BottleOfLies

Author's Note

- The big exporting companies were making drugs of different quality for different markets. This meant that, even with the manufacturing shortcuts and sterility lapses in drugs bound for the EU and US markets, the drugs being sold into the developed markets, including India, were even worse

Prologue

- In the United States, FDA investigators simply showed up unannounced and stayed as long as was needed. But for overseas inspections - due to the complex logistics of getting visas and ensuring access to the plant - the FDA had chosen a different approach: to announce its inspections in advance
- The next day, Wockhardt's CEO held an emergency conference call with anxious investors to assure them that the company would bring the plant into compliance "in a month or two months maximum"

The Man Who Saw Further

- To go from the brand-name sector in the US to the generic one in India. By name, it was the same work - pharmaceutical research - but it was a seismic identity shift. The BMSes of the world invented. The Ranbaxys of the world duplicated. BMS did innovative science versus Ranbaxy's copycat engineering

The Gold Rush

- Best-selling drug of all time: Lipitor. Pfizer's vaunted cholesterol fighter was "the Sultan of Statins," as Wall Street analysts called it. The molecule itself, atorvastatin calcium, was a descendant of Nobel Prize-winning science. Coupled with Pfizer's marketing might, it had become the world's first $10 billion a year drug
- The first company to file its application, if approved, won the exclusive right to sell the generic for six months, before others joined in
- Prior to 1984, the Ranbaxys of the world had no way to challenge the Pfizers. There was no clear pathway for a generic drug to be approved in the US. Under FDA rules, even if a drug's patent had expired, generic drug companies were required to repeat extensive and costly clinical trials, even though the brand companies had already proven the safety and effectiveness of their drugs
- A crusading journalist at the time, Willian F. Haddad, who relished his role as an underdog, set out to change that. According to one of his colleagues, Haddad had an "extra gland that produces publicity instead of sweat," and he became a

media-savvy advocate for generics. Politically, the brand companies “had control of every avenue,” he recalled. So Haddad and his group walked the hallways of Congress, trying to make their argument to the few who would listen

- They pressured the Big Pharma CEOs into agreement and drafted a law that established a scientific pathway at the FDA to get generic drugs approved. It was the Abbreviated New Drug Application. No longer did generic drug companies have to prove the safety and effectiveness of their drugs from the ground up, as the branded companies did with costly long-term clinical trials. Instead, the companies could win FDA approval with limited tests to prove their drugs were bio-equivalent and performed similarly in the body
- What incentive was strong enough to justify the up-front costs of developing a generic version of a drug, the possibility of litigating against brand-name drug companies intent on defending their patents, and perhaps failing on both counts? The solution, called the “first-to-file” incentive, transformed the generic drug industry. It allowed the company that first filled its generic application with the FDA to reap a big reward: the right to sell its drug exclusively for six months at close to the brand-name price, before other generic competitors jumped in and the price plunged. Being first became the difference between making a fortune and making a living
- It was also clear from the outset that generic drug companies could make a huge profit. The day the bill went into effect, companies sent “tractor trailers full of ANDAs” to the FDA, recalled a former agency bureaucrat. “We got one thousand applications within the first month of the program.” The volume of bids - coupled with the potential jackpot of first-to-file - underscored that a generic drug factor was, as one of the FDA’s earliest generic drug chiefs, Dr. Marvin Seife, claimed, “a place where you put raw materials into a mixing vat, turned the spigot and out comes gold”
- In the run-up to a patent expiration date, it was not uncommon to see generic drug executives asleep in their cars in the FDA parking lot overnight in order to be first at the door when the building opened. Periodically, a tent city would sprout in the parking lot, with executives camping out for weeks at a time. Each company had a strategy for how to wait and how to be first. The FDA struggled to put a stop to the camping problem. In July 2013, the agency amended its rules so that any generics company that delivered its application on a certain set day could potentially share six months of exclusivity. Though shared exclusivity was less attractive, first-to-file remained the most lucrative opportunity for generic drug companies

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The Language of Quality

- The FDA’s investigators codify their findings in three ways: No Action Indicated (NAI) means that the plant passes muster; Voluntary Action Indicated (VAI) means that the plant is expected to correct deficiencies; and Official Action Indicated (OAI), the most serious designation, means that the plant has committed major violations and must take corrective actions or face penalties

- In 1995, the FDA imposed on Sherman Pharmaceuticals its most stringent penalty, a so-called Application Integrity Policy (AIP) - one of only about a dozen such restrictions imposed by the FDA. This placed the plant under strict monitoring and required it to prove that it was not committing fraud. Sherman Pharmaceuticals went out of business shortly afterward
- There is no doubt that in the world's estimation, the FDA is viewed as the gold standard. If you hold its regulators up against those from most other countries, it's like comparing "the latest model Boeing to an old bicycle," said a senior health specialist for the World Bank
- Part of the FDA's vaunted reputation comes from its approach. It does not just regulate with a checklist or scrutinize the final product. Instead, it employs a complex, risk-based system and scrutinizes the manufacturing process. Under FDA standards, if the process is compromised, the product is considered compromised too
- The process, known as "process validation," gained currency in the late 1980s. The data from each manufacturing step became the essential road map. The acronym ALCOA stipulated that data had to be "attributable, legible, contemporaneously recorded, original or a true copy, and accurate." As Kevin Kolar, formerly Mylan's VP of Technical Support, explained, a finished drug cannot be separated from the data created in the process of making it. "One without the other is not a product… If it's not documented, it didn't happen. Meticulous attention to detail. That's your business, your entire business"

Red Flags

- In the United States, it could cost a minimum of $3 million to develop each generic drug. The cost in India could be about half of that, since labor was so much cheaper

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Freedom Fighters

- Yuku left to study Chemistry at eighteen and earned his PhD by the time he was twenty three
- The 1970 Indian Patents Act made it legal to copy an existing molecule, but illegal to copy the process by which it was made. This gave India's chemists freedom to remake existing drugs so long as they altered the steps to formulate them. The law created fierce antagonism between India's generic drug makers and the multinational brand-name drug companies, many of which left the Indian market
- During License Raj, India's antiquated business regime in which the government set every quota and dispensed every permit and license. The system required high-level connections and wads of rupees, not just to get licenses but to block the licenses of competitors

One Dollar A Day

- As GlaxoSmithKline's CEO Jean-Pierre Garnier declared of Cipla and the Indian generic companies at a 2001 health care forum, "They are pirates. That's about what they are. They have never done a day of research in their lives." Some Big Pharma accused Hamied of trying to grab market share in Africa, to which he responded: "I am accused of having an ulterior motive. *Of course* I have an ulterior motive: before I die, I want to do some good"
- For Big Pharma, PEPFAR was a nightmare scenario: a US taxpayer funded effort to spend billions on generics bound for Africa. Just days after Bush unveiled the plan, some CEOs of multi-national drug companies petitioned the White House to undo the commitment of the $1 a day cost
- Beyond the problem of cost, another question still loomed: quality. How could the West guarantee the quality of all AIDs drugs it was buying for Africa? The generics advocates turned to the WHO, which agreed to serve as an international clearinghouse for quality generics. It would inspect companies that wanted to sell AIDS drugs internationally and, if approved, would add those names to a prequalified list. But this solution didn't satisfy everyone. Suddenly, under Tobias's leadership, PEPFAR introduced a new requirement: any AIDS drugs being purchased for sale to Africa with US taxpayer dollars had to be approved by the USFDA. The requirement triggered an avalanche of criticism. To AIDS activists, this was the ultimate bait-and-switch. Most of the Indian companies had never gotten FDA approval for any of their drugs. Activists suspected that this was a needless safeguard whose real purpose was to funnel money to Big Pharma and keep out generic manufacturers. Finally, in the face of intense bipartisan pressure, a compromise emerged. The FDA created an accelerated review process for PEPFAR drugs, resulting in a perceived win for public health. Affordable generic drugs available in Africa would have the benefit of FDA review

A Clever Way of Doing Things

- Some in the industry claim that it costs about 25 percent more to follow the good manufacturing practices required for regulated markets like the United States. That leaves companies with difficult choices. What if a sterile mop costs $4 (far more than a regular one), and in a typical day you are supposed to use nine mops? What if your customers want a vaccine for 4 cents a dose but it costs 40 cents to make? But the central problem is the generic drug business model itself. How can you maintain quality when a brand-name pill that costs $14 one day is going to cost 4 cents as a generic the next day? This dynamic "doesn't motivate you to invest" in maintaining high manufacturing quality, as Malik himself acknowledged
- Brand companies often resort to "shenanigans" and "gaming tactics" to delay generic competition, as the exasperated FDA Commission Scott Gottlieb put it. They will erect a fortress of patents around their drugs, sometimes patenting each manufacturing step - even the time-release mechanism, if there is one. They may make small alterations to their drugs and declare them, to add years to their

patents, a move known as “ever-greening.” Rather than sell samples of their drugs, which generic makers need in order to study and reverse-engineer them, brand-name companies will withhold samples, which in 2018 led the FDA to begin publicly shaming the companies accused of such practices by posting their names on its website

- Brand-name companies must test new drugs on thousands of patients to prove that they are safe and effective. Generic companies have to prove only that their drug performs similarly in the body to the brand-name drug. To do this, they must test it on a few dozen healthy volunteers and map the concentration of the drug in their blood. The results yield a graph that contains the all-important bio-equivalence curve. The horizontal line reflects the time to maximum concentration (Tmax) of drug in the blood. The vertical line reflects the peak concentration (Cmax) of drug in the blood. Between these two axes lies the area under the curve (AUC). The test results must fall in that area to be deemed bio-equivalent

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The Assignment

- At a company like Bristol-Myers Squibb, the regulator affairs directors had absolute control over what was submitted to the FDA, and for good reason. When regulatory executives signed submissions, they were asserting the data was accurate. It was a criminal offense to make a false statement on a government record
- Testing drugs for India was just a waste of time, he explained, because no regulators ever looked at the data. So the regional representatives just invented the dossiers on their own and sent them to the Drug Controller General of India (DCGI). What was needed for the DCGI was not real data but good connections, which they had
- Every two batches of the same drug made by the same company at the same plant under the exact same conditions will have slight variations. Test results for a similar or copycat drug made by a different company with slightly different formula should look different

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The Global Cover-up

- In theory, the agency tried to inspect every facility making drug ingredients for the US market roughly every two years, whether the plant was in Maryland or Mumbai. But the FDA’s actual rate of inspections overseas was closer to once a decade, and the backlog of applications from foreign drug facilities was growing rapidly
- But the rules for overseas inspections were muddy at best. Seeking to avoid confrontations that might involve a foreign government and lead to an international incident, the FDA prioritized diplomacy over confrontation. It announced its visits to the plants weeks, even months, in advance, and relied on the companies to act as hosts and travel agents for its investigators, booking hotels and ground transportation

- Hyderabad is the bulk-drug capital of India

The Pharaoh of Pharma

- The bureaucrat's hands were tied by the agency's inexorable machinery: to keep approving drug applications almost no matter what

"Do Not Give To FDA"

- Fraud was typically limited and select - a rogue employee, a single incident, or a poorly managed plant. How could *everything* at a company be fraudulent?

Congress Wakes Up

- Within roughly fifteen years, the amount of pharmaceutical ingredients, by weight, that the US imported from China would grow by over 1700 percent, from roughly 5 million kilograms in 1992 to over 90 million kilograms by 2008. This meant that the FDA, which had struggled to regulate companies within driving distance of its headquarters, now had to regulate companies halfway across the globe. With the agency's oversight precarious at best, foreign drug supplies became "a string of ticking time bombs," as former FDA associate commissioner William Hubbard later told Congress
- A loophole in Chinese regulations allowed certain pharmaceutical plants to register as chemical plants, which made them subject to far less oversight

Solving For X

- The FDA was so understaffed, however, that "only a fraction" of "filthy" food was caught and stopped at the border, said Hubbard. The rest was "slipping through the net"

A Deep, Dark Well

- As Graedon scrutinized the FDA's standards for bio-equivalence and the data that companies had to submit, he found that generics were much less equivalent than commonly assumed. The FDA's statistical formula that defined bio-equivalence as a range - a generic drug's concentration in the blood could not fall below 80 percent or rise above 125 percent of the brand name's concentration, using a 90 percent confidence interval - still allowed for a potential outside range of 45 percent among generics labeled as being the same. Patients getting switched from one generic to another might be on the low end one day, the high end the next. The FDA allowed drug companies to use different additional ingredients, known as excipients, that could be of lower quality. Those differences could affect a drug's bio-availability, the amount of drug potentially absorbed into the bloodstream

- Typically, generic manufacturers test only the highest does, known as the “reference listed drug.” The FDA assumes that the lesser doses are proportional and will behave similarly in the body. But in the case of Budeprion XL, the higher 300 mg dose was never tested “because of the potential risk of seizures” in volunteers, the FDA explained

The Light Switch

- Typically, a compliant manufacturing plant will reject a certain percentage of drug batches for many different reasons. But in India, investigators rarely saw a rejected batch. Somehow, almost all of them passed. Plants were also missing documentation
- Exacting controls cost about 25% more, according to some industry estimates
- Most of the employees lived on one meal a day. In their daily lives, many lacked access to a toilet or running water. To Baker, it seemed ludicrous to expect them to walk into a sterile manufacturing plant and suddenly follow all the rules

Crashing Files

- So Bresch - the glamorous, stiletto-heel-wearing daughter of US senator Joe Manchin - began an unlikely campaign to tackle the inspection disparity. She sought to convince her colleagues and competitors to pay fees to the FDA in order to be inspected more. That seemed like a tall order. Why would any company part with money to place themselves under a great scrutiny? But Bresch had a convincing argument. The fees could go not just toward increasing inspections overseas, but also toward speeding up application reviews, thus reducing the notorious backlogs that slowed down approval. The result, the Generic Drug User Fee Amendment (GDUFA), was signed into law in January 2012. The achievement, largely credited to Bresch, enhanced Mylan’s reputation for being on the right side of the story. Ideally, GDUFA would allow the FDA to more effectively regulate a global industry, while also levelling the playing field for disadvantaged American companies, which faced far more scrutiny at their plants in the United States. The result could be higher-quality drugs everywhere, said Bresch: “I still am very hopeful and optimistic that we’re raising the bar across the world”
- But in fact, Mylan was changing, and not for the better, some of its employees believed. Internally, as Malik moved with laser-like focus to bring drugs to market, employees in both India and the United States began to experience a shift in the company. Malik and his deputies seemed to prize speed above all else, said several former employees. Those who insisted on adhering to the well-articulated rules of good manufacturing practices felt sidelined, said one senior executive who resigned. “When you’re rigid,” he said, “you’re tagged as being slow”
- Under Malik’s leadership, Mylan-India became a hothouse of productivity. Malik’s own compensation was based, in part, on the number of applications Mylan filed with global regulators. Year after year, he and his team exceeded targets. With their development pipeline full and their laboratories humming with favourable

data, they often filed dozens more applications than expected by the company. But employees - some of whom allegedly quit after being asked to tamper with data - were left to wonder: had Malik's handpicked team left behind their Ranbaxy training - or brought it to Mylan instead?

- Under Rajiv Malik's leadership, Mylan's research and development center in Hyderabad had become a hub for data fraud that had disseminated its methods of falsification throughout Mylan's India operations. The whistleblower alleged that people who now held key leadership positions at Mylan, among them former Ranbaxy employees, were using their skills at data manipulation
- "Honestly - I had supreme faith & trust in the agency's approach - towards bringing those to justice who commit fraud," he wrote. "However, I learn that Mylan's strategy of providing employment to FDA members has been working very well"
- Malik's team used an array of deceptive methods to hasten approval of critical products, he said. They did "what's needed" to make the development data pass and "managed" the manufacturing of the submission batches. They generated the bio-equivalence data by switching the samples, if necessary. "Wise people" prepared the submission packages to regulatory agencies. Post-approval manufacturing was "taken care" of by specialists. Global experts, held in esteem by regulatory agencies, were consulted to "bless" the packages, but given only partial information. All of these interventions served to "short-circuit" the timeline typically required to develop and manufacture a generic drug

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The Ultimate Testing Laboratory

- In a world of scarcity, Africa was saturated with Indian and Chinese made generic drugs that too often didn't work. Doctors throughout the continent had adjusted their medical treatment in response, sometimes doubling or tripling recommended does to produce a therapeutic effect. Many hospitals kept a stash of what they called "fancy drugs" - either brand-name drugs or higher quality generics - to treat patients who should have recovered after a round of treatment but didn't
- One reason he rarely saw a rejected batch in India was that, no matter how evidently defective the drug, there was always some world market where it could be sent
- Substandard drugs do not contain enough active ingredient to effectively treat sick patients. But they do contain enough to kill off the weakest microbes while leaving the strongest intact. These surviving microbes go on to reproduce, creating a new generation of pathogens capable of resisting even fully potent, properly made medicine
- Treating patients with drugs that contain a little bit of active ingredient is like "putting out fire with gasoline," said Raymond, former chief of party for the USP in Indonesia. From his vantage point in South east Asia, Raymond could see a clear correlation between regions with high volumes of substandard drugs and "hotspots" of drug resistance

Files Too Numerous To Count

- The CDSCO was the Indian equivalent of the FDA, and the downtrodden air of its headquarters seemed to reflect the accusation that had surrounded it for decades: that the CDSCO had done far more to protect India's drug companies from regulation than it had to protect Indian consumers from bad drugs. Forty years of national reports had excoriated India's drug regulators as inept, understaffed, and corrupt and called for the overhaul of the CDSCO. With the Indian market awash in poor-quality drugs, the reports had noted the agency's paralytic inertia, yawning staff vacancies, and missing files
- FDA wanted to approve more generic drug applications, reduce drug shortages, and show those numbers to Congress. Restricting companies and their drugs would have the opposite effect

Standing

- Thakur contacted the nongovernmental organizations that purchased medicine in bulk for the world's poorest patients: the Clinton Foundation, the Global Fund, the Gates Foundation, Doctors Without Borders. These organizations focused on the cost of medicine and the world's access to it, but in Thakur's view did not prioritize issues of quality in their purchasing. Thakur asked for meetings. Most did not respond. One operations officer at the Global Fund replied, and Thakur flew from New Delhi to Geneva at his own expense to meet him. There, he urged the Global Fund to add language to its purchasing contracts stating that medicine had to be of a certain quality
- Instead of serving as a check on the pharmaceutical sector, Indian regulators were serving as its Praetorian Guard. Even less surprising was that the GVK company's chairman, D. S. Brar, had been the managing director and CEO of Ranbaxy during its most feverish development, from 1999 through 2003. He had presided over the meeting in Boca Raton, when top company executives had decided to launch the company's dangerous Sotret drug onto the US market, despite knowing it was defective. Nonetheless, Brar, a titan of Indian industry, had emerged unscathed. He sat on corporate boards across the world from the Wall Street Investment firm Kohlberg Kravis Roberts to the Indian subsidiary of Suzuki, the Japanese car company

Epilogue

- The FDA's investigators had been trained for a different era, when the data printed out on paper was the only data that existed. The agency had not significantly rethought or overhauled its training program in decades. As one FDA consultant put it, "People are using brains from 1990 to do their thinking" today
- Most of the FDA's investigators who were sent to China did not speak the language. They couldn't read the manufacturing records. The FDA did not provide independent translators. Instead, the companies provided the translators who, more often than not, were company salesmen. Too frequently, FDA investigators

simply gave plants a pass, deeming them to be No Action Indicated because they had no way to tell otherwise

- Sometimes a group of companies pooled their resources and invested in the same “show” factory, so that different FDA inspectors returned to the same plant at different times, each one thinking they were inspecting a different facility
- In Baker’s view, only a critical mass of investigators who knew exactly where to look and what to look for could truly protect consumers and change the industry for good. In December 2015, at an hour long meeting with the acting FDA commissioner, Baker proposed a program for training the FDA’s investigators to detect data fraud
- From now on, for all routine inspections, the FDA would notify India’s companies in advance