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Fighting Fake Drugs

Solving Africa's Counterfeiting Problem

One of the foremost tasks facing aid organizations in developing countries is finding a way to provide quality medication at reduced expense. Their strategies include buying in bulk, advocating for shorter periods of patent exclusivity—that is, allowing cheaper, generic versions of drugs to hit the market sooner—and encouraging pharmaceutical companies to tier their prices, offering drugs for lower prices in developing countries while higher prices in richer countries allow companies to recoup the research and development investment that drives pharmaceutical innovation. Approximately 90 percent of the nearly five hundred medicines that the World Health Organization deems "essential" for developing countries are, according to the WHO, generic.

But low-cost drugs can also come with hidden dangers. If regulation is imprecise or arbitrarily applied, careless and unscrupulous manufacturers can peddle poorly-made or outright fake products purporting to be brand-name and generic drugs. Sometimes other players in the supply and distribution chain, such as wholesalers, pharmacists, health care workers, and general traders, are themselves complicit in the substandard drug trade.

Although some of the fraudulent products may work to an extent, others contain too little or none of the active ingredients. Some antimalarial medicines have been shown to include nothing more than chalk and water; others have been found to contain drugs such as aspirin, which reduces fever and gives the false impression that the drugs are working, but within a day the fever rises again, sometimes with fatal consequences. A child who contracts *Plasmodium falciparum*, the severest form of malaria, and does not get good quality drugs may die within days.

Poor quality drugs also increase drug resistance. Where there is not enough of the active ingredient, the drug initially kills off only some of the parasites, bacteria, or viruses. The pathogens that are not killed adapt, passing on to their progeny genetic mutations that protect against the drug. The next time the infection flares up, it could be resistant to even full-strength, high-quality versions of the drug. For example, chloroquine was for decades a cheap and effective malaria treatment in Africa. Today, however, it has become almost useless on the continent; most cases do not respond to it. New versions of old drugs and entirely new drugs have been developed for drug-resistant strains, but these tend to be more expensive and sometimes carry stronger side effects.

Fake drugs abound in areas where government oversight is poor and private-sector accountability is weak. It is another, perhaps counterintuitive, evil of poverty: not enough bureaucracy. While we in the developed world often complain about the inefficiency or intrusiveness of government inspectors, we recognize that they largely contribute to keeping us safe. We are willing to invest considerable amounts to ensure that public health is sustained. Additionally, our legal systems usually remedy any party harmed by negligent corporate producers, and compensate for governmental harms. Many developing countries in Africa and Asia lack the necessary human and financial resources for rigorous, regular inspections, and have no consistently applied civil or criminal law.

As the saying goes, "If you think education is expensive, try ignorance." We simply don't know how many fake drugs are on the market in developing countries. The WHO reports that 30 percent of medicines in some countries in Africa and Asia are fake, but that assessment is based on small samples; the real figure could be radically different. My research colleagues and I recently reported in the *African Journal of Pharmacy and Pharmacology* that over a third of antimalarial, antibiotic, and antimycobacterial drugs sampled from pharmacies in five African countries and in India failed at least one quality test (our sample sizes were also small).

In the West, counterfeiters target expensive "lifestyle" drugs like Viagra, often hawking their imitation wares online. In the United States, these counterfeiters occasionally manage to circumvent the rigorously policed wholesale market (which is dominated by three major companies) and physical-location pharmacy markets. But fortunately, fakes account for far less than one percent of all drugs on the U.S. market.

In developing countries, counterfeiters target drugs sold in large volumes, including treatments for HIV/AIDS, tuberculosis, and malaria, because until recently, few government agencies or aid organizations were adequately assessing the quality of these products. Even today some agencies buy inadequately tested drugs.

But even when poor quality products were identified, it was often difficult to determine who was to blame: Some drugs, while manufactured at a high standard, degrade during transportation and storage if they are exposed to high temperatures or humidity. Some retailers keep drugs beyond their sell-by date and just re-label them. When a patient dies, health practitioners do not know if a poorly manufactured product is to blame, if the product had passed its expiration date or been incorrectly stored, or if the disease simply ran its fatal course.

Over the past decade, with increased publicity about the devastation caused by diseases like AIDS and malaria and more recently about the quality of drugs distributed in Africa, the situation has begun to improve. Some brand-name and generic drug companies have increased production of essential drugs, making products available to aid programs at cost or donating them for free, providing the imprimatur—staked on their reputation—of a high-quality product. Some, like Bristol-Myers Squibb or Merck, are even operating complete treatment programs, training staff and building clinics.

Developing countries, too, are strengthening their regulatory systems, following the example of Nigeria. Ten years ago, Nigerian health authorities reported that more than 50 percent of drugs in the country were fake or adulterated. In response, a reinvigorated National Agency for Food and Drug Administration and Control, under the charismatic leadership of director-general Dora Akunyili and with the full political support of then-president Olusegun Obasanjo, launched a rigorous anti-counterfeiting campaign. The agency introduced stiffer penalties for counterfeiting offenses, closed down the notorious Onitsha Market, a hotbed of counterfeit activity, and banned several dozen Chinese and Indian companies from importing their products into Nigeria. By 2009, the percentage of fake drugs had fallen to between 10 and 16 percent. In October 2008, Nigerian president Umaru Yar'Adua acknowledged that "no one country has all it takes to combat drug counterfeiting" and pledged to "woo" other African countries to play active roles in fighting fake drugs.

Other countries have begun to acknowledge the problem of substandard and poor quality medicines, even if some of their efforts have been misguided. (Kenya, for example, has come under fire for considering legislation that would label generic versions of drugs "counterfeit" if their non-generic counterparts were under patent protection in Kenya—or anywhere else in the world.) Countries such as Ghana and Nigeria have been aided by technical assistance from pharmaceutical companies; rigorous drug regulatory authorities like the U.S. Food and Drug Administration; and government-funded independent agencies such as U.S. Pharmacopeia, which monitors drug quality standards and provides training for officials in poor countries. Their efforts have been bolstered by the availability

of several new technologies that can help identify bad drugs in places where regulatory bodies and testing labs are not yet fully developed.

One such resource is the Minilab, a portable "lab-in-a-crate." The Minilab was designed specifically for developing countries by the Global Pharma Health Fund, a charity funded by the German branch of the pharmaceutical company Merck, with the support of the WHO, U.S. Pharmacopeia, and the German aid agency GTZ, among others. It was first launched in 2007 after more than twenty years of development, and today three hundred Minilab units have been deployed across seventy countries, many financed by the United States Agency for International Development. In Tanzania, twenty-five Minilabs are being used by health officials as the main defense against fake and substandard drugs as part of a project supported by the Gates Foundation and the London School of Hygiene and Tropical Medicine.

A Minilab uses simple techniques—thin layer chromatography, disintegration, and dye tests—to rapidly verify drug quality and detect counterfeits. Generally, a product will "pass" the Minilab test if it contains 80 percent or more of the labeled active ingredient.

A Minilab is reasonably cheap to buy, costing about $10,000 for the unit, initial training, and support. The tests are inexpensive to run; sufficient reagents are included with the original lab to undertake 1,000 tests, and each additional set of 1,000 tests costs perhaps $1,500. The Minilab's tests have been often replicated in the peer-reviewed scientific literature and are considered trustworthy.

But Minilabs cannot be easily deployed in all places. While they are, in theory, portable, they require drinking-quality water, reliable electricity, and air conditioning (to maintain a cool and dry environment) to operate. They require trained personnel who possess the patience and precision to conduct sensitive chemical tests. Because of these restrictions, Minilabs cannot be used in field settings such as most dockside ports or air freight terminals—the entry point for the lion's share of drugs in developing countries that lack their own pharmaceutical industries. Here, customs officers can verify a product's listing on a ship's manifest or on a manufacturer's import documents. But only with adequate facilities can customs officers conduct chemical testing, and even then, only with a time delay. Products can be transported to a separate lab for testing, but this will delay approval even longer, meaning that ships or planes must wait for several hours or days before unloading their freight, and not always in the best conditions for heat- and humidity-sensitive products.

Absent a Minilab, some other method of authenticating imported drugs must be found. Relying exclusively on visual inspection to identify fakes is problematic, as many counterfeiters use extremely high-quality packaging. Some may even include sophisticated holograms indistinguishable from the original, even by a trained observer.

Luckily, there is a remedy for this problem: Hand-held spectrometers, originally used by the U.S. military to detect explosives, chemical weaponry, and other dangerous substances in the field, have been adapted for pharmaceutical products. The operator simply points the instrument at a pill or liquid or powder, allowing it to scan the contents. The instrument then creates an electronic spectral fingerprint that can be compared against a reference standard of a good-quality product to determine whether the sample matches. This is all done in a matter of seconds, with the added benefit, for most products, of keeping the entire package intact.

This seemingly simple process is complicated, however, by the problem of creating the reference standard. The spectral fingerprint depicts all components of the drug, both active ingredients and excipients such as binding agents, fillers, and pill coatings. This means that a high-quality, approved generic drug with excipients that differ from those in the brand original—a common practice—could fail the test if the instrument only had a scan of the brand holder's drug. (Furthermore, temperature degradation or moisture degradation of a sample affects the spectra.) Effectively, customs officers must have access to spectral fingerprint scans for drugs from every manufacturer whose products may pass through that port. Some pharmaceutical companies may be unwilling to share their products with private agencies or manufacturers of spectrometers, perhaps for fear that such samples may fall into the wrong hands, enabling rogue manufacturers to create unlicensed knock-offs. So it will probably take national drug regulatory authorities in all countries to push for samples so reference spectra can be made.

The need for reference standards from all manufacturers also represents a logistical challenge, since spectrometers with different techniques are currently being used in the field. The Phazir RX, produced by Massachusetts-based start-up Polychromix, uses near infrared (NIR) spectrometry to excite molecules in a material. It then captures the unique pattern of vibrations emitted; that pattern can then be compared to a reference standard based on both quantitative and qualitative attributes such as optical resolution, wavelength accuracy, wavelength range, signal-to-noise ratio, and linearity of the NIR platform.

An alternative spectrometer, the TruScan, by another Massachusetts-based company, Ahura Scientific, collects Raman spectra to characterize the individual chemical components of a material. Raman uses laser photons to excite molecules, and then measures the interaction of light and molecular bonds. Different bonds create peaks of varying intensity resulting in a spectrum that is a unique fingerprint. If the material assessed against the method fails the first test, the TruScan provides a "Discovery" mode that accesses TruScan's database of drugs and chemical substances to determine the material's identity.

Some scientific literature, as well as my own field experience, suggests that the two spectrometers may have slightly different strengths. According to some scientific literature, Raman spectrometry is preferable for molecules that include sulfur-sulfur bonds as well as double carbon bonds, which exist in many pharmaceutical drugs. Some drugs such as SP, a popular antimalarial drug, however, have considerable fluorescence, an attribute that makes them difficult to test using Raman spectrometry. In these cases, the Raman spectrometer may pass an SP drug even if its active ingredients are too low.

NIR (Phazir) allows users to change the relative importance of various aspects of the spectral measurements. Unlike the Raman spectrometer, it does not include a high-powered laser component, meaning that it need not be registered with the customs authority in some foreign countries. But the Phazir is sensitive to surrounding light, so it must be used in a controlled environment, and may not be appropriate for inspections in busy ports.

Specific strengths and weaknesses aside, in general, both spectrometers are lightweight and easy to use. They weigh under two kilograms and are battery powered. They give precise readings in less than half a minute. They *are* expensive, however—each spectrometer costs approximately $50,000—and may not be in the budgets of cash-strapped drug regulatory agencies in many developing countries.

Still, these techniques are impressive and deployable. While they won't solve all drug quality problems—the corruption of regulatory authorities remains one of the greatest enduring problems in developing countries—aid agencies might consider investing in them on a limited basis, as one more powerful tool in the battle against substandard and counterfeit medicine.

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