their operations in the US. This approach provides a strong financial incentive to the Indian government and the industry to get its act together.

If India wants its companies to export to the US, then India should finance and equip its inspectors properly, so as to build a cadre of talented, professional inspectors. Training is an investment that the US FDA can and should make, but it must first ensure that it has a trusted and honest partner that wants to be trained. Providing advance notice of upcoming inspections and sharing inspection plans ahead of the visit at this time is foolhardy.

**What Should the US Congress Do?** There are no data today to help assess the impact of generic substitution in the US. Despite many anecdotal stories about lack of effect and worse in physician’s offices and on social media sites, no structured data exist today to validate the experience of these patients and physicians. Changes in prescription (generic-to-generic and generic-to-brand substitution) and their associated outcome should be reportable to the US FDA, much like how adverse events are now reported by health care professionals. This will allow the real impact of generic substitution in the US to be assessed. Legislation should be adopted to make this mandatory.

US Congress should further strengthen the FDA Safety and Innovation Act and impose severe penalties on any country that repeatedly allows exports of poor-quality medicine to the US. It should sunset funding for most foreign operations of the US FDA at a future date. That will both save money and give the Indian government a deadline to strengthen the CDSCO to a point where it ensures ongoing market access to the US. Ultimately it will improve safety for US patients. After all, we do not worry when we get on a plane in the United States, regardless of its carrier, but right now we cannot be sure of all medicines consumed in the US that come from overseas.

The situation will only worsen if the FDA office in India becomes captured by Indian pharma interests, as some Indians suggest is happening. Regulatory capture is a well-known phenomenon to economists and policy wonks. Agencies designed to oversee an industry can be co-opted by businessmen to further the aims of the industry rather than the public. We are also used to the revolving door of business and government, where staff from agencies leave their low-paying jobs to work at high-paying industry jobs to help comply with the regulations they either helped design or oversee.

One of the “skills” those new employees exhibit is knowing the people still at the agency, so that they can get them to answer questions, even if the extant agency staff do not actively help. Numerous former FDA employees have been advising Indian companies to help them comply with the regulations. There is nothing wrong with this in principle, but it can lead to ties that may become too close.

When an agency is operating overseas and is captured by a domestic industry there, regulatory capture is hard to spot and even harder to combat. Indian media are most interested in the financial reporting of Indian drug companies and will not publicly rock the boat on quality concerns with companies for fear of losing access to newsworthy financial updates. But they air their concerns privately all the time. So what is US FDA up to? Well, it is certainly promoting India as a location supporting quality.69

The latest Indian scandal shows that companies are deploying techniques, similar in intent, although far more dangerous, to what certain car companies did to fiddle emissions tests. They are adding chemicals to make it harder to spot failings of their products.70
From 2016, all FDA investigations have involved the local office and often employees of the CDSCO. As I suggested in 2014, providing the Indian regulator (considered corrupt by India’s own government) with the FDA playbook and specific information on investigations might lead to inappropriate warnings to local companies about impending investigations. When the US FDA cleared the Mohali facility for Sun Pharmaceuticals in early 2017, sources tell me that they had a lot of help from the local FDA office in Delhi. Is this true, and if so, what are the implications for Indian drug quality and the FDA’s role in finding future problems?

Other questions the new head of the agency, Scott Gottlieb, will have to address include what specifically the FDA expects from its collaboration with the CDSCO. Recall India’s own parliament called the CDSCO “corrupt.” Does the US FDA honestly expect the CDSCO to keep secret information given to them in confidence?

Frankly the only way to resolve the matter is to put someone beyond repute in the top FDA job in India. I can think of only one uniquely qualified person—Dinesh Thakur. Thakur runs a firm, Medassure, that assists companies in improving quality controls. But he is best known for being the Ranbaxy whistle-blower, who brought that company to account for its fraudulent production of substandard medicine, which led to seven felony counts in a US court and $500 million in fines and penalties in 2013. Thakur demonstrated through that decadelong farrago that he is fearless, honest, smart, and dedicated to ensuring high drug quality. For those who would break the rules, he is the one person they would not want in charge of the US FDA Indian office, and for that reason Scott Gottlieb should ask him to do it and staff it with folks he trusts.

The one thing that the FDA and Congress should do is change the way that generics are marketed in the US. As I have documented elsewhere, the FDA assumes the fiction that all generics are equal. This is convenient to the players in the distribution chain because it allows for interchangeability of generics. But some products are simply not as good, even in the US.

Right now the highest-quality generics cannot compete against cheaper but inferior versions because the only competition is price. The FDA and Congress are aiding inferior producers, all to assuage the demands of the distribution chain. Allowing producers of higher-quality products to differentiate themselves by pointing out the flaws in competitors would drive patients to better products, lowering the demand for inferior products and hopefully changing production practices, notably in India.

Conclusion

The rise in volume of the Indian pharmaceutical business has not been matched by quality production. The Indian government protects its industry at all costs, attacking the industry’s critics, but it does little for health domestically. Western health activists overlook quality flaws in Indian medicines because they want the cheapest medicines available for the poor and they despise Western industry—sometimes it is hard to tell which is their prime concern.

There is ample anecdotal evidence, independent data (including my own), and multimillion-dollar fines against Indian firms due to flaws, sometimes intentional, of Indian producers. And while the FDA and other domestic interests refuse to allow competition based on quality, Indian companies can get away with slack quality.

Change is required in both India, which must update its laws and improve its regulator, and the US, which must better identify and punish quality infractions. Patients must be able to buy the best generic drugs. Assuming all generics are the same quality—the biggest lie in the pharmaceutical market—must end.

About the Author

Roger Bate is a visiting scholar at AEI. He is an economist who researches international health policy, with a particular focus on tropical disease and substandard medicine. His most recent research work revolves around illicit trade in products with public health consequences.
Notes

7. Vijay Karan (former chief of police in Delhi), discussion with the author, March 3, 2010.
10. Anna Adjoa (obstetric nurse), discussion with the author, May 15, 2013.
11. Stephen Opuni (chief executive, Food and Drugs Authority), discussion with the author, May 16, 2013.
12. For media who wish to follow up on the companies whose products failed, the original report can be found on www.searchingforsafety.com.
27. Shetty, “Can Data from Indian Companies Be Trusted.”
31. Shetty, “Can Data from Indian Companies Be Trusted.”
33. Shetty, “Can Data from Indian Companies Be Trusted.”
34. Ibid.
35. Edney and Gokhale, “Indian Labs Deleted Drug Test Results, Documents Show.”
37. Shetty, “Can Data from Indian Companies Be Trusted.”
40. The subset had a slightly higher minilab fail rate—7.1 percent vs. 5.1 percent (in the larger sample)—partly because some of the products tested in more detail were suspicious in some way.
42. See www.searchingforsafety.net for examples.
44. Eban, “Dirty Medicine.” WHO is not equipped to follow up and investigate any wrongdoing from companies whose medicines it qualifies for the PQ list. Specifically, in the Ranbaxy case, the whistle-blower gave extensive documentation of wrongdoing to WHO, along with the US FDA. While the FDA eventually prosecuted the company for data falsification and manufacturing adulterated medicines, there is no public record of WHO ever acting on the information it received.
47. K. K. Kumarasamy et al., “Emergence of a New Antibiotic Resistance Mechanism in India, Pakistan, and the UK: A Molecular, Bio-


65. The 79th Report on the Drugs and Cosmetics (Amendment) Bill was presented to the Parliament in December 2013. The bill is said to contain “more comprehensive provisions for regulating clinical trials and exports and a revised composition of the Central Drugs Authority” and is intended to replace the Drugs and Cosmetics (Amendment) Bill, 2007. The new bill drew some criticism from representatives of SME Pharma Industries Confederation and Confederation of Indian Pharmaceutical Industry that centralization of drug licensing would be detrimental to the small and medium-scale pharmaceutical industry. Upon examination by the committee, several recommendations were made. The committee noted that since companies exporting drugs must comply with WHO GMP guidelines: “Hence no further regulation on the export of such drugs would be necessary. The Committee is of the view that if export of drugs is brought within the ambit of Drugs and Cosmetics Act/rules, it will severely affect Exports of Drugs and put domestic
pharma manufacturing units/exporters at serious disadvantage. The Committee therefore decided that the word ‘export’ may be omitted from this clause.” Further, the committee did not find the new composition of the Central Drugs Authority as proposed in the new bill to be acceptable. The committee recommended renaming the Central Drugs Authority as the Central Drugs Administration and proposed it answer to the Ministry of Health and Family Welfare. Parliament of India, Seventy-Ninth Report on the Drugs and Cosmetics (Amendment) Bill, 2013, December 18, 2013, http://www.prsindia.org/uploads/media/Drugs%20and%20Cosmetics/SCR-Drugs%20and%20Cosmetics.pdf.


