Drugs:
Access or Innovation?

Actually, Both

BY ROGER BATE

Parties to the debate over the enforcement of pharmaceutical patents – and therefore the determination of how much new drugs will cost – are inclined to play hardball.

Public health campaigners, health officials in developing countries and their representatives in international organizations generally view any attempt to price drugs significantly above their manufacturing costs as an outrage, just another way Scrooge exploits Tiny Tim. The World Health Organization concurs: "In many countries, patents hamper the public's access to life-saving medicines – in other words, profits are being put before public health."

But the big pharmaceutical houses (and the governments that defend them) argue that creators of drugs must be allowed to set prices high enough to cover their research and development expenses and other overhead costs, which can cost hundreds of millions of dollars per drug. Far from being immoral, they assert, flexibility in pricing is in everyone's interest, enabling inventers to keep innovating. As Miles White, former chairman of the Pharmaceutical Research and Manufacturers Association of America, put it, "We must extend the benefits of innovation to those who need them; but, first, we must have that innovation. If we take away the fuel, the fire will soon burn out."

Although fights over cross-border intellectual property rights occur in a variety of international forums, the World Trade Organization, where the Agreement on Trade-Related Aspects of Intellectual Property Rights (Trips, for short), was hammered out, has been the primary battleground. The continuing debate has hardened both sides' positions, and negotiations have ground to a standstill. Even the provisions of Trips specifically carved out to

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provide space for compromise, like compulsory licensing to generic drug manufacturers in times of emergency, typically go unused. Indeed, a formal diplomatic fix for the profits-versus-access problem seems more remote than ever because the issue of pricing drugs has become entwined with the separate issue of how best to regulate the quality of drugs that cross borders.

Yet, while the rhetorical battles admit to no middle ground, the gulf is not as wide as it initially appears. First, according to researchers from the Royal Institute of International Affairs, most of the drugs that patients in poor countries need are not under patent. Thus, for most patients in most places, tougher enforcement of intellectual property rights would have little impact on drug access. Second, beneath the heated façade, cooler heads are prevailing. While governments have failed

to chart a way forward, drug producers are recognizing that it is possible to craft private solutions that increase access to drugs without compromising their property rights. A path breaking win-win deal between California-based Gilead Sciences and the Indian generic-drug maker Matrix offers a model for how this can be done.

THE STATE OF PLAY

Money talks – and in the home countries of the companies that own the lion's share of drug patents, pharmaceutical makers have no problem getting politicians and policymakers to sympathize with their position. In the legislative battle over Obamacare, for example, Big Pharma was able to brush aside efforts to open the border to cheaper imported drugs. By contrast, the World Health Assembly, the one-country, one-vote governing body of the World Health Organization, regularly proclaims the urgent need to increase drug access, demanding that intellectual property rights protection be relaxed. Although their demands haven't led to substantive policy changes, patentholders still see them as threatening.

Since its inception in 1994, the World Trade Organization has been the most important international arbiter of property rights in drugs, primarily because the Trips clause in the World Trade Organization's founding charter lays out all members' responsibility to protect intellectual property rights. Many middle- and low-income signatories to the World Trade Organization, notably India, did not initially recognize pharmaceutical-product patents; they were able to negotiate a transition period (lasting until 2005) during which they agreed to establish drug-product patent systems and credible means of enforcement. India has since graduated, but the transition period for 32 "least developed" countries (the euphemism of choice for really, really poor countries) was extended through 2015.

Some health campaigners and developing-country officials protested that Trips undermined sovereign nations' ability to intervene in domestic health emergencies – in particular, in infectious-disease epidemics. 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." Two years later, the WTO went a step further, allowing developing countries that lacked the technical capacity to manufacture drugs at home to transfer rights covered by the 2003 provisions to another country. Pharmaceutical companies in the designated producer country would then sell the relevant drugs to the country in need.

RWANDA, MEET CANADA

Trips thus allows governments to sidestep intellectual property rights protection in the face of emergencies. (For that matter, virtually every national patent system includes provisions that give the government the power to break a patentholder's exclusive rights to produce a drug and to license production by a competitor if doing so is plainly in the public interest.) But the Trips safety valves have rarely been used, both because the pharmaceutical industry has shown that it is prepared to fight each evocation of emergency powers on a case-by-case basis and because the World Bank looks askance at client states that resort to it.

In fact, the 2003 mechanism has been used only once, when Rwanda asked Canada to produce antiretroviral drugs for use against AIDS in 2008. Apotex, a Canadian generics maker, accepted the commission, manufacturing and shipping some seven million doses. But managing this transaction proved to be anything but simple. As a spokesman for Apotex noted,

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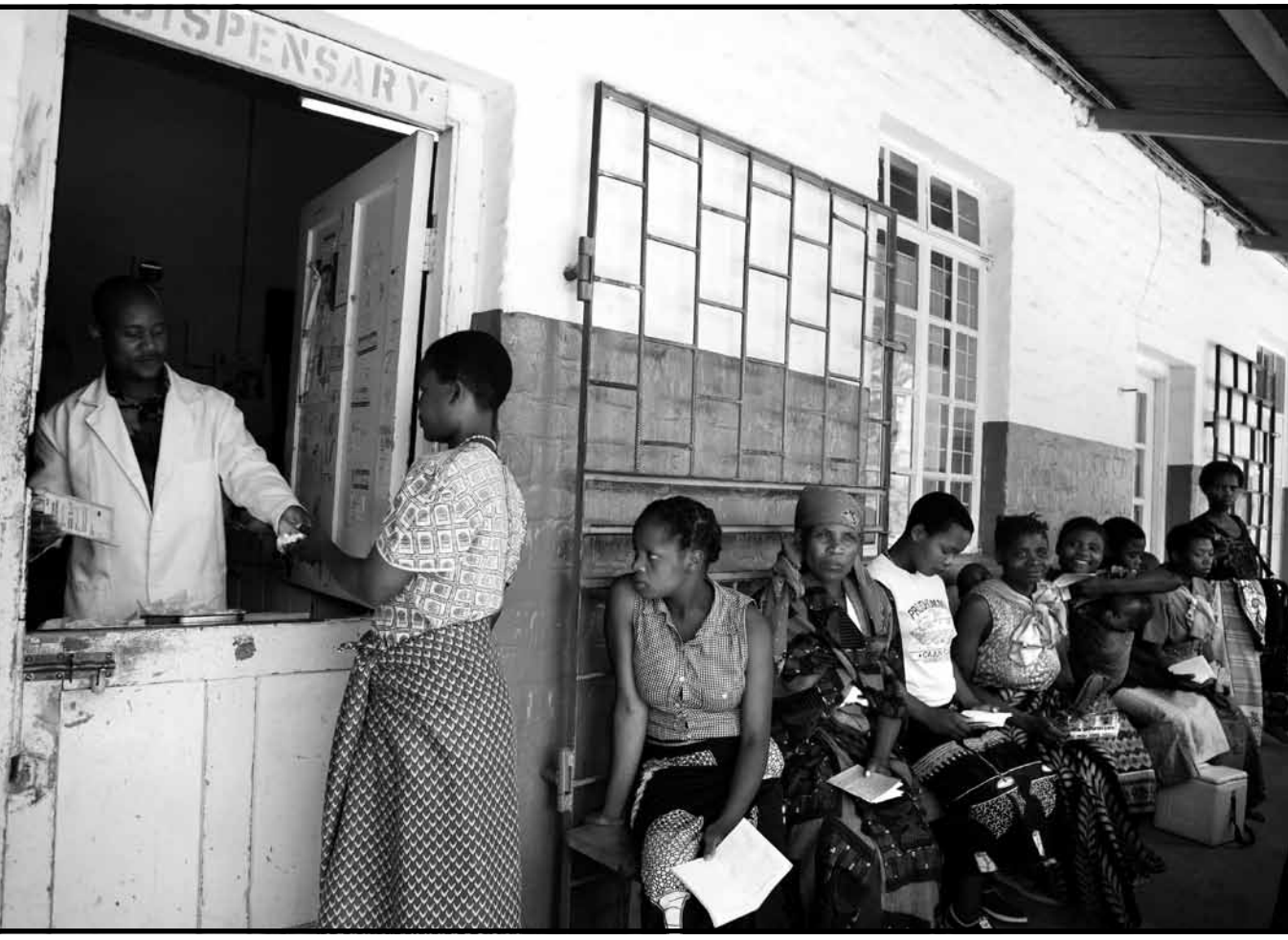

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"the biggest flaw is that we are asking the developing world to navigate the First World's legal nightmare." While Rwanda's business-savvy president, Paul Kagame, was able to map a course through the legal minefield, it has deterred other countries from trying.

STALLED NEGOTIATIONS AND DRUG QUALITY

International conflict over other intellectual property rights measures (notably trademark enforcement) are continuing and were stoked by the signing of the Anti-Counterfeiting Trade Agreement by most industrialized countries in October 2011. Although the agreement has not yet been formally ratified, India is worried that the strict patent protection that the agreement extends to participating countries will allow those countries to aim at exports by India's sophisticated generic drug manufacturing industry. Meanwhile, at the urging of Western member countries (including the United States), the World Trade Organization secretariat is considering ways in which intellectual property rights enforcement could raise the quality of drugs sold and how penalties could be used as deterrents when producer countries turn a blind eye to the issue. To no one's surprise, India led the charge to limit the World Trade Organization's intervention on the drug-quality issue at a Trips council meeting in the spring of 2011. New Delhi argued

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that intellectual property rights issues are "distinct from issues of quality and safety" and therefore not part of the Trips mandate.

India has a point; poor-quality pharmaceuticals do not necessarily violate intellectual property laws, while high-quality ones may well violate them. Poor-quality drugs come in three forms:

- Products that were legally and properly produced, but were stored improperly or used past their expiration date (i.e., degraded).
- Medicines that are unintentionally substandard due to negligence or corner-cutting by the manufacturer (i.e., substandard).
- Out-and-out fakes, whose producers lied about the drugs' contents or origin (in other words, falsified).

Degraded and substandard drugs are typically the consequence of a lack of manufacturing expertise or the failure to store products properly. These products do not violate intellectual property rights, but they are a menace to public health. Indeed, drugs that are substandard because they contain the correct ingredients in insufficient strength can pose an even greater danger than falsified products. They may not cure, but they often do contribute to drug resistance, which is a critical problem for antibiotics used against many infectious diseases, including tubercu-

losis and malaria. My own research in emerging markets, documented in my book, *Phake*, found that over half the drugs failing basic quality tests were either degraded or, more often, substandard.

Only the final category, falsified products, may constitute an intellectual property violation. Where the fakes imitate protected products, the legitimate producer can complain that the drugs are counterfeit. And, depending on the laws of the country in which the fakes are sold, their sale may bring civil suits or criminal charges, or both. So, in principle, India's position that the World Trade Organization should not become involved in quality-control issues is reasonable.

But India is not an honest broker here: the government also blocks most efforts by other multilateral agencies, like the World Health Organization, to combat substandard and fake pharmaceuticals. And with no concrete action against poor-quality products in other governmental forums, it makes pragmatic sense for the WTO to show an interest in the link between intellectual property rights protection and poor-quality products.

Though I have studied this subject closely for seven years, I am still not sure why India objects to policing fake and substandard products. Indian negotiators are plainly instructed to block measures that would undermine the profits of India's generics industry. But, on balance, inaction probably harms India's drug industry more than it helps, because inferior producers (both Indian and Chinese, which counterfeit Indian products), tarnish the reputation of the quality Indian producers and steal business from them.

I suspect that the explanation is inertia: India has long opposed the West's stance on pharmaceutical policy, and it is not about to change quickly. Meanwhile, health campaigners, pharmaceutical makers and Western governments shout the virtues of their positions past each other. Rather than addressing its own failure to enforce Trips, India (among other developing countries) focuses on the costs that strong enforcement of intellectual property rights would create for its generic producers – and, therefore, for impoverished patients.

India's patent office and courts have seemingly bowed to pressure from domestic producers to deny patent protection to several deserving oncology drugs, including Novartis' Glivec and Roche's Tarceva and HIV products, including Gilead's Viread. This pressure also likely influenced the Indian government's recent decision to grant India's first compulsory license to Natco Pharma to produce a generic form of Bayer AG's Nexavar, an anticancer drug that is still under patent protection. Such compulsory licenses can be particularly difficult for Western Pharma to swallow, since Indian law allows the government to revoke a drug patent outright if, after a meager two years under compulsory licensing, the government decides the market price is still too high for most Indians to pay.

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AN END RUN AROUND TRIPS

The bitterest fights between drug companies and their activist critics have been over HIV

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drug access. But, ironically, these conflicts have led to breakthroughs in manufacturing and distribution that are well worth emulating for other drugs.

The HIV epidemic spread rapidly across sub-Saharan Africa in the 1980s and 90s, and by 1999, the Joint UN Program on HIV/AIDS estimated that 24.5 million people in the region had contracted HIV. But most patients could not afford the newly developed antiretroviral treatments, and fewer than 10,000 Africans were being treated. African governments – led by South Africa – began importing generic versions of antiretrovirals from India at discount rates, even though the drugs were still under patent in South Africa.

The conflict between Big Pharma and developing nations reached its apogee that year, when 42 drug companies sued the South African government for the patent-breaking imports. But the very act of bringing the lawsuit was a public relations disaster. Opponents worldwide portrayed the pharmaceutical companies as greedy and unscrupulous. As Ramon Castellblanch, then the director of the health administration program at Quinnipiac University in Connecticut put it, "the tens of millions perishing there (Africa) are more important than high salaries and profits."

After much media criticism, the companies withdrew the suit. But while the lawsuit was a mistake from just about any perspective, it did highlight a legitimate concern that many of the therapeutic compounds being produced in India did not meet reasonable quality standards. Bypassing international intellectual property rights laws is only truly beneficial to patients if the cheaper drugs are, in fact, effective.

Since 1999, quality standards have risen, in part because some Western pharmaceutical companies have decided that if they can't lick 'em, they would be wise to join 'em. Using their technological and economic leverage, innovator companies have crafted licensing agreements with generic manufacturers in India and other emerging-market nations that give both parties a leg up. The deal Gilead Sciences offered Matrix Laboratories illustrates the approach.

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Note that much of the money used to buy drugs for poor Africans comes from foreign governments and nonprofit organizations; indeed the Joint UN Program on HIV/AIDS estimated that 84 percent of expenditures on antiretroviral therapies in sub-Saharan Africa between 2007 and 2010 came from international sources. These donors care a lot about quality, and retain the last word on the sources of drugs purchased. Indian producers have historically struggled to maintain the high-quality production standards needed to win large pharmaceutical contracts from donors that include the U.S. government and the Global Fund.

Shortly after the pharmaceutical maker Gilead released its blockbuster HIV drug Viread

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(the generic name is tenofovir disoproxil fumarate, or TDF), it entered into negotiations with Indian generic manufacturers to allow select firms to manufacture the product in return for royalties. Viread is arguably the best HIV drug available, and Matrix Laboratories of India (among other companies) jumped at the opportunity to sign a licensing agreement in 2006.

India denied Viread's patent application in 2008. Nonetheless, Gilead continued to pursue 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. Matrix has proved to be Gilead's most successful Indian partner. Over the past four years, it has sold far more TDF than Gilead, producing treatments for over 500,000 patients, most of them in Africa.

Under Indian law, of course, Matrix does not need Gilead's approval to make and sell TDF. Why, then, did it agree to pay royalties to the patent owner? Gilead's manufacturing skill, along with its assistance with quality control, allowed Matrix to get tentative approval from the U.S. Food and Drug Administration – approval vital to raising donor funds – to market TDF in just five months. Even after paying the modest royalty, Matrix's costs were lower than those of competitors that chose to go it alone. The royalty payment agreement also specified that Matrix would get access to

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future refinements in Gilead's manufacturing and quality-control technology.

Gilead subsequently made deals with other Indian generics producers, including Hetero and Aurobindo. And it also submitted its HIV medicines to patent "pools," where any qualified generic manufacturer can bid for the right to produce drugs that are still under patent protection. Gilead's willingness to go a new way has significantly expanded its reach: some 1.1 million people have been treated with Gilead's antiretrovirals since 2006. Prior to 2006, fewer than 50,000 people in developing countries were treated with Gilead's antiretrovirals.

The licensing approach cannot resolve all disputes about drug-related intellectual property rights between India and the West. But it does offer a path for expanding access to medicines without threatening patentholders' intellectual property rights claims – which is the stated aim of most pharmas. The approach even provides innovator companies with modest royalties, which will grow as wages and living standards in developing countries rise.

TODAY TDF, TOMORROW...?

In June, Dr. Reddy's Laboratories, another successful Indian generics makers, negotiated an agreement with Merck Serono to start development of "biosimilars" (replicas) of the company's high-priced biologic drugs that are under patent protection until 2014. This process needs to get started early, since gaining approval from a stringent regulatory authority like the FDA often takes years. For Merck, the deal will allow its cash-strapped Serono division to continue drug development. Dr. Reddy's stands to gain access into the lucrative biologics market, and will benefit from its partner's expertise.

The agreement came at a critical moment for Dr. Reddy's. Last year, the company was forced to recall its generic cholesterol medicine simvastatin (Merck's brand name: Zocor), because traces of insecticides were found in the pills – even after the FDA approved Dr. Reddy's version and it went on sale in the

United States. Joint research and production with a global drug leader will likely help the company rehabilitate its image.

Some Western companies, like the biotech giant Amgen, are recognizing the benefit of manufacturing and distributing in emerging markets. Amgen agreed to purchase Mustafa Nevzat Pharmaceuticals, a Turkish generics maker that primarily produces injectable drugs, for $700 million. Mustafa Nevzat was the first Turkish drug maker to receive FDA approval to create both active pharmaceutical ingredients and finished products. Such activities demonstrate U.S. pharma's new flexibility in pursuit of profit, both in innovator drugs and generic production, thereby breaching the Chinese wall between developing new drugs and expanding drug access.

Other firms are following suit. GlaxoSmithKline now has licensing agreements with the South African-based generics firm Aspen Pharmacare. Merck, for its part, has launched a joint venture with the Chinese generics manufacturer Simcere Pharmaceutical Group, with the goal of providing "improved access to quality medicines in major therapeutic areas." Merck joined with Sun Pharmaceuticals to the same end in India.

However, there are risks here for both innovator- and generic-drug companies. They must maintain the highest standards of production regardless of the destination of products. In my own research, I discovered that some generics producers sent lower-quality products to markets overseen by less-competent regulators. Chinese antibiotics sold in Angola and Ethiopia failed quality control far more often than those sold within China.

Innovator companies must also conduct business at the highest ethical standards, even in markets where cutting corners is the norm. In 2002, GlaxoSmithKline made a deal with Dong-A Pharmaceuticals of South Korea to provide exclusive production rights for its patented antinausea drug Zofran. The deal stipulated that Dong-A cease production of its own generic version of the product, even after GlaxoSmithKline's patent had expired. This anticompetitive arrangement violated Korean antitrust law, leading to a $3.4 million fine when it came to light in 2011.

CHARTING A PATH FORWARD

Stricter Trips implementation is in the broad public interest because it increases incentives to innovate. But Trips is really a distraction from the task of increasing access to medicines in poor countries. The solution lies in win-win deals between drug companies and institutional purchasers (domestic health agencies or foreign donors) – deals that segment the market and adjust prices sensibly. Thus, while the media will no doubt continue to focus on intellectual property rights and pricing, the industry has moved on. The focus now is on crafting agreements that acknowledge the political realities, yet generate minimal loss in profits.

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Operating in this environment means coping with new sorts of challenges – notably maintaining quality control at a great remove from headquarters in Switzerland or Britain or the United States. But it is the future. And it holds out the promise of the best of both worlds, sustaining incentives for innovation without denying drug access to the poor. M

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