

By Art Jahnke

BAND MEDICINE



Heart patients return faulty medicine at a hospital in Lahore, Pakistan, where more than 200 people died after a hypertensive drug was contaminated with an antimalarial, creating a deadly mixture.

IN JANUARY 2012, biomedical engineer Muhammad Zaman received a disturbing call from a friend. There was trouble in Lahore, the Pakistani city where, coincidentally, Zaman's father had spent most of his life. People were dying from a mysterious illness, and all of the victims had one thing in common: they had been treated at the Punjab Institute of Cardiology. More than 200 people would die before the government of Punjab province stepped up and seized several drugs that had been used to treat the patients, then sent them to be tested in the United Kingdom. It was a long way to go for an answer, but local drug testing in Lahore was known to be unreliable. The British labs reported that a hypertensive drug, one that was manufactured in Karachi, had

Fake and substandard drugs endanger hundreds of thousands of people around the world. Two BU professors and an alum are doing something about it.

ENG's Muhammad Zaman has built a toolbox-size device that uses a microfluidic sensor to detect molecules that bind to different drugs. Medicines are dissolved in a small amount of water, a second solution is added, and a chemical reaction fluoresces in a way that indicates the amount of active ingredient in a particular medicine.



been contaminated with an antimalarial, whose active ingredient in raw form looked very similar to the active ingredient in the hypertensive drug. The combination of chemicals allowed the antimalarial to enter the bone marrow in lethal amounts. The killer, in pharmacological language, was “substandard drugs.”

Zaman, a College of Engineering professor of biomedical engineering and a Howard Hughes Medical Institute Professor, was not surprised. As a child in Pakistan, he and his mother would make their way across town to buy medicine at a particular pharmacy, one whose drugs were thought less likely to be adulterated than those from pharmacies closer to his home.

“It was just part of the system,” he says. “It’s like you go to a good bakery or a good restaurant. It was much later in life that I realized that that’s not how it’s supposed to be.”

For Zaman, the Lahore deaths were one more reminder of a serious health risk that plagues many developing countries: fake or substandard drugs.

“Substandard” is the term most often used to describe medicines so poorly manufactured that they contain ingredients that are either toxic or have little or no effective ingredient. Sometimes the deficiency is deliberate, as in the case of falsified, or counterfeit, drugs, although the term “counterfeit” is also used to describe effective drugs made by unlicensed manufacturers. Most often it results from the kind of sloppy or unsanitary manufacturing that is common in developing nations, where quality control is not a priority and enforcement of safe manufacturing practices is feeble or nonexistent. In Pakistan, for example, a country of nearly 200 million people, the number of federal inspectors is around two dozen.

Researchers say that determining the financial impact of substandard or falsified medicines is challenging. In terms of impact on health, a recent study estimates the number of lives lost in children in 39 African countries because of poor-quality malaria medicines to be in the hundreds of thousands.

One study conducted by the World Health Organization (WHO) and written in part by Paul Newton, an Oxford University professor of tropical medicine and

a BU School of Public Health visiting professor, found that substandard antimalarials killed more than 120,000 children under the age of five in sub-Saharan Africa in 2013. Another WHO study, conducted in 2008, found that 64 percent of antimalarial drugs tested in Nigeria were substandard. When the same study looked at antimalarials in Cameroon, Ethiopia, Ghana, Kenya, Nigeria, and Tanzania, it found that 28 percent of 267 samples were substandard.

And the problem is not limited to the developing world. In 2012, more than 60 people died after a steroid used to treat back pain was contaminated with a fungus at the New England Compounding Center in Framingham, Mass.

Zaman says there are no truly accurate estimates of the number of deaths caused by substandard drugs because many people don’t always die immediately. It could take weeks or months for a drug to kill someone. Even if the drug is not toxic, but merely ineffective, it could eventually result in the death of patients who are counting on it to save them.

By 2012, he had heard so many stories of death and injury from substandard drugs that he decided to do something about it. He has been developing a portable device that can test the purity of medicine in the field quickly and easily.

Zaman is quick to say that the solution to the substandard drug problem does not lie in technology alone. The answers will come from many quarters, including the regulatory agencies and policymakers that are the focus of the research of Veronika Wirtz, an SPH associate professor of global health. Other answers are offered by the remarkable tracking capabilities of network technology. That is the province of Shabbir Dahod (CGS’82, CAS’85), the president and CEO of TraceLink, a cloud-based supply chain management company that makes it possible to check a drug’s authenticity from factory to pharmacy.

All three are working independently to solve a global problem that has been flourishing for three decades and that authorities say gets worse each year.

Cheap, Portable, and Easy to Use

In the last five years, Zaman has traveled throughout Africa and Asia, learning about the tools that were available to test drugs. Many didn’t work. Some hadn’t been used in years, often because no one knew how to use them. What was needed, he realized, was a cheap, portable, easy-to-use device that could quickly determine if a drug was real, fake, or something in between.

Working with researchers Darash Desai (ENG’12,’12), Nga Ho (ENG’15,’15), Andrew Acevedo (ENG’19), Zohar Weinstein

(MED’20), Katie Clifford (SPH’12, Questrom’18), and Andrea Fernandes (SPH’10, Questrom’15) and research scientist Atena Shemirani, Zaman has built a toolbox-size unit that uses a microfluidic sensor to detect molecules that bind to different drugs. Medicines are dissolved in a small amount of water, a second solution is added, and within 15 minutes, a chemical reaction fluoresces in a way that indicates the amount of active ingredient in a particular medicine.

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Muhammad Zaman is testing his device in Ghana, starting with antimalarials, a big problem in Africa. “Anywhere from 30 to 50 percent of the patients are getting poor-quality drugs,” he says.

Called PharmaChk, the device was sufficiently impressive to win an initial grant from the US Pharmaceutical Convention under the Promoting the Quality of Medicines program funded by the US Agency for International Development and a seed grant of \$250,000 from Saving Lives at Birth: A Grand Challenge for Development in 2012. Zaman has also received funding from the Center for Integration of Medicine and Innovative Technology, with critical assistance from medical device entrepreneur Wolfgang Krull and the National Collegiate Inventors and Innovators Alliance, now called VentureWell. In 2014, he won a \$2 million “transition-to-scale” grant from Saving Lives at Birth.

He is now testing PharmaChk in Ghana, starting with antimalarials. “They are a huge problem in Africa,” he says. “Out of the 215 million cases of malaria every year, a significant number are in Africa, and anywhere from 30 to 50 percent of the patients in Africa are getting poor-quality drugs.”

So far, he says, his team has run extensive tests in Ghana, and the device is working as well as other more expensive or more cumbersome state-of-the-art instruments used for similar purposes in developing nations. If PharmaChk performs as expected, providing accurate results quickly and easily, Zaman says, he will expand the kinds of drugs tested to include uterotonics, which are used to reduce postpartum hemorrhage. He will also extend his reach, into Indonesia, where he will test the device on antimalarials.

“The next step is to leave PharmaChk in Ghana for three months in real-world scenarios such as large public hospitals and see what happens,” he says. “We want to demonstrate that we can handle a small problem really well, then expand it.”

Tracking Pharmaceuticals

The US Food and Drug Administration (FDA) had a problem. Shabbir Dahod had a solution.

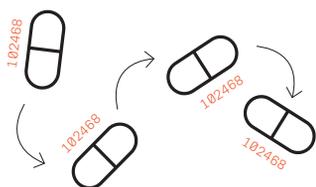
It was 2003, and Dahod had returned to Massachusetts after several years on the West Coast, most recently at Microsoft, where he oversaw much of the company’s knowledge management and collaboration. He was intrigued by research being conducted in the MIT Auto-ID lab of Sanjay Sarma, where engineers were trying to teach computers to recognize individual objects by seeing them.

“Finally, they said, ‘Why don’t we put some kind of identifier, like an RFID code, on every object,’” says Dahod.

Radio frequency identification, or RFID, codes serve as a kind of bar code on steroids, enabling researchers to store and share so much information that Walmart soon put them to work in its supply chain management system. Dahod, who was looking around for a new opportunity, learned that the FDA was looking for a technology that could help track pharmaceutical products, from manufacture to retail.

Such tracking, the agency believed, could distinguish legitimate drugs from the adulterated and substandard products that were feeding a dangerous gray market of substandard drugs that had been growing around the

TraceLink tags drugs with serial numbers that allow users to easily see when a product was purchased, when it was shipped, and when it expires. The company tracks such data for almost 50 percent of pharmaceutical manufacturers, preventing substandard drugs from infiltrating the market.



world for decades. It was also required by a federal law that had yet to be enforced.

As long ago as 1988, concern about substandard drugs compelled Congress to pass the Prescription Drug Marketing Act (PDMA), which prohibited the sale of drug samples as well as the reimportation of drugs that had been sold overseas at low prices. The new law also required wholesalers to track and report the pedigree of their products, and required states to keep records on which wholesalers sold which drugs. Aimed largely at wholesaler and pharmaceutical industry practices, the PDMA was opposed by several industry groups, whose pushback persuaded the FDA to water down some pedigree regulations and put tracking requirements on hold.

By 2003, after more attempts to enforce the law and more pushback, the agency was looking around for a solution that might get less resistance. Voluntary compliance with a comprehensive tracking system for all of the industry groups' products seemed like a safe bet. Dahod, who had an excellent understanding of the business value of supply chain management—"The supply chain," he says, "is the heart and soul of most businesses"—had an idea, based on the work in Sarma's lab.

"In my experience with start-ups, you look for a specific market to pursue," he says. "We were looking for a specific problem and what we found was at that same time the FDA was evaluating the technology being developed at MIT; it had a special task force to study counterfeit drugs."

Working with researchers from Sarma's lab, Dahod turned his attention to "the pharma space," he says. His start-up company, SupplyScape, built a prototype that used RFID and serialization technology capable of tracking millions of items through the dozens of stages of a supply chain. To test its marketability, he called supply chain leaders in pharmaceutical companies across the country ("anyone who would call me back"), and he met with FDA representatives, who liked what they saw, he says. His prototype tagged items with RFID codes that were encrypted to protect the data, which could include a range of info, from the origin of ingredients to the address of the drugstore where they were sold. In theory at least, it would enable anyone on any node of the supply chain—manufacturer, wholesaler, distributor, pharmacy owner—to scan the packaging of a pharmaceutical product and see its entire pedigree. And while it couldn't guarantee that counterfeit drugs wouldn't find a way to customers, it would make it a lot easier to check on a product's provenance.

At a February 2004 press conference in Maryland, the FDA released "Combating Counterfeit Drugs," a 37-page

report asserting that in searching for a solution, it had found "universal support for the adoption of electronic track and trace technology" and that "RFID was cited as being the technology with the strongest potential for securing the supply chain." Pharmaceutical honchos were on hand, and so was Dahod, who had been asked to demonstrate his prototype. The FDA announced eight months later its intention to promote the voluntary use of RFID tags. The agency asked industry to adopt the technology by 2007 and asked SupplyScape to set up a pilot program so pharmaceutical companies could test the waters. The first company aboard was Pfizer, eager to track the pedigree of its most often counterfeited drug: Viagra.

"From that point on we started working on core standards and technologies," says Dahod. In 2009, SupplyScape evolved into TraceLink, which has grown into a global company with 260 employees in London, Mumbai, Singapore, and its corporate headquarters in North Reading, Mass. TraceLink moved its data to the cloud, creating a network architecture where more than 260,000 life sciences entities in the pharmaceutical supply chain can rapidly exchange data to meet global regulations on tracking and tracing prescription medications.

"We work with life sciences companies to manage their information and to onboard their trading partners," says Dahod. "We give them serial numbers and they tell us the batch number, expiration date, and other information. We know when the product was purchased and when the product was shipped. It's a complex network with lots of entities exchanging information with each other. This will create billions of records that the industry needs to store for up to nine years."

The company now tracks data for almost 50 percent of pharmaceutical manufacturers. Dahod says it prevents substandard and counterfeit drugs from infiltrating the market

by keeping them out of the TraceLink network. "If the information doesn't match up," he says, "it would fail to get in our system," and its absence would sound a cautionary note to system users.

Although the PDMA has been slow to take hold since 1988, the system is about to shift into warp speed. Come November 2017, a new federal law passed in response to the New England Compounding Center tragedy will require drugmakers and their contractors to tag singular prescription drug units with unique serial numbers. Similar laws soon become effective in several European countries, as well as in India, Turkey, South Korea, and Brazil, opening new markets to TraceLink.

Bigger Problem or Better Reporting?

While Dahod attacks the substandard drug dilemma with

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a global computer network that shares billions of bits of information, SPH's Wirtz takes a very different tack. She identifies policy and regulatory changes that could stem the sale of substandard medicines, with a special focus on developing nations.

Between 2014 and 2016 Wirtz was the cochair of *The Lancet* Commission on Essential Medicines Policies, which last year published a 74-page report on the global availability of necessary drugs, including an investigation of the quality and safety of drugs in developing nations. The commission found several reasons for hope: some countries are stepping up efforts to agree on quality standards, and several new technologies, including cell phone apps, promise to help health providers and consumers detect problematic drugs. But the commission also reported some bad news: "the sophistication of falsified medicines seems to be increasing, as does their number," adding that the perceived increase may be the result of better reporting.

"The problem of quality-assured medicine is so important, not just in terms of harm, but in terms of efficiency," says Wirtz. "Particularly in low- and middle-income countries, where there are very little resources, it's very important to have products that actually work. Otherwise we waste scarce resources."

The Lancet Commission report relates the story of Adwoa, a two-year-old girl whose three-day fever sent her mother, Grace, to a local shop for antimalarial drugs. Grace was given three loose tablets and told to give her

child a half-tablet at once and the rest over two days. When the medicine failed to cool Adwoa's fevered body, her family rushed her to a hospital, where she was diagnosed with cerebral malaria, a syndrome that would almost certainly have killed her had she not been treated, and one that often causes permanent brain damage. Investigators later found that the antimalarial that Adwoa had been given lacked enough of the active ingredient necessary to be effective.

For Wirtz, Adwoa's story is all too familiar. *The Lancet* Commission reports that just last year in Myanmar, the packaging on two different drugs used to treat hepatitis C was falsely marked with the name of a manufacturer that never actually produced either of the drugs. And when the WHO looked at the quality of misoprostol, used to jump-start labor, in 15 middle-income countries, its researchers found that only 55 percent of 215 products contained the correct quantity of the active ingredient and 7 percent

did not contain any of the active ingredient. *The Lancet* Commission also notes that more than 100 children were killed in Panama in 2006 when toxic diethylene glycol ended up in a paracetamol—also known as the pain reliever acetaminophen—oral liquid.

The Lancet Commission found more than 1,000 reports of substandard and falsified drugs had been filed by national medicine regulatory (NMRAs) (country-specific FDA-like agencies) and other procurement agencies with the WHO's Rapid Alert System since the organization started to encourage such reporting in 2011. But even when authorities like the NMRAs are alerted to bad drugs, the commission determined, many of them lack the resources needed for meaningful action.

The NMRA, says Wirtz, "is not necessarily the most beloved child of the minister of health." Most agencies have little staff and very little money. "The result is they'll say, 'Oh, do we really need another quality check? We just did one two years ago. Let's wait another two years.'"

In some cases, efforts to spot substandard drugs are undermined by drug suppliers themselves. "Some agencies might make money procuring medicine or shipping medicine," Wirtz says. "They might not be interested in learning the quality of the medicine."

Even when the origin of a medicine is known, she says, there can still be questions about its risk. That's because different countries have different ideas about what makes a good manufacturing practice (GMP) standard, and many of those national definitions are not in sync with the definition established internationally. One study mentioned by the commission found that 44 generic drugmak-

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ers in low- and middle-income countries were in compliance with their national GMP standards, but less than a third of those met the global standards set by the WHO or the Pharmaceutical Inspection Co-operation Scheme, an extension of the Pharmaceutical Inspection Convention founded by the European Free Trade Association.

Wirtz believes that the battle against substandard drugs must be fought on several fronts, from the bureaucratic to the technological. She and commission members would like to see the significant expansion of the successful WHO program Prequalification of Medicines Programme (PQP), which prequalifies drugs sold by international vendors. PQP, started in 1987 with childhood vaccines, now prequalifies vaccines that immunize 64 percent of infants worldwide. It has earned the allegiance of the nonprofit Global Fund, which fights against AIDS, tuberculosis, and malaria and now buys only drugs that have been prequalified.

“The program works,” says Wirtz, whose research is funded by the Bill & Melinda Gates Foundation. “It publishes all of the results on its website, so you can go and see which products have been quality-tested.”

Still, she says, the WHO program is put to work in far too few countries. In January 2016, only six countries in Africa and six in Asia had medicine quality-control laboratories prequalified by the WHO. Wirtz would like to see more countries get on board or do something similar to what was done

in Kenya, where the Mission for Essential Drugs and Supplies, a collective of faith-based health organizations, operates its own quality-control laboratory. From 1997 to 2015, the well-published results of the collective’s testing have helped reduce the failure rate of drugs from about 35 percent to 5 percent.

Other answers to the problem will likely be found in technology, says Wirtz. She cites Zaman’s PharmaChk as a promising example, and there are others, such as the Minilab, which uses chromatography to identify false or substandard products. She says more than 700 Minilabs, which can be used in the field by people with almost no training, are now in use in 70 countries. And while the commission doesn’t mention TraceLink by name, it cites the general promise of track and trace technologies like that used by the company.

“A wide array of technologies have been proposed,” the commission’s report states, “from unique serial numbers to radio frequency identification tags, miniature edible tablet tags, and short message service verification.”

Wirtz’s *Lancet* study also mentions mobile phone technologies that enable consumers to scratch a panel on a packet and scan a special single-use code verifying a product’s authenticity. As is often the case with technology, the commission warns, the solutions offered may well be undermined by more technology. In fact, attempts to game one such phone-based system have already been seen in Nigeria.

“We are going to need multiple tools,” Wirtz says. “We need the right tools for the right context. We are coming closer, but it’s still a field that is relatively young.”

Even when the origin of a medicine is known, says Veronika Wirtz, questions may remain about its risk. Countries have different ideas about what makes a good manufacturing practice standard.

