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With local impetus, drug firm takes on TB Boston doctors' call spurs massive pledge



Drs. Paul Farmer and Jim Yong Kim, working in Peru, had desperately needed batches of two drugs developed nearly a half-century earlier by Lilly, capreomycin and cycloserine. (The Boston Globe/file)

By John Donnelly, Globe Staff | March 26, 2007

WASHINGTON -- For several years in the mid-1990s, two Boston doctors treating dying patients in Peru couldn't find enough of long-forgotten but effective tuberculosis drugs. They turned to their mentor, Howard Hiatt, a former dean of Harvard's School of Public Health, who called a contact inside Eli Lilly and Co.

That call ultimately triggered one of the most ambitious philanthropic efforts ever in global health by a pharmaceutical company, a pledge by Eli Lilly in 2003 to spend \$70 million to fight multidrug-resistant tuberculosis. On Thursday, the company announced it would expand that commitment by \$50 million more.

Those extra millions arrive at a crucial time. Deadly new extreme drug-resistant strains of tuberculosis, called XDR-TB, were discovered a year ago in South Africa, killing 52 of 53 patients within 25 days, and since have been identified in at least 35 countries, including the United States.

For epidemiologists, the potential spread of such a virulent airborne disease that is nearly impossible to treat is one of their worst nightmares.

A drug company coming to the rescue, however, is sharply at odds with the pharmaceutical industry's image.

AIDS activists and the industry have frequently clashed over the price and availability of cutting-edge drugs. Activists say drug firms took too long before sharply reducing the price of their life-extending anti-AIDS medicines to developing countries, and many of those firms sued South Africa because the country wanted to make less expensive generic versions of those drugs.

Lilly's story, in this case, is different.

It unfolded quietly, advancing because of connections, convictions, scientific proof of success, and multiple trips, phone calls, and e-mails between Boston and Lilly's headquarters in Indianapolis.

In October 1997, Hiatt called Gail H. Cassell, who had just become Lilly's vice president for infectious diseases research and clinical development; the two had served together on a National Academy of Sciences panel.

Hiatt told Cassell that doctors Paul Farmer and Jim Yong Kim, working in Peru, desperately needed batches of two drugs developed nearly a half-century earlier by Lilly, capreomycin and cycloserine.

"Howard told me: 'Look, Gail, I have these two young physicians at Harvard who are using their own money for two of Lilly's drugs to treat [patients] in Peru. They have run out of funds, they're running up an account. Isn't there anything Lilly could do?' " Cassell recalled. She made sure the doctors received free drugs. But she wanted to do more, and invited Hiatt and Kim to meet Lilly's CEO, Sidney Taurel.

"Their story was so compelling," she said in a telephone interview from Lilly's headquarters.

Over the next several years, as the Boston doctors' organization, Partners in Health, and several physicians at Brigham and Women's Hospital proved they could successfully treat the majority of patients with multidrug-resistant TB in Peru and Russia, Lilly gradually increased the amount of drugs it donated and studied a more ambitious plan to fight the disease.

In February 2003, at a closed board meeting, a Lilly official announced that the company was putting together a \$70 million deal to battle multidrug-resistant TB. The board applauded a rare moment, recalled board member Alfred G. Gilman.

"There is very little applause at stuffy board meetings," said Gilman, executive vice president for academic affairs and provost at University of Texas Southwestern Medical Center. "The board was pleased because it meant we were doing important things for world health."

Tuberculosis, which infects 8.8 million people a year and kills an estimated 1.6 million annually, can be passed in tiny droplets through a sneeze or cough. Routine cases of TB are curable: A patient must take a combination of pills daily for six months.

But when a strain of TB doesn't respond to the most widely used drugs -- often because a patient didn't adhere to a drug regimen -- doctors must resort to older antibiotics, which are still made in small amounts. Those drugs, such as Lilly's, are effective but often have serious side effects.

Multidrug-resistant TB is a major global health threat, but XDR-TB is even more dangerous. It is resistant not only to at least two of the widely used drugs, but also to a fluoroquinolone drug and one or more of three injectable drugs.

In its gift, Lilly decided the best way to stop the spread of resistant TB was to pass on its knowledge to partners around the world.

Cassell and others decided the company should turn over the recipe for the drugs to pharmaceutical companies in developing countries, buy them the necessary equipment for factories, train the employees, and then teach health workers how to administer treatment.

In the past three years, the company spent \$37 million to do just that in China, India, and South Africa. A fourth manufacturing plant is expected to open later this year in Russia. Lilly also donated \$33 million in drugs.

"We felt we had to be involved in training people how to use the drugs appropriately," Cassell said. "Otherwise, resistances [to the drugs] would develop."

Farmer said he and others were "pretty shocked when they first started talking about technology transfer. We were just asking to get the medicine for free."

Several drug companies have started anti-AIDS donation programs, but the only other pharmaceutical gift similar to Lilly's has been Merck & Co.'s fight against river blindness, a scourge in developing countries. That program started 20 years ago, resulting in the donation of 1.8 billion Mectizan tablets to fight the disease -- medicine worth about \$2.7 billion.

Still, Lilly's idea has been fraught with difficulties, and not all problems have been solved.

Its old TB drugs are difficult to make. Capreomycin, for example, requires fermenting a broth with fish meal, corn, and other ingredients for seven days, filtering and purifying the brownish liquid, then shipping it in a sterilized container to another factory, which then puts it into vials.

Michael Spink, who oversaw regional manufacturing projects for Lilly until he retired at the end of last year, said that when he began to help Hisun Pharmaceuticals, a Chinese company south of Shanghai, he realized he needed to do much more than teach how to make the raw ingredients for capreomycin. The factory, he said, was full of hazards.

"They had multiple accidents with lots of people getting injured and some accidents resulting in people dying," he said. Spink hired a Chinese safety consultant who helped significantly reduce workplace accidents, he said.

Spink also found that while Chinese scientists were "brilliant in their understanding of technology, they struggled a bit" with quality control. Lilly flew a team of Chinese scientists to Purdue University to learn how to make sure the drugs they manufacture meet all standards.

Lilly's program faces at least one significant hurdle. The worldwide distribution of cycloserine has been delayed because Lilly's partner, Aspen Pharmacare of South Africa, has yet to pass World Health Organization quality tests. Even though Aspen submitted a request for tests more than a year ago, WHO, facing a backlog, still hasn't completed its work.

"Certainly it's a frustration," said Mario Raviglione, director of WHO's Stop TB program, who attributed the delay to a lack of personnel in the WHO evaluation unit. Lilly, meanwhile, is moving ahead with its next gift of \$50 million, which will mostly go toward training healthcare workers in the developing world.

"You have to make medicines matter, and the only way to matter is get them to the patient," Cassell said. "And that means trying to overcome lots of barriers."

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