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India's paradox – the largest drug exporter and the most isolationist drug industry

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The reach of the Indian pharmaceutical industry is enormous. India supplies a large and increasing amount of the generic drugs sold globally, and the country is home to over 150 drug manufacturing facilities approved by the US Food and Drug Administration[1]—including many run by multinational players. The value of pharmaceutical exports from India to the United States rose nearly 32 percent in 2012, to $4.2 billion.[2] India supplies nearly 40 percent of generic drugs and over-the-counter products as well as 10 percent of finished dosages used in the US.[3] Some of these products are very substantial: Ranbaxy, one of India's largest pharmaceutical companies, won the right to make the only generic version of Lipitor for sale to Americans when it was the world's best-selling drug with peak annual sales of over $12 billion.[4] India is one of the largest suppliers for the Internet market in western countries and is the dominant provider in most emerging markets, too.

Yet India is also failing to police its drug industry and putting human lives at risk around the world. Earlier this year, one of India's most aggressive export-oriented drug companies, Ranbaxy, pleaded guilty to criminal charges, which included falsifying clinical data and distributing adulterated drugs in the United States—crimes totally without precedent in the pharmaceutical industry, and for which it paid fines and settlements totaling half a billion dollars.[5] In our own studies of over 6,000 drug samples purchased from pharmacies and retailers across Africa and Asia, nearly half originated in India, many of which were substandard or even outright fake.[6,7,8,9,10,11] In certain states, such as Gujarat, Kerala or Tamil Nadu, the authorities have found hundreds of drug samples failing quality tests, and yet the number of persons arrested or drugs seized remains zero—clear proof that the authorities do not want to act.[12]

Perhaps the bitterest irony is that when Indian federal and state governments are

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reluctant to admit or address the Indian pharmaceutical industry's quality problems, the victims—who may get sick or die—are mostly Indian. Basically India's government is tolerating the harming of its own people. What's more one has to wonder whether India's low regulatory standards are causing drug resistance domestically and further afield too.

Dangerous or not, India's pharmaceutical industry continues to grow because of price. India is home to the cheapest drugs in the world. As Gregg Alton, Vice President at the US drug company Gilead explains, India has some of the "best process chemists in the world."[13] They reverse engineer existing products and often work out cheaper ways of making the same product. Gilead works with Indian companies to provide its breakthrough HIV drug, Tenofovir, at the lowest cost possible to patients in emerging markets. "They make it for half the cost we do," Alton says.[14]

Compared to its competitors, Gilead has taken a relaxed attitude to working in India. Most other western companies have been more combative in opposing India's protection of its domestic pharmaceutical industry. India has denied patents on many western products, when those same products were granted patents in myriad other jurisdictions. Oftentimes this leads to litigation, as when Roche sued—and lost—to enforce patent protection for one of its cancer drugs.[15] Gilead was also denied an Indian patent on Tenofovir, but, unlike most brand holders, has worked with Indian companies anyway. In turn, those companies have paid Gilead a royalty. The least discussed part of this arrangement is probably the most crucial one: Gilead assists Indian producers to maintain quality control in their manufacturing.

Such collaboration has historically been rare; western companies and western governments typically have frosty relationships with India, chiefly over its avoidance of patent protection. These are not straightforward disagreements: India often has had valid arguments in law, economics and public health to resist patenting. But India's forty-year history of patent battles and aggressive rhetoric now has led it to the dangerous and wrong position where, because it mistrusts the west, it ignores legitimate western concerns about the poor quality of Indian-made drugs and refuses to take action against corruption and fraud in India's drug regulatory establishment.

The extent of India's denial is almost Orwellian. Earlier this year, authorities in Jammu and Kashmir discovered that a very large number of patients in that state's most advanced hospital received fake "antibiotics" containing no active ingredient: many, possibly thousands, died.[16] The discovery triggered twin investigations by the federal government and the Doctors Association of Kashmir, both of which found dozens of poor quality medicine samples on the market. At first, the Jammu and Kashmir government quoted these grim findings, only to recant a few months later with the totally inconsistent statement that "only one case

of [a] spurious drug" had been found.[17] Plainly, the Jammu and Kashmir government could not have been telling the truth both times. The authorities' dishonesty appears motivated by a desire to sweep thousands of Indians' deaths under the carpet.

If the regulators were honest and diligent, then most drug quality problems of this kind would be simple to detect and resolve. If a manufacturing plant isn't hygienic or methodical, it is fairly easy to order it shut down until procedures improve. Old or broken equipment can be repaired or replaced; incompetent workers can be fired. Companies that do not do these things are playing defense and building a business model based on evasion rather than compliance with regulations—and at times government has encouraged them to do exactly that. For example, India's government in the past sought to obstruct western regulators' oversight of export-oriented drug manufacturers, by ruses such as delaying visas, or scheduling inspections ahead of time.

Those looking for a deeper explanation of why India's government covers-up for the weaknesses of its pharmaceutical industry have to consider not just profit, but also nationalism. India's generic pharmaceutical industry began when Dr K A Hamied in 1935 set up Chemical Industrial and Pharmaceutical Laboratories (Cipla) with the express purpose of making India self-sufficient in pharmaceuticals by making a positive virtue of patent-breaking. He succeeded, attained hero status and enjoyed government protection. After his death in 1972, his son, Dr Y K Hamied, carried on the family tradition and positioned Cipla as an Indian national champion. On his retirement earlier this year, the younger Dr Hamied was quoted as saying, "My only purpose in life today is how to get the 2005 patent bill revoked so that it suits India."[18]

India's main problem now is that nationalism has replaced health protection as the guiding principle of drug regulation. A clear example of this is found in India's drug price-capping measures. While these are intended to keep foreign companies out of the Indian market and to make essential medicines affordable to average Indians, in practice even India's local drug manufacturers have long complained that they cannot make drugs to the proper quality standard at the unrealistic prices offered by government contracts, never mind produce sufficient profit to enable research and development.[19] The government has therefore responded by exempting new drugs from the price controls for five years, if they are the result of an Indian innovation.[20] What began as a well-intentioned policy to serve Indians' health by keeping essential medicines affordable therefore has ended in an incoherent and dangerous policy jumble, where Indian companies succeed either by submitting to severe price controls that force them to compromise quality and harm Indian patients' health, or by innovating to escape the price controls so that they are free to overcharge Indian

patients exactly as foreign companies are said to do.

Meanwhile, the quality of drugs made for export in India is persistently unreliable – witness the string of actions taken by FDA and MHRA against imports to US and UK including issuing warning letters and import alerts to numerous Indian drug manufacturing facilities for companies such as Ranbaxy, Strides Arcolab Ltd. and Wockhardt.[21,22,23,24] The Ranbaxy fraud, mentioned earlier, is the worst episode to date.[25] Found guilty of criminal fraud and fined $500 million, it became clear that the previously highly-respected company routinely, systematically and callously, made substandard products, including HIV medicines supplied to African aid organisations, and faked safety reports.[26] While according to a recent news report the Indian Pharmaceutical Alliance has requested a dialogue with the FDA regarding recent concerns raised by the agency,[27] no action has yet been taken against Ranbaxy by Indian regulators. In fact, the Indian regulator has certified that the products manufactured and sold in India by Ranbaxy are safe and effective.[28]

This failing points to another Indian quirk, which does nothing to boost international confidence in India's ability to regulate the quality of drug exports: although there is a federal drug authority (CDSCO), export licences are granted by individual states, which jealously guard the revenue from fees generated. Indeed, drug regulators from importing countries (certainly the US FDA and the UK Medicines and Healthcare Products Regulatory Agency) are forced to engage directly with exporting states to ensure quality control, sending their own officers on secondment to Indian state regulators and running training programmes for Indian operators. This significantly increases the cost of importing 'cheap' generic drugs as Indian states effectively export the cost of regulation.

On the other hand, despite acknowledgement by the Indian Parliament about the lack of competence of the Indian regulator in two scathing reports,[29,30] one of which concluded, "India undoubtedly needs a strong, transparent, equitable, efficient and professionally managed drug regulatory system/authority urgently to meet global standards and ensure the confidence of the politicians, industry and the public at large that the health of the nation is well taken care of,"[31] precious little has been done to address the issue. The recent ruling by the Indian Supreme Court to suspend 157 clinical studies approved by the Indian regulator[32] doesn't inspire any confidence either in the scientific review or the decision making process at the CDSCO. India seems to want to continue its disjointed and seemingly corrupt regime which leads to the often asked question, can data from Indian companies be trusted?[33] The incredulous response of the Indian government in the wake of enforcements from the west reinforces the notion that there is little desire to fix the systemic problems that plague the regulatory framework in the country.

Regulators respond

Regulators are a conservative bunch: their priorities are set domestically, and most of their influence is at home, too. That worked when the pharmaceutical business was largely domestic, but as it has globalized, regulators have had a tough job to monitor and oversee the globalized aspects of a formerly domestic industry.

Personal communications with western national regulators leads us to believe that they have increasingly collaborated with each other over the past decade. They meet frequently to discuss problems, challenges and opportunities of joint interest. The formation of a European Medicines Agency has improved coordination within Europe. Australia and Japan have been regular participants on email fora and face-to-face meetings with their European colleagues over the past fifteen years. And in the past two years the Brazilians and Chinese (two nations which have fought intellectual property battles with the west) are being invited to these meetings and are becoming more heavily involved. In an increasingly collaborative world that is collectively formulating policy for access to quality, safe and effective medicines, the one significant country that remains outside the fold is India. [34]

A recent editorial in *The Hindu* concluded: "Until a deeper, institutional change takes place to break the nexus between drug companies and India's regulatory regime — a change that incorporates everything from surprise checks on manufacturing facilities to greater transparency in, and policing of, drug approvals processes and clinical trials — there is a strong likelihood that Indian consumers of drugs made by these companies have poison coursing through their veins."[35] Only a change of attitude within India will see India's important pharmaceutical industry reach the heights it undoubtedly can achieve. Regulators, pharmaceutical directors, trade associations and myriad health professionals, must demand greater accountability and performance. Funding additional inspection staff at CDSCO is a first vital step. CDSCO must also attract and hire qualified people in all other areas of drug safety and quality. History has shown that these functions have been staffed with bureaucrats with limited or no experience in administering public health policies. Leadership of this organization which has been found to be incompetent at best or colluding with vested interests at worst by no other than the Indian Parliament cries out for integrity and competence, as quoted in the Report submitted to the Rajya Sabha: "On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK."[36]

The response of the Indian government to the dysfunction of the CDSCO has been to establish an oversight board, comprising of more bureaucrats and a few medical professionals to oversee the regulatory body. This is hardly a lasting solution to the

continuing ad-hoc approach to solving a fundamental public health problem in India.[37] The will to nominate an empowered, qualified and experienced public health professional in the role of the Drug Controller General of India is the need of the hour.

Not that the CDSCO is alone in having problems. Manufacturing is overseen by the States, many of which have failed to enforce quality. CDSCO should be restructured so it has authority to oversee quality, superseding the power of the states. Harmonization of standards and procedures inline with international standards is an absolute must. The enforcement on adulterated drugs cannot be different in India just because good manufacturing practices are so laxly interpreted for Indian manufacturers. Ultimately the entire Indian regulatory structures must be more responsible for public health than protecting the Indian generic pharmaceutical industry. If this doesn't happen, India will lose business to rivals, notably China, as risk-averse westerners search for safe products over the coming decade.

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