



WHITE PAPER

Seeking Solutions to a Global Health Crisis

Eli Lilly and Company's Technology
Transfer for Multidrug-Resistant
Tuberculosis Medicines

Lilly

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For more information about the Lilly MDR-TB Partnership and Lilly's other global health problems, please visit www.lillyglobalhealth.com.

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Seeking Solutions to a Global Health Crisis: Eli Lilly and Company's Technology Transfer for Multidrug-Resistant Tuberculosis Medicines

INTRODUCTION

Tuberculosis (TB) is an ancient disease that continues to wreak havoc today, competing with HIV/AIDS as a top killer among infectious diseases worldwide.¹ Despite significant advances against TB throughout the mid-20th century, by the end of the century, the disease was back on the rise. Even more alarming, doctors started documenting new strains of TB that were resistant to many of the indicated medicines. These strains came to be known as multidrug-resistant TB, or **MDR-TB**. A highly contagious disease, MDR-TB spreads, like other forms of TB, through the air. The **World Health Organization (WHO)** notes that every country has reported cases of MDR-TB, although most deaths (95 percent) occur in low- and middle-income countries.²

In 2003, Eli Lilly and Company (Lilly) decided to donate the intellectual property rights and manufacturing know-how for two Lilly antibiotics, capreomycin and cycloserine, that had been identified as effective in the treatment of MDR-TB. This decision led Lilly to establish the Lilly MDR-TB Partnership to improve treatment options for those living with MDR-TB. A philanthropic initiative convened and supported by Lilly, the Lilly MDR-TB Partnership was designed in collaboration with leading public health organizations around the globe, including government leaders, global health organizations, country-level healthcare providers, community and advocacy organizations, and others. From 2003 through 2016, Lilly would commit \$170 million in cash, medicine, and training to the partnership—the largest philanthropic undertaking in the company's history. As part of this initiative, Lilly:

- Partnered with global organizations to train doctors, nurses and community healthcare workers in target countries to recognize, treat, monitor, and prevent the spread of MDR-TB

- Funded research for the development of new medicines to treat TB and MDR-TB
- Worked extensively with manufacturers in high-burden countries to manufacture and increase access to quality-assured capreomycin and cycloserine.

Training other manufacturers to produce capreomycin and cycloserine involved a complicated process of pharmaceutical manufacturing technology transfer. In this process, Lilly worked side-by-side with the recipient companies to transmit the knowledge and systems needed to produce these trademarked drugs.

THE LILLY MDR-TB PARTNERSHIP

Since its launch in 2003, the Lilly MDR-TB Partnership has:

- Worked to improve access to quality-assured MDR-TB medicines
- Invested \$20 million to discover new tuberculosis medicines
- Trained more than 100,000 healthcare professionals to better recognize, diagnose, and treat MDR-TB
- Distributed more than 45,000 guidelines and toolkits to hospitals and clinics on appropriate treatment of MDR-TB
- Educated millions of people in high-risk communities through public awareness campaigns about TB and MDR-TB.

The technology transfer aspect of the Lilly MDR-TB Partnership is the main focus of this paper, which attempts to document Lilly's experience; this includes a discussion of how and why Lilly made the initial decision to transfer its technology and the lessons the company and its manufacturing partners learned along the way.

THE MDR-TB CHALLENGE

Although preventable and treatable, MDR-TB is frequently fatal. In fact, the prevalence of MDR-TB has reached massive proportions, likely due to multiple factors, including: inaccurate diagnosis, poor supervision of traditional TB therapies, lack of effective prevention, use of badly prepared drug formulations, inconsistent prescribing practices, erratic drug supplies that prevent regular and predictable treatment, and unregulated sales of medicines of unknown quality. Moreover, identifying and treating those affected by TB and MDR-TB has occurred slowly compared to other illnesses that strike on a global scale, such as HIV/AIDS and malaria, although many organizations have shown progress in accelerating MDR-TB diagnostic tests.³

It is estimated that only 25 percent of people with active MDR-TB were diagnosed in 2012.⁴ Of those who are diagnosed, even fewer are receiving treatment, and only a small fraction of these are being treated with internationally quality-assured medicines.

450,000

Estimated number of MDR-TB cases annually*

170,000

MDR-TB deaths each year**

60

Percent of reported MDR-TB cases that occur in Brazil, China, India, Russia, and South Africa ("BRICS" countries)***

*www.who.int/mediacentre/factsheets/fs104/en/

**www.stoptb.org/wg/mdrtb/assets/documents/MDR_tuberculosis_2013update.pptx

***www.who.int/tb/publications/MDRFactSheet2012.pdf

ABOUT THIS WHITE PAPER

This white paper is written from the perspective of Eli Lilly and Company. It is not intended to be a comprehensive analysis of the complexities of diagnosing and treating MDR-TB, nor a step-by-step guide about how to transfer manufacturing technology. Rather, it is meant to document the process of technology transfer in the context of the Lilly MDR-TB Partnership.

By sharing our experience, we hope to support decision-making by interested companies, public health entities, and other concerned parties, and to spur important discussions about:

- MDR-TB treatment and product supply
- The viability of the MDR-TB market for drug manufacturers
- The broader role of technology transfer in improving access to medicines for other global health challenges.

This paper also underscores Lilly's belief in public/private partnerships. In sharing our experience—including both challenges and achievements—we hope to encourage private and public entities to find innovative ways to work together, learn, and take action to combat the world's public health challenges. No single organization can solve complex global health problems alone. We believe in achieving meaningful results through cross-sector collaboration in which organizations tap their core expertise to help solve problems in comprehensive, sustainable ways. In that spirit, Lilly would like to acknowledge and thank its many partners who helped make the technology transfer of capreomycin and cycloserine, and ultimately this paper, possible.

WHY TECHNOLOGY TRANSFER?

Over the course of its history, Lilly's product portfolio has evolved numerous times, and in the late 1990s, as the MDR-TB crisis grew, Lilly's portfolio was in the midst of another evolution. The manufacturing unit was preparing for a new wave of products, and management decisions included exiting a large number of older products that the company produced. Capreomycin and cycloserine were two of the products on that list; the market for these drugs was very small, and since the medicines were off-patent, some manufacturers were already producing **generic** versions of them. Lilly planned to cease production in the near future.

However, as Lilly looked to phase out commercial production of capreomycin and cycloserine, doctors working with MDR-TB patients were compiling findings that showed these two medicines were proving effective, and indeed necessary, in the treatment of MDR-TB. This provided Lilly with an interesting challenge and a unique opportunity. In the late 1990s, the global production volume of quality-assured capreomycin and cycloserine was insufficient to meet the growing need for treatment of MDR-TB. To meet this need, Lilly agreed to increase manufacturing capacity for both capreomycin and cycloserine. Even with this expanded capacity, however, Lilly would still fall short of forecasted demand for the drugs. For example, despite doubling internal capacity for manufacturing capreomycin, production levels were only sufficient to reach approximately 7,000 patients; in 2003, TB experts forecast that the number of MDR-TB patients needing treatment would be close to 500,000 or more. In addition, the flow of internationally quality-assured medicines was solely dependent on Lilly's ability to deliver, and Lilly was donating or selling the majority of the medicines below the actual cost to manufacture them. It was clear that a more sustainable approach was needed.

The decision to transfer technology for the manufacture of capreomycin and cycloserine was informed by a desire to think long-term about the problem of MDR-TB. We recognized that our cost structure was not compatible with the need to make medicines available at as low a price as possible for MDR-TB patients, especially those living in lower-income countries. Additionally, our manufacturing facilities were located far from the majority of patients in need.

AT A GLANCE: LILLY'S MDR-TB TECHNOLOGY TRANSFER

Over the course of a decade, Lilly chose and partnered with seven manufacturers—four in countries with a high burden of MDR-TB—to reduce the cost of and improve local access to medicines. In the process, Lilly:

- Committed the time and expertise of multiple staff members over the lifetime of the project
- Offered on-site technical and quality assistance
- Funded local facility upgrades or the purchase of specialized equipment aimed at minimizing future costs for manufacturers receiving technology
- Worked with manufacturing partners to improve process efficiency so that they could reinvest in local staff and facilities on an ongoing basis
- Helped partners build additional manufacturing capacity to strengthen long-term sustainability
- Offered Lilly's intellectual property in both MDR-TB medicines, capreomycin and cycloserine, including trade names and manufacturing know-how
- Used external contract manufacturers to expand supply of capreomycin during technology transfer.

We reasoned that by transferring the manufacturing technology to companies located in the countries with the highest need, overall capacity would be increased at a lower cost structure. Our best understanding at the time was that local manufacturers could help improve local access to MDR-TB medicines and might be able to reduce end costs for patients. Our intent was to help treat more patients by increasing overall market volume and establishing a sustainable, long-term supply of the drugs.

THE LILLY MDR-TB PARTNERSHIP

In 2003, Lilly formally announced the Lilly MDR-TB Partnership, a key component of which was donating its trademarks and manufacturing know-how to local manufacturers in countries suffering a high burden of MDR-TB. The goal was to treat more patients by:

- Moving manufacturing closer to where people needed the medicines most
- Increasing manufacturing capacity and volume globally
- Lowering manufacturing costs to enable low-cost medicines for patients and payers
- Establishing a sustainable, long-term, high-quality supply of capreomycin and cycloserine.

Lilly carefully identified capable manufacturers in several high-burden countries—China, India, Russia, and South Africa—and offered to transfer the complex technology for the production of capreomycin and cycloserine. For the receiving manufacturers, the transfer was free of charge and included access to know-how and technical support, as well as funding for facility upgrades so they could manufacture the medicines on their own. In addition, Lilly identified and worked with companies in the United States and Greece to provide additional capacity and increase supply of these products to global markets.

As discussed in detail later in the paper, the regulatory approval process is a complicated one and even more complex for those partners that manufacture more than one product. However, as of June 2014, all of the manufacturing partners engaged in the technology transfer have achieved regulatory approvals. Of the nine products these partners have produced, six have received approval from countries with **stringent regulatory authorities (SRAs)**, and two have received approval from the WHO.

WERE THE PARTNERSHIP'S GOALS ACHIEVED?

Despite the known—and unanticipated—challenges that Lilly and its manufacturing partners faced, three important goals of the technology transfer were achieved:

- Moving manufacturing closer to people who needed the medicines most
- Increasing global manufacturing capacity and volume
- Establishing the foundation for a long-term, high-quality supply of capreomycin and cycloserine.

Part of the fourth goal—lowering manufacturing costs—has been achieved. However, the related goal of lowering end prices of the medicines (those quoted by the partners to customers) has proven more elusive. Those end prices, in many cases, have been above Lilly's subsidized prices. While a number of market challenges have likely prevented further cost and price reductions, a key factor is that while actual need remains high, market demand has fallen far short of the 500,000 patients that were expected to require treatment. These market challenges and others are discussed in greater detail in the Observations and Analysis section of this paper.

LOOKING TO THE FUTURE

Technology transfer may help improve the supply of, and access to, quality-assured medicines. Yet technology transfer is only one piece in a complex puzzle for which many integrated solutions are needed. Pharmaceutical manufacturers acting alone cannot bring about all of the changes needed to reduce costs and therefore lower end prices of MDR-TB medicines; various market and public health infrastructure factors need to be addressed as well.

It will take a multi-pronged, focused effort by governments, public health advocacy groups, manufacturers, and others, working together, to effect these changes. If patient treatment expansion plans are realized, supply chain operations for drug forecasting and disbursement are improved, and barriers to treatment are removed, it is likely that the resulting competition among suppliers may lead to lower prices and a more sustainable supply of medicine. For a more detailed discussion of these issues, see the Observations and Analysis sections of this paper.

To understand the course the Lilly MDR-TB Partnership took, it's important to trace the history of the disease. Against a backdrop of rising MDR-TB rates, Lilly faced a number of unique circumstances that shaped the ultimate decision to transfer its technology to other companies. Doctors were finding that two of Lilly's medicines, soon to be discontinued for commercial production, were effective in combination with other drugs in treating drug-resistant strains of TB. At the same time, a new medical protocol was emerging, aimed at establishing strict drug regimens to better treat and control the disease.

A BRIEF HISTORY OF TUBERCULOSIS

Tuberculosis (TB) is far from a new illness; in fact, it's one of the oldest recognized diseases in the world, with DNA evidence dating back 9,000 years. Known throughout history by various names—phthisis (to the ancient Greeks), consumption, the White Plague—TB has cut a wide swath through history, killing millions of people. Today, it is estimated that one-third of the global population is infected with the bacterium, *Mycobacterium tuberculosis*, that causes TB.⁵

In active cases, pulmonary TB is characterized by high fevers, a persistent cough, bloody sputum, and weight loss. It is also one of the most infectious diseases in the world: a person with active TB can infect 10 to 20 people during the course of the disease. Not all of those infected will go on to develop TB, though people living in poverty and those who are immunocompromised, such as people living with HIV, can be especially susceptible.

With the advance of **chemotherapy**—the treatment of disease through chemicals—TB cases began to decrease in prevalence during the 20th century. The drug streptomycin began curing TB patients in 1944, and through the 1940s and 1950s, a host of antibiotic drugs such as isoniazid, rifampicin, and ethambutol were found to be effective against TB. When administered properly in combination, these drugs cured the sick. Optimism was high that TB might be eradicated by 2025.⁶

THE RISE OF MULTIDRUG-RESISTANT TUBERCULOSIS

Unfortunately, instead of becoming a disease of the past, TB has proven to be more resilient than health officials had hoped. During the 1980s and '90s, TB cases started to rise again, especially in developing countries. By 1993, there were between 7 and 8 million known cases of TB and 1.3-1.6 million deaths per

year.⁷ The World Health Organization (WHO) declared TB to be a global emergency: the first disease ever to receive this dubious distinction. Several interrelated factors contributed to this resurgence, but two of the most important were the HIV/AIDS epidemic and the emergence of MDR-TB.

Only 5-10 percent of healthy people infected with TB will go on to develop active TB in their lifetimes.⁸ In fact, those with strong immune systems can carry the TB bacterium in their lungs for years without developing—or spreading—the disease. However, people whose immune systems are compromised by HIV/AIDS have a one-in-ten chance of developing active TB within one year, dramatically increasing the incidence of the disease worldwide.

Effective management of regular, or **drug-susceptible TB**, requires a treatment regimen that utilizes four antibiotic drugs in combination: isoniazid, rifampicin, ethambutol, and pyrazinamide. The administration of these **first-line drugs** according to the regimen recommended by the WHO is considered first-line TB treatment, which, when taken correctly over 6 months, cures drug-susceptible TB in 87 percent of patients.⁹ In 2014, this is the protocol recommended by the WHO.

However, when not followed exactly, this first-line protocol becomes a double-edged sword; failure to administer the complete combination of antibiotics for the full period enables drug-susceptible TB bacteria to mutate into drug-resistant bacteria and multiply.¹⁰ The mutated bacteria spread to other patients with the same ease of contagion as drug-susceptible TB, except the disease is now that much stronger and more difficult to combat.

Unfortunately, in countries with under-resourced healthcare systems, the stringent first-line TB treatment regimen can be hard for patients to complete, for a variety of reasons. Undersupplied healthcare

providers, not having access to all four drugs, may prescribe only one or two. Or, supplies of a drug may run out, so patients are unable to complete treatment. Undertrained healthcare providers may prescribe the wrong treatment regimen. Patients from remote areas may fail to return for treatment, taking only part of the required regimen and then stopping. And, in some countries, lack of governmental regulation can mean that patients are taking non-quality-assured drugs that may not be fully effective.

In countries with such circumstances, the result over the past several decades has been catastrophic: the birth of an increasingly resistant, airborne, and highly contagious disease. According to the WHO, 3.6 percent of all new TB cases are resistant to multiple drugs,¹¹ with the majority of these cases in Brazil, Russia, India, China, and South Africa (the "BRICS" countries). In patients previously treated for TB, the incidence of multiple drug resistance rises to 20 percent.¹² These numbers only tell part of the story; some areas of Eastern Europe have MDR-TB rates as high as 20 percent for new TB cases and 50 percent for those previously treated for TB.¹³ With increased global migration, the spread of MDR-TB has become a true global threat.

As difficult as TB is to treat, MDR-TB is even more complex. The current treatment regimen for MDR-TB takes 18-24 months to complete, requires injectable as well as oral medication, and can involve serious and unpleasant side effects.¹⁴ Proper monitoring and follow-up are imperative to ensure that the regimen is completed and the patient is cured. Failure to do so not only puts the patient at risk and increases the likelihood of the disease's spread, it also promotes the development of increasingly drug-resistant strains of the bacteria.

The tale of drug resistance is one of diminishing treatment options. As with drug-sensitive TB, poor or incomplete treatment of MDR-TB causes resistance to even more drugs. Alongside the spread of MDR-TB, in recent years public health monitors have recorded many outbreaks of **extensively drug-resistant TB (XDR-TB)**, and even a strain of TB that appeared to be totally drug-resistant (so-called 'XXDR-TB', or 'TDR-TB').¹⁵ With proper care, most patients with MDR-TB can be cured; however, the rise of this disease is outpacing efforts to rein it in.

LILLY AND MDR-TB

In the 1940s, Lilly became one of the first manufacturers to mass-produce penicillin, marking the beginning of a sustained effort by the company to fight infectious

diseases. Throughout the 20th century, Lilly launched a number of antibiotics including vancomycin, erythromycin, and new classes of oral antibiotics like cephalosporins and carbacephems. Among Lilly's product developments were two TB antibiotics, capreomycin and cycloserine, that were among a group of medicines considered **second-line drugs** for TB, to be used when drug resistance causes first-line medicines to fail. Capreomycin and cycloserine were brought to market in 1971 and 1955, respectively. But waning reports of TB meant that Lilly experienced diminishing demand for both medicines through the second half of the 20th century. By 1996, capreomycin and cycloserine were used to treat fewer than 1,000 TB patients per year, and the company manufactured the drugs only intermittently. Some years, Lilly had no orders for capreomycin and cycloserine and made none at all.

85%

Success rate of doctors treating MDR-TB in Lima, Peru with a drug regimen that included capreomycin and cycloserine

In the mid-1990s, MDR-TB was barely on the radar of the global health community. In reality, MDR-TB had been on the rise for some time, but it was largely under-diagnosed and under-treated. In 1996, the global nonprofit organization **Partners in Health (PIH)** was working in impoverished areas outside of Lima, Peru, training healthcare workers in the appropriate treatment of TB. While there, they found themselves confronted with an alarmingly high level of drug resistance in the population: 16 percent of the TB cases were already resistant to the two most effective first-line drugs. Drug resistance to first-line drugs was not a new phenomenon; it had existed since antibiotics were first used to treat TB in the 1940s.¹⁶ However, this was the first time it had been discovered on such a large, concentrated scale.

PIH approached Lilly to ask for access to a small amount of capreomycin and cycloserine, which we provided at a deep discount. Over the next two years, PIH used these drugs in combination with a variety of other second-line medicines to provide individualized treatment for MDR-TB. They achieved a successful treatment rate of more than 85 percent: a level similar to that of U.S.-based medical centers that relied on

more expensive treatments, including lengthy hospital stays and surgery.¹⁷

PIH's work in Lima was a turning point for the treatment of MDR-TB—and for Lilly. Prior to PIH's study, MDR-TB was considered too expensive and difficult to treat in low-income countries. Prevailing wisdom held that the limited funds available for TB treatment should be directed to drug-susceptible TB, not to drug-resistant varieties. The WHO-approved TB management plan, which emphasized active monitoring of patients to ensure completion of treatment, had achieved high success rates with drug-susceptible TB. It was thought that strict adherence to this program would eventually eradicate TB altogether.

But in their 1998 article in the *British Medical Journal*,¹⁸ PIH's Paul Farmer and Jim Yong Kim laid out the benefits of an aggressive, community-based treatment plan for MDR-TB. Other studies—and successes—followed in subsequent years. In 1998, the international nonprofit organization Doctors without Borders (**Médecins Sans Frontières**, or **MSF**) replicated PIH's study in areas where MDR-TB was a rampant problem. Like PIH, MSF also asked Lilly for capreomycin and cycloserine at well below market prices, which the company provided. For both these projects, Lilly understood that its subsidy of the drugs was an important factor in making the treatment not just available, but affordable, to some of the world's poorest and most disenfranchised populations.

ENSURING A QUALITY MDR-TB DRUG SUPPLY

By the turn of the century, it had become clear that Lilly's two drugs could be vital to the treatment of MDR-TB, and that the disease was growing into a larger threat than anyone had anticipated. It was further becoming evident that improper use of MDR-TB drugs would lead to increased drug resistance. As demand for second-line drugs rose, so did concern among medical professionals about the best use of these drugs. To address this concern, a coalition of concerned organizations including PIH, MSF, and the U.S. **Centers for Disease Control (CDC)** banded together to form the **Green Light Committee (GLC)**—a multi-institution partnership hosted by the WHO with the goal of increasing access to quality-assured second-line drugs in countries with limited resources.¹⁹ The GLC's role would be to validate national TB and MDR-TB treatment programs to make sure that they adhered to the WHO's treatment guidelines.

The creation of the GLC and the WHO's commitment to treat MDR-TB signaled a shift in the landscape. Knowing that the quality and usage of MDR-TB medicines would be validated globally by the GLC gave Lilly confidence that its donated medicines would be used responsibly and would not contribute to greater drug resistance. At this point, however, MDR-TB case diagnoses were increasing every day and were projected to outstrip Lilly's capacity to supply medicines. The company was at a crossroads, needing a solution that would address both the immediate demand for capreomycin and cycloserine and the equally important, longer-term issue of how to produce the medicines at a lower manufacturing cost.

THE DECISION TO TRANSFER TECHNOLOGY AND THE LILLY MDR-TB PARTNERSHIP

Like all pharmaceutical manufacturers, Lilly's product portfolio is in a constant state of evolution. In the late 1990s and early 2000s, Lilly was in the process of phasing out many of its antibiotics, including capreomycin and cycloserine. But with the steep rise of MDR-TB, it was clear that there would be a growing need for these two medicines. This presented an opportunity to transfer technology for the drugs to the places that needed them most.

To take advantage of this opportunity, Lilly introduced the Lilly MDR-TB Partnership in 2003. The Partnership adopted a two-pronged approach:

1. For the short term, subsidize the price of capreomycin and cycloserine
2. For the long term, build capacity and capability at the local level for sustained access to treatment.

Lilly began the first phase—subsidizing the prices of the two medicines—immediately. Although capreomycin and cycloserine were scheduled to be phased out, we maintained—and even scaled up—production of these two medicines to ensure that the supply of medicine would not be interrupted.²⁰ Although these drugs were already off-patent and Lilly was not the only supplier, Lilly was the only one approved by a stringent regulatory authority, and we continued to supply these drugs at prices well below our manufacturing costs.

Lilly considered these subsidies to be an important way to jump-start treatment, but ultimately wanted to provide a more sustainable supply of medicine by transferring the manufacturing technology to companies based in countries with the greatest need. In choosing locations for the transfer of technology, Lilly executives considered countries hit hard by the MDR-TB epidemic, and sought out local manufacturers that

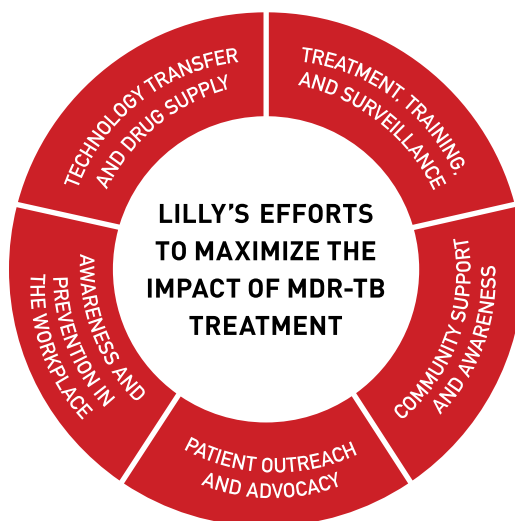
would be good candidates to develop significant capacity at sustainable costs. The manufacturing processes for capreomycin and cycloserine are complex and difficult to perform consistently; for example, producing capreomycin requires sterile **fermentation** and sterile **lyophilization** (freeze-drying). Given the complexities of MDR-TB drug formulation and production, we wanted to be sure that the manufacturing partners chosen had the best possible chances for success.

The manufacturers we approached were unsure that they had the technical expertise needed to successfully manufacture the drugs to meet stringent international quality requirements. They were also unsure about how to produce the medicines at a cost that would enable them to sustain supply to the marketplace.

In response, Lilly decided to significantly expand the scope of its partnership with these selected manufacturers. With an initial commitment of \$70 million, the Lilly MDR-TB Partnership was born. A primary goal was to help dramatically boost global supply of the needed drugs through sustained partnership with the manufacturers, guiding them to develop the internal systems, know-how, and employee expertise to produce medicines that would meet international quality standards.

Simultaneously, the Lilly MDR-TB Partnership launched a number of initiatives aimed at ensuring proper diagnosis and treatment of MDR-TB and maximizing the impact of the treatment:

- Training healthcare professionals in treatment and surveillance
- Building community awareness of, and support for, MDR-TB treatment
- Patient outreach and advocacy to reduce the stigma of TB and encourage more people to seek care
- Workplace awareness and prevention.



To pursue these objectives, the Lilly MDR-TB Partnership worked with numerous organizations including the International Council of Nurses, the World Medical Association, Partners in Health, the International Federation of Red Cross and Red Crescent Societies, and the International Hospital Federation. Together, these groups and other partners created online training materials in multiple languages, educated healthcare workers on the ground, and employed a “train-the-trainer” system to further spread best practices in MDR-TB treatment.”²¹

This section explores the steps in a successful manufacturing technology transfer and documents Lilly's experience in transferring capreomycin and cycloserine to illustrate key activities and learnings, including insights into MDR-TB-specific issues.

WHAT IS TECHNOLOGY TRANSFER?

Within the pharmaceutical industry, technology transfer involves one organization teaching another how to make a particular medicine. Technology transfer entails much more than just handing over the chemical formula; it involves the transmission of experience that the sending organization has gained over an extended period of time. Ultimately, it must encompass whatever is necessary to safeguard the quality of the medicines that will be produced. People put medicines into their bodies, and ensuring their safety requires stringent controls.

Technology transfers are complex undertakings with a wide range of variables that both the receiving and sending organizations must address. The sending organization may need to help create a new manufacturing infrastructure and provide consulting, training, and technical support. The receiving organization must assemble the appropriate equipment, skills, and quality processes to receive and implement the new manufacturing process. For the transfer to be completed successfully, the medicine needs to meet the same specifications at the receiving site as at the sending.

7 YEARS

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The time it can take to successfully transfer pharmaceutical technology from one company to another

However, two manufacturing sites are never exactly the same, and the transfer needs to account for differences in operational processes, procedures, environments, skills, philosophies, and many other factors.

Technology transfers—especially from companies in higher-income countries to those in lower-income countries—can generate far-reaching value within the recipient communities. In countries with developing economies, the receipt of pharmaceutical technologies can increase access to medicines that improve public health, and can also contribute to economic stability and improved manufacturing infrastructure.²² However,

Technology transfer involves much more than simply turning over a formulation for a particular pharmaceutical product. It can also require building facilities capable of the precise conditions necessary to manufacture the drugs, as well as consulting, training, and technical support. According to the International Federation of Pharmaceutical Manufacturers and Associations, several factors can increase the chances of a successful technology transfer to companies in developing countries that encounter barriers to new drug production:

BARRIERS	TYPE OF ASSISTANCE REQUIRED
<ul style="list-style-type: none"> • Lack of facilities capable of safely processing sophisticated chemical and biological reactions • Lack of facilities able to ensure precise product processing • Lack of packaging facilities 	<ul style="list-style-type: none"> • Facility upgrades, capital investments in new equipment, or the transfer of equipment from the originator, such as specialized equipment for sterile manufacturing
<ul style="list-style-type: none"> • Lack of skilled labor 	<ul style="list-style-type: none"> • Training: Skills and human aspects of technology management and learning, such as training courses in good manufacturing practices (GMPs)
<ul style="list-style-type: none"> • Lack of intellectual capital, licenses, or regulatory approval 	<ul style="list-style-type: none"> • Intellectual content: Techniques, blueprints, or licenses for specific technological processes
<ul style="list-style-type: none"> • Lack of policies and procedures to help facilitate the manufacture of safe and effective medicines 	<ul style="list-style-type: none"> • Organizational improvement: Procedural knowledge needed to operate a given technology or meet regulatory standards²³

significant obstacles often exist within developing countries that can create barriers to the effective and successful transfer of technology. Identifying the challenges at the outset can significantly increase the chances for success—but only if ways to overcome the obstacles are found.

THE STAGES OF PHARMACEUTICAL TECHNOLOGY TRANSFER

Pharmaceutical technology transfers are complex processes, encompassing hundreds of steps, checks, and double checks. Both the “hardware” (e.g. the laboratory and manufacturing equipment, utilities, equipment layout, process control capability) and the “software” (e.g. good manufacturing practices, procedures, training) need to be assessed, a transfer plan developed, gaps closed, and the manufacturing process implemented. It is crucial that every aspect of the manufacturing process be replicated as closely as possible in each new location to ensure quality.

The capability of the receiving manufacturer can have a significant impact on the scope of the project. When manufacturers have been inspected and licensed by stringent regulatory authorities (SRAs) like the U.S. **Food and Drug Administration (FDA)**, they will be familiar with **good manufacturing practices (GMPs)** and have well-developed business processes supporting the manufacture of quality medicines. However, when manufacturers have been inspected and licensed by regulatory authorities with less well-developed oversight, the scale of the technology transfer and the effort required may be significantly higher. Before considering a technology transfer, companies, funders, and sponsoring governments should consider the full range of assistance that may be required to achieve the desired outcome.

Generally speaking, there are six stages to any pharmaceutical technology transfer, with each stage requiring the successful implementation of the previous stage. At any of these stages, unexpected delays may arise, holding up the rest of the process.

STAGE 1: IDENTIFY

This stage involves finding companies that are interested in undertaking the transfer and have the appropriate infrastructure to receive the technology.

Lilly's Experience

When Lilly began to design the MDR-TB technology transfer process, our goal was to provide local, sustainable access to treatment in the places with the greatest need. We felt that partnering with manufacturers in countries with the highest burden of MDR-TB would accomplish four goals:

- Move manufacturing closer to where people needed the medicines most
- Increase manufacturing capacity and volume globally
- Decrease manufacturing costs to improve access to low-price medicines for patients and payers
- Establish a sustainable, long-term, high-quality supply of capreomycin and cycloserine.

We decided to offer the receiving manufacturers access to all of Lilly's knowledge about our two MDR-TB medicines, as well as access to technical experts, and where available, product registrations, trademark licenses, and existing customers.

A disincentive for potential partners was the small market size for capreomycin and cycloserine. There was concern that this small market size would

not provide a return on investments in the facilities and people required to manufacture the drugs. In helping the manufacturers plan for the technology transfer, Lilly looked to growth in treatment targets set out by the WHO as evidence of the market's potential.

Lilly identified a set of criteria for selecting manufacturers. These included the company's capabilities to manufacture the medicines, and more generally, their willingness to tackle this particular public health challenge.

SELECTION CRITERIA FOR MANUFACTURING PARTNERS

1. Interest in accepting the transfer of technology for the two drugs
2. Sufficient baseline technical capabilities and manufacturing facilities
3. Sufficient quality systems and business processes
4. Willingness to support the goals of the STOP-TB Partnership.

After a search of more than a year, Lilly found manufacturing partners in four of the identified high-burden countries: China, India, Russia, and South Africa. Ultimately, Lilly would make six separate technology transfers to these four companies:

COUNTRY	MANUFACTURING PARTNERS	PRODUCT(S) TRANSFERRED
CHINA	Zhejiang Hisun Pharmaceutical Co. Ltd.	<ul style="list-style-type: none"> • Capreomycin Active Pharmaceutical Ingredient • Capreomycin drug product
INDIA	Shasun Pharmaceuticals Ltd.	<ul style="list-style-type: none"> • Cycloserine Active Pharmaceutical Ingredient
RUSSIA	JSC Biocom	<ul style="list-style-type: none"> • Cycloserine drug product
SOUTH AFRICA	Aspen Pharmacare Holdings Ltd.	<ul style="list-style-type: none"> • Cycloserine drug product • Capreomycin drug product

To meet expected global demand, Lilly identified three additional transfer candidates that could begin production sooner:

COUNTRY	MANUFACTURING PARTNERS	PRODUCT(S) TRANSFERRED
GREECE	Vianex S.A.	<ul style="list-style-type: none"> • Capreomycin drug product
USA	The Chao Center for Industrial Pharmacy	<ul style="list-style-type: none"> • Cycloserine drug product
	Akorn Pharmaceuticals	<ul style="list-style-type: none"> • Capreomycin drug product

STAGE 2: ASSESS

In this stage, potential partners are assessed for their current capability to manufacture the medicine and to meet appropriate quality standards.

Lilly's Experience

Assessment is a crucial stage in the technology transfer process, and one of Lilly's first steps was to assess our own manufacturing processes and gather appropriate documentation.

The production methods for capreomycin and cycloserine had changed little since the products were originally launched in 1971 and 1955, respectively, so preparing to transfer the processes meant reviewing decades-old technology and documentation. The manufacturing processes for the two products differ markedly, and they provided a range of interesting challenges because of the complexity of both the basic chemistry and the processes involved.

Before beginning the actual knowledge transfer, we analyzed the areas at all receiving sites that would be involved in the manufacturing process, including facilities, staff, availability of raw materials, manufacturing practices, and quality control and assurance processes. We also looked at broader factors, such as the company's culture and financial sustainability.

After assessing requirements to transfer the technology to the manufacturing partners, we reached an agreement with each partner on what would be required to implement the project. This included Lilly's committing multiple employees: experts who would offer on-site technical assistance and training to ensure project success. Additionally, where necessary, we committed funding to support building, converting, or upgrading local facilities to meet the needs of the program. We hoped these investments would help to reduce the partners' costs as well as the end prices of the medicines.

STAGE 3: PLAN AND PREPARE

This stage involves creating detailed plans and preparing the recipient's facilities, organization, and business to accommodate the new processes.

Lilly's Experience

From the onset of the project, Lilly staff worked on-site with our partners to identify what capital investments would be required. For example, we determined we would need to help build a production facility for Hisun in China and a sterile drug product manufacturing facility for Aspen Pharmacare in South Africa.

In China, Lilly supported the construction of a suitable downstream purification facility so that Hisun could complete the process of capreomycin **active pharmaceutical ingredient (API)** manufacturing.

To improve Hisun's chances of success, we provided detailed information regarding the design, construction, and start-up of a sterile drug product manufacturing facility, as well as specific technical information relating to capreomycin production. Our engineering, technical, and quality staff reviewed designs for Hisun's new facility, and Lilly provided financial contributions contingent on Hisun completing specific milestones.

In South Africa, Aspen already had ambitions to build a sterile production unit at its Port Elizabeth facility to develop new lines of business. We provided technical and financial support for this new plant, as well as technical expertise in the design and operation of the facility, which enabled Aspen to produce both MDR-TB medicines and other products.

STAGE 4: IMPLEMENT

At this stage, trademarks and technological know-how, as well as manufacturing and testing methods, are actually transferred to the receiving company. The sending and receiving manufacturers work together to complete experimental process runs and create all the necessary documentation.

Lilly's Experience

The technology transfers covered a wide range of manufacturing processes, as well as specific technical and scientific knowledge associated with each product. We also worked with partners in areas such as:

- Establishment and maintenance of master and working cell cultures
- Sterility control and assurance programs
- Vendor certification
- Data management: trends, analysis, and interpretation
- Statistical control procedures
- Data management in decision-making
- Change control for quality management
- Design of experiments to assess new raw materials and process changes
- Investigation of out-of-specification results
- Equipment selection and acceptance testing
- Operator certification procedures
- Manufacturing validation and controls.

One of the major focal points of the transfer was training in GMPs. A partner of Lilly's, Purdue University College of Pharmacy in Indiana, United States, offered training in GMPs to interested manufacturers. Representatives from some of the manufacturing partners visited Lilly and Purdue for intensive training

A PRIMER ON PHARMACEUTICAL MANUFACTURING

What actually goes into the production of the medicines that are so crucial for global health? Pharmaceutical manufacturing comprises two separate processes: making the active pharmaceutical ingredient (API), and formulating the final drug product, which involves turning the API into the final form in which it will be sold and distributed to patients. Each process has different technical challenges. For instance:

- Manufacturing capreomycin API requires sterile fermentation, a process that requires unusual technology and is difficult to implement
- Capreomycin drug product is injected into a patient and must therefore meet the highest sterility standards. Its manufacture involves freeze-drying the liquid API to create a vial of capreomycin powder, a process that must also be carried out under sterile conditions.

courses. The focus of the Purdue program was graduate-level education in regulatory and quality compliance, while the focus of the Lilly program was sharing practical, real-life applications of the theory that the participants had just learned at Purdue.

Each partner worked diligently to demonstrate that it could adequately replicate the manufacturing technology that Lilly provided, first at laboratory or pilot plant scale, and then in larger production environments. This hands-on, step-wise process enabled local operations personnel not only to learn about the technology and processes, but to identify and resolve issues at the earliest possible stage.

Sometimes, the flow of information went both ways. For instance, after Hisun employees visited Lilly's Liverpool, UK facility, the Liverpool team traveled to Hisun's

Zhejiang facility to develop a joint action plan. Since imported raw materials for capreomycin fermentation can add significantly to the final cost of the medicine, the joint project team conducted laboratory-scale tests with locally sourced Chinese ingredients. When these tests were successful, production was expanded to include pilot plant studies, which revealed that the local ingredients could be used on a larger scale. This pilot plant work resulted in an increase in the yield of capreomycin as well as a more consistent and reproducible process compared to the initial batches. In turn, this helped to reduce the cost of the final API. Several enhancements identified during this period of joint investigation were introduced into Lilly's own production process in Liverpool for improvements in yield and process reliability.

STAGE 5: VERIFY

In this stage the receiving manufacturers, with the help of the original developers of the pharmaceutical formulations, make validation runs of the process, including analytical testing. For the technology transfer to progress to the next stage, the tests must show that the product meets the required specifications.

Lilly's Experience

This stage of technology transfer is crucial for quality control, and it is also a stage that can add significant delays to the overall process. One project that met unexpected roadblocks was our technology transfer in India. Initially, Lilly and staff from our partner company Shasun were unable to obtain consistently acceptable results in the production of the cycloserine API. The technology transfer team could not determine whether this was due to the production process or an analytical error. The cause of the issue was finally traced to the fact that the local production reaction tanks and dryer had slightly different properties from Lilly's equipment in Indiana.

Another challenge arose with the quality of the final product. Following a series of pilot plant experiments that traced the issue to a raw material purchased locally, the joint team decided to import this key ingredient from the same supplier that Lilly had used in our Indiana plant. The imported item was more expensive, but it gave the necessary results.

Identifying and addressing the above issues added many months to the technology transfer project. However, Lilly and Shasun jointly succeeded in fixing the problems, and the end result was a reliable and high-quality product.

Transfers of technology may present technical challenges that require both parties to resolve collaboratively. These issues are rarely predictable and can affect the timeline and ultimately the success of the project. The response to such challenges relies not only on the experience of the sending organization, but also on the skills and insights of the recipient company.

STAGE 6: REGISTER

In this final stage, the manufacturers prepare dossiers and submit them to regulatory authorities for review.

Lilly’s Experience

To be accepted for purchase by the **Global Drug Facility (GDF)**, which procures TB drugs for national TB programs and other customers, a medicine must have regulatory approval through one of two paths: the **WHO Prequalification (PQ) Programme** or a stringent regulatory authority (SRA).

The registration and approval process turned out to be a difficult one for some of our manufacturing partners. Regulatory requirements changed during the course of the projects, leading to additional work for partners. In general, the review time has been longer through the WHO PQ process than the SRA route, though both regulatory processes have produced surprises.

In August 2013, the WHO PQ Programme approved the cycloserine drug product from JSC Biocom (Russia): almost four years after the company submitted its registration dossier, and more than six years after beginning the technology transfer process. The WHO’s approval of Biocom’s cycloserine marks the first time a Russian facility and drug product have been on the WHO’s PQ list. Despite the registration delays, Biocom executives say they would participate in a technology transfer project again, and they would recommend it to others. Biocom can now sell cycloserine through the GDF

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BENJAMIN POTASHNIKOV, BIOCOM

“Receiving the technology transfer of the formulation of cycloserine has been a very valuable experience for the Russian market. If other companies get the opportunity to participate in such a project, it will raise their good manufacturing practices level.”

.....

beyond Russia, dramatically increasing its potential market. This is a true case of building capacity at the national and international level.

However, during the lengthy technology transfer and pre-qualification process, customer requirements can also change, resulting in additional steps. For instance, when Lilly supplied the WHO with cycloserine, it was packaged in bottles, and that is how the technology was transferred to Biocom. However, since that time, the GDF’s customers have indicated a preference for cycloserine packaged instead in blister packages. To meet this change would require Biocom to invest in new tools to produce the blister packs, design and carry out experiments to demonstrate product stability in the new packaging, and submit data to the WHO PQ regulators. This additional investment would put blistered product availability several years into the future.

During the course of the Lilly MDR-TB Partnership, Lilly has learned a great deal about the factors needed to successfully transfer technology, particularly to companies in developing countries. These factors fall into two broad categories: considerations relating to the technology transfer itself, and considerations relating to supply chain impacts on local drug manufacturing. This section highlights these important lessons and considerations in the hopes that they will prove helpful for other companies, governments, and public health organizations considering technology transfer projects.

CONSIDERATIONS FOR TECHNOLOGY TRANSFER

Although it is impossible to anticipate every eventuality, the following considerations are a good place to start before embarking on a pharmaceutical technology transfer project:

1. Technology transfer of internationally quality-assured drugs is enormously complex and resource-intensive.

The transfer of technology for pharmaceutical manufacturing is a vast undertaking, particularly in developing countries, where manufacturers often need training in specific product skills and help in other manufacturing elements to be successful. Technical assistance must be delivered on-site and in-country, and it must be facilitated by experts with scientific depth and experience as well as an ability to teach new skills and protocols to others.

Pharmaceutical products are unique in the technology transfer arena, since they must be manufactured according to the comprehensive set of standards and safeguards of GMPs. Serious health risks can occur from impurities or variability in the amount of active ingredient used, and product effectiveness can be compromised by many factors.

In some countries, regulatory oversight of medicine manufacturing may not be as well-developed as that of SRAs or the WHO PQ process, and local manufacturers may therefore be operating below **International Quality Assurance (IQA)** standards. Achieving more stringent manufacturing standards usually entails significant effort and expenditure in areas such as facilities,

COMPLEXITY OF MANUFACTURING MEDICINES FOR MDR-TB

Most of the medicines used to treat MDR-TB were developed decades ago and have less well-defined profiles than medicines developed more recently. In most cases, this makes them complicated to manufacture consistently. For instance, the three recommended injectable medicines used to treat MDR-TB are all produced from fermentation and capital-intensive formulation activities such as freeze-drying. Medicines produced using fermentation are more difficult to manufacture than those made from chemical synthesis, requiring very precise calibrations of environmental factors like temperature, Ph, and dissolved oxygen.

Oral MDR-TB drugs are somewhat less complex, but they still require tightly controlled conditions for formulation. These layers of complexity make manufacturing such drugs a challenge.

laboratories, training, and additional resources. Such improvements take time, which may also increase expenses for the manufacturer. When a multinational company transfers technology to a smaller company in a developing country, it's often the larger company that bears many of these associated costs.

2. Duration of engagements with technology transfer partners is lengthy, and each step can be very time-consuming.

Providing technical assistance is a significant endeavor, not a brief consulting engagement of just one or two short visits. Depending on the needs of the transfer recipient, the duration of a technology transfer can range from several months to several years. Companies seeking to transfer technology to other manufacturers should be prepared to be engaged for the duration—likely multiple years—to ensure a successful outcome.

3. It is important to choose partners carefully and understand their motivations and dedication to the technology transfer project.

The ultimate success of a technology transfer is dependent on the relationship between, and the motivations of, the sending and receiving companies. The sending partner must be committed to a successful transfer despite the challenges. The recipient partner should have a well-developed plan for the new business and be prepared to stay the course for the project. Resource availability and communication between partners are crucial.

4. Regardless of where initial funding comes from, it is wise to establish a “go-to-market” strategy with a receiving company ahead of time.

Most manufacturers do not have the capacity to treat drug development and supply as an act of philanthropy; their interest is a business one. For a technology transfer to be financially viable for them, receiving partners will want to understand:

- The market value of what they will produce, and what their return on investment will be
- How the application of the technology or capabilities gained may be applied to other product lines.

5. It is critical to engage those responsible for quality at all stages of decision-making.

Ultimately, it is the quality of the medicine that matters most. To assure consistency, up to a quarter of the total staff at a receiving manufacturer might need to be dedicated to quality assurance and control. It will likely be necessary for the sending company to provide extensive skill-building specifically focused on quality issues, including education on microbiology, GMPs, and other processes.

CONSIDERATIONS FOR LOCAL MANUFACTURING OF MEDICINES

Increasing production of medicines in countries with high disease burdens may be an ideal solution: it has the potential to build a local, self-sustaining infrastructure, while lowering the costs of medicines and making them more readily available where they are needed most. The reality is that several market barriers can hamper the success of local manufacturing programs. Following are some of the supply chain issues we encountered:

1. Small and fragmented markets require broader scale-up and diagnosis.

Even if the technology transfer is targeting a disease with a relatively large affected population, the available market for the resulting medicines may be much smaller, depending on whether local healthcare systems are capable of diagnosing (i.e. finding) eligible patients and dispensing treatment, and whether other medicines are also required and available to treat the same condition. If the medicines that are newly available through the technology transfer effort cannot be used to treat other conditions as well, securing a sufficient market size is even more important, as that becomes the only way to recoup costs.

In the case of MDR-TB, the global market for medicines has yet to catch up with the volume of patients who need them. In 2013, the WHO estimated that 450,000 MDR-TB patients a year should be receiving treatment. Yet in that same year, the WHO Global Drug Facility (GDF) supplied medicine for only approximately 33,000 patients. (See the chart on the following page for more details on estimated incidence of MDR-TB as well as diagnosis and treatment rates.) Some patients may be receiving treatment in non-approved programs, while others may not have even been diagnosed. In 2012 alone, it was estimated that three out of four people with MDR-TB went undiagnosed.²⁴

The market for MDR-TB medicines is fragmented among donors, governments, and the private sector, with no single dominant purchaser. Some countries with large estimated patient populations prefer local procurement mechanisms that may not be open to foreign manufacturers. National governments are becoming increasingly significant purchasers, but many struggle to fully understand the complexity of MDR-TB market size and treatment patterns, as well as other relevant dynamics, all of which will affect the reliability of supply. As a result, for most international manufacturers, the most visible and accessible

demand for their products comes from the GDF, a relatively small market compared to that of many other medicines.

Furthermore, there exists a range of treatment regimens for MDR-TB patients, which shrinks market size for any one treatment element. For example, the WHO recommends that programs use one of three possible injectable medicines as part of the regimen, further fracturing an already small and disaggregated market.

COMPLICATIONS OF GATHERING MDR-TB DATA

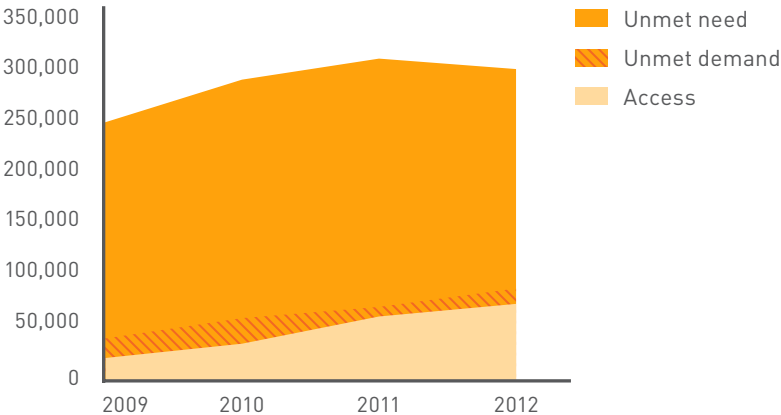
It is important to note that the country-level TB programs that gather MDR-TB data are subject to a number of limitations, including incomplete reporting of diagnosed cases, non-standardized methods for detection of TB and MDR-TB, lack of uniformity in the effectiveness of treatment regimens administered, and outdated national estimates of MDR-TB cases. For these reasons, the figures in the chart to the right do not capture all of the estimated new MDR-TB cases that are eligible for treatment in a given year.²⁵ In 2012, for example, there were an estimated 300,000 cases of MDR-TB among TB cases reported to country-level TB programs. For that same year, however, the WHO estimates that approximately 450,000 people had MDR-TB and needed treatment.

In any given year, some countries enroll more cases in treatment protocols than have been detected in that same year. For this reason, a more nuanced discussion of detected cases versus enrollment in treatment can be found by looking at data at the country level, detailed in the WHO Global Tuberculosis Report 2013.

The Need for MDR-TB Medicine

The chart below has been compiled using WHO estimates and from data the WHO has collected over time from country-level TB programs. This graphic represents data aggregated across these countries, and is intended to provide a high-level overview of the gaps between diagnosis and treatment of MDR-TB worldwide. The graphic highlights the large gap that exists globally between those who have been diagnosed with MDR-TB and placed on treatment and those who are estimated to be in need of treatment.

MDR-TB MEDICINES: GLOBAL TRENDS IN NEED, DEMAND, AND ACCESS TO MEDICINE



DATA KEY

- Access** = the number of TB patients placed on MDR-TB treatment
- Unmet demand** = the difference between the number of MDR-TB cases notified* and those placed on treatment as reported to the WHO by national TB programs
- Unmet need** = the difference between the number of cases placed on MDR-TB treatment and those estimated to occur among cases notified each year*

* Notified cases refer to cases reported by a country's national TB program to the WHO during a given year.
Note: All data represented here focuses on patients with pulmonary tuberculosis.
Source: Figures taken from the WHO Global Tuberculosis Report 2013, p. 53, WHO Global Tuberculosis Control 2010, p.1, and WHO Global Tuberculosis Control 2012, pps. 38, 41.

2. Country and donor funding can be subject to delays.

Organizations responding to diseases such as MDR-TB rely on national governments and international donor agencies as primary funders for medicines and treatment infrastructure. This can lead to significant process complexity and cycle time as organizations at the local, regional, national, and international levels seek to align priorities and funding requests. Even after payers approve funding, transfer of funds may be subject to several approval steps across multiple organizations. This leads to delays in disbursement of funds, slowing the procurement of medicine and therefore delaying the start or continuation of treatment. All of these processes add significant uncertainty to manufacturers' ability to forecast market demand beyond programs that are currently funded and have financial resources available.

An estimated 60 percent of the world's MDR-TB cases are in Brazil, Russia, India, China, and South Africa (the "BRICS" countries). In these countries, national contributions provide the bulk of financing for TB control and care. However, these contributions remain insufficient for scaling up diagnosis and treatment of MDR-TB. According to the WHO Global Tuberculosis Report 2012, between 2013 and 2015, up to \$8 billion per year is needed in low- and middle-income countries to combat TB, with a funding gap of up to \$3 billion per year. It is important to note that while national TB plans may cite proposals to treat a certain number of MDR-TB patients, these planned scale-ups may not match reality. Countries don't always hit their targets, and manufacturers may be left with unsellable surplus.

A common wish among manufacturers of MDR-TB drugs is for funding of the medicines to be more predictable and flexible. Some in the global health community have suggested innovative financing mechanisms to improve the way MDR-TB drugs are procured.

THE QUESTION OF LOCAL MANUFACTURING OF PHARMACEUTICALS

The local manufacture of pharmaceutical products (that is, manufacturing in a country where there is a patient population in need of the end product) is often cited as a promising way to solve the "access to medicines" problem. Countries around the globe, especially in low- and middle-income regions, often view this approach as a way to bring down costs of pharmaceuticals, theorizing that local production should render a cheaper finished product.

However, it's important to consider external economic and capacity realities when making this calculation. Not all countries have companies with the necessary technology or operating capability, or markets sufficiently large to achieve economies of scale. The end price of the medicines must also be at a level that funders or purchasers are willing to pay. This pressure on both the price of the medicine and the cost structure of the supplier may mean that importing medicines from large-scale operators can be more economically sustainable than local production.

Some larger, middle-income countries, such as India and China, already possess a scientific and manufacturing industry base to tackle the complex task of manufacturing and formulating active drug substances. The large size of the home markets in both these countries allows them to achieve economies of scale, producing individual units at low cost. In fact, the success of these countries in manufacturing pharmaceuticals could represent a challenge to other, less-developed countries seeking to sustain local production of medicines. All these factors must be weighed to determine if local manufacturing can improve product supply and reduce prices.

3. Manufacturers need incentives and support to achieve International Quality Assurance (IQA) standards.

To supply drugs to many national and international programs, drug suppliers must prove that their medicines meet pre-established, internationally sanctioned GMP standards, often referred to as International Quality Assurance (IQA). These guidelines are in place to assure the safety and efficacy of the end product. Many companies meet IQA guidelines by securing approval from a regulatory agency that is a member of the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)**.

In the case of MDR-TB, to be a supplier to the GDF, drug manufacturers must be approved either through a regulatory authority that is a member of the ICH or through the WHO Prequalification (PQ) process. ICH members are the United States Food and Drug Administration, the European Medicines Agency, and the Japanese Ministry of Health, Labour, and Welfare. Approval by any of the three ICH members or the WHO PQ process defines a medicine manufactured by a particular supplier as meeting IQA standards.

For manufacturers in markets not currently subject to oversight from one of these four agencies, upgrading manufacturing and laboratory equipment, work processes, quality assurance and control standards, policies, human resources, and other areas can be onerous. Implementation of these changes may take months or even years, and compiling data and dossiers for submission can be extremely time-consuming. Ultimately, these costs need to be paid for somehow. The Lilly MDR-TB Partnership supported its receiving manufacturers in achieving IQA standards. But if such support is not provided, the costs of this onerous approval process could easily deter potential in-country manufacturers, especially when there are not clear market signals of an expected return on investment.

4. Procurement, packaging, and regulatory requirements vary by country and add costs for manufacturers.

After pharmaceutical companies have manufactured a drug, every additional step required to bring that drug to market adds time and cost. When selling in multiple countries, varying rules and specifications can complicate even relatively routine processes, such as securing orders for product or packaging the drugs for end use. This complexity necessitates additional organizational and management controls.

It is no different for manufacturers of MDR-TB drugs. To be eligible for procurement by the GDF, MDR-TB manufacturers may also be required to register their products in countries to which the GDF supplies medicine. For example, China, India, and Russia, representing a significant percentage of the total MDR-TB population, each require registration of medicines under their own regulatory mechanisms. This means that manufacturers who want to supply these countries through the GDF mechanism must obtain multiple registrations: one for IQA for eligibility purposes and another in each country they will be supplying. More than 17 of the 29 countries considered to have the highest global burden of MDR-TB expect some form of local registration, although some do offer accelerated or abbreviated processes if IQA approval has already been obtained, or if the GDF can obtain specific waivers, on a case by case basis.

If local country registrations are required, dossiers for each country need to be supplied in specific formats, in the local language, and with special packaging developed to meet local expectations. Typical dossiers may stretch to 1,000 pages or more, and filing of a dossier may need to be accompanied by a fee to the government agency. Procurement mechanisms also vary widely among countries, and meeting these various requirements adds layers of complexity to an already complicated process.

All of this activity in the registration step increases the cost and delays the availability of medicine to patients. At the global level, this leads to further fragmentation of the market and is not helpful in driving economies of scale, which could lead to lower prices.

5. Supply chain logistics are often not well understood, making it difficult to respond to actual demand for medicines.

Global agencies like the GDF are responsible for managing the purchase of medicines from suppliers, the consolidation of multiple medicines into country shipments, and the delivery of the medicines to the first port of entry of a country. Each country is then responsible for managing its own distribution of medicines. In many countries, there is practically no integration of information across this extended supply chain, leading to inefficiencies at best and gaps in the supply of medicine to patients at worst.

In-country product supply chain management—encompassing everything needed to get medicines to patients, including monitoring, forecasting, ordering, storage, and delivery—can also be variable. This can manifest itself in the waste of expired medicines or in the placement of “emergency” orders with very short lead times to prevent interruption of patient treatment.

The drugs that treat MDR-TB have shelf lives as short as 18 months.²⁶ Despite the need for the medicines to be used relatively quickly, in many countries information is lacking about product use and patient

treatment rates, so such information can't be translated into any forecasting mechanism. This means that the overall process for ordering MDR-TB drugs is unpredictable. Under-forecasting can result in drug shortages; unrealistically high forecasts mean that countries may have to destroy expired goods. Absent reliable forecasts, many manufacturers will not begin preparations or even order raw materials until they have an order for the end product in hand. The result can be long lead times for the drugs: sometimes as much as several months.

These uncertainties contribute to inefficient, slow, and costly operation of the supply chain and can add to manufacturers' reluctance to enter the market or to engage in the process of transferring technology. Reducing these uncertainties and improving the availability and visibility of information across the supply chain should increase confidence in the operation of the marketplace. This, in turn, should encourage manufacturers to enter markets and receive transfers of technology as a means to do so. Last but not least, improving supply chain operation should increase access to medicines for patients.

Historically, MDR-TB has been a low global priority. More recently, many have called for greater investment, collaboration, and collective action. Due to the access and treatment barriers described in the previous section of this paper, as well as low rates of diagnosis, demand for MDR-TB medicines has been much smaller than it would be if most infected patients were being diagnosed and promptly started on treatment. This low market demand for medicines has contributed to higher costs.

In starting the Lilly MDR-TB Partnership, Lilly embarked on the largest philanthropic endeavor in the company's history, which included subsidizing MDR-TB medicines at prices below our costs. We acknowledge that current prices for MDR-TB medicines are now, in some cases, higher than they were when Lilly's was subsidizing the price. However, while prices have not fallen in all cases for patients, the cost of production has fallen as a result of technology transfer.

We are proud of the Lilly MDR-TB Partnership's achievements, but we are aware that there are still vast numbers of patients awaiting treatment. The reality is that if MDR-TB is not treated with effective drugs taken over the full course of therapy, the disease will continue to spread. Globally, tackling MDR-TB has proven more challenging than anyone had imagined. Over the course of our work in this area, Lilly has learned about the myriad obstacles blocking patient access to diagnosis and treatment. The strategy of transferring technology to produce MDR-TB drugs in key affected geographic areas has proved especially timely, as the need for quality-assured medicines is only getting larger. However, technology transfer is but one piece of a broader puzzle needed to eradicate this deadly disease.

To effectively address MDR-TB for an individual patient, several things need to happen:

- A patient must feel empowered to seek help for his or her disease
- The patient must have access to healthcare services that can provide testing, accurate diagnosis, prompt access to treatment, and follow-up support
- The patient must receive the appropriate therapeutic course of medicines and observation over time to ensure compliance and effectiveness.

For too many MDR-TB patients, one or more of these needs is not met. Overcoming barriers to timely diagnosis, production of an adequate supply of medicines, and distribution of these drugs to patients in need will take a focused, coordinated effort from a global health community committed to stamping out TB and MDR-TB.

For Lilly, the lack of demand for MDR-TB drugs, despite the ever-increasing numbers of people suffering from this disease, is a call to action; it means that too many people living with TB are not receiving lifesaving treatment. However, without the right infrastructure to ensure correct administration of the medicines, even the act of providing the medicines could unwittingly lead to greater drug resistance. Our wish is that all patients with MDR-TB have access to affordable, quality-assured treatment within a sustainable MDR-TB drug market. To this end, we are involved in several programs, including continued work with multiple stakeholders to improve access to quality-assured MDR-TB medicines. The [Lilly TB Drug Discovery Initiative](#), the TB Drug Accelerator, and other programs funded through the Lilly MDR-TB Partnership address these and other critical issues.

Through 2016, Lilly has committed \$170 million in cash, medicines, and support to our distinguished partners for much-needed programs and to companies that will make lifesaving medicines. Ultimately, however, the solutions to stemming the growing tide of MDR-TB must be systemic, multi-sector approaches that support proven, sustainable clinical and market-based solutions. Success depends on a sustained, joint commitment by governments, NGOs, and businesses to bring an end to this disease.

API (active pharmaceutical ingredient): A substance used in the manufacture of medicines that provides the desired pharmacological activity

CDC: The Centers for Disease Control and Prevention, the national public health institute of the United States

Chemotherapy: The treatment of disease through chemicals

Drug-susceptible TB: TB that can be treated by first-line TB drugs

FDA: The Food and Drug Administration, the agency in the United States' government responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, and veterinary products

Fermentation: In the pharmaceutical manufacturing process, the stage in which the biologically active drug substance, or precursor, is produced by an organism grown in a controlled environment

First-line drugs: Four drugs—isoniazid, rifampicin, ethambutol, and pyrazinamide—that when used in combination can cure drug-susceptible TB in 87 percent of patients

GDF: The Stop TB Partnership Global Drug Facility, established in 2001, is a one stop procurement mechanism for quality assured TB commodities that provides a package of services, including technical assistance as well as procurement of quality TB drugs and diagnostics. It serves countries and other customers around the world

Generic drug: A pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights²⁷

GLC: Green Light Committee, a multi-institution partnership housed at the World Health Organization with the goal of increasing access to quality-assured second-line drugs in countries with limited resources. As of 2014, the GLC is a component of the GLC Initiative that serves as a technical advisory body to the Stop TB Partnership and the WHO²⁸

GMPs (good manufacturing practices): A system that aims to ensure quality production by eliminating inconsistencies and errors in the manufacturing process

ICH: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, an organization working to promote standardized regulations among the United States, Europe, and Japan

IQA (International Quality-Assured) medicines: Medicines that have been approved by one of the ICH members (U.S., EU or Japan) or the WHO PQ process

Lyophilization: A method of freeze-drying for preservation

MDR-TB: Multidrug-resistant tuberculosis

MSF: Médecins Sans Frontières (Doctors Without Borders)

PIH: Partners in Health

Second-line drugs: TB medicines that are used to treat TB that is resistant to one or more first-line drugs

SRA (stringent regulatory authority): A regulatory agency that is a member of the ICH, which presently comprises the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Japanese Ministry of Health, Labor and Welfare (MHLW)

WHO: World Health Organization

WHO PQ (Prequalification Programme): A United Nations program, managed by the World Health Organization, that aims to verify and guarantee the quality of medicines

XDR-TB: Extensively drug-resistant tuberculosis

- ¹ Return of the 'White Plague': Fears over the rise of 'incurable' TB. CNN.com. <http://www.cnn.com/2014/05/28/health/return-white-plague-incurable-tb/index.html>. Accessed June 4, 2014.
- ² Tuberculosis. World Health Organization. Available at <http://www.who.int/mediacentre/factsheets/who104/en/print.html>. Accessed April 14, 2014.
- ³ Expand-TB Project: Progress in Diagnosis. World Health Organization. Available at http://www.who.int/tb/features_archive/EXPAND_TB_project_factsheet.pdf. Accessed April 14, 2014.
- ⁴ Global tuberculosis report 2013. World Health Organization. Available at http://www.who.int/tb/publications/global_report/en/. Accessed April 14, 2014.
- ⁵ Tuberculosis. World Health Organization. Available at <http://www.who.int/mediacentre/factsheets/fs104/en/>. Accessed April 14, 2014.
- ⁶ Tuberculosis: Age of Optimism. National Institute of Allergy and Infectious Diseases. Available at http://www.niaid.nih.gov/topics/tuberculosis/Understanding/history/Pages/historical_optimism.aspx. Accessed August 21, 2013.
- ⁷ TB and Me: History. Médecins Sans Frontières/Doctors Without Borders. Available at <http://blogs.msf.org/tb/files/2012/03/TB-infographic-history-final.pdf>. Accessed August 21, 2013.
- ⁸ The Difference Between Latent TB Infection and TB Disease. Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/tb/publications/factsheets/general/tbdiandactivetb.htm>. Accessed April 10, 2014.
- ⁹ Executive Summary: Global Tuberculosis Report 2013. World Health Organization. Available at http://www.who.int/tb/publications/global_report/gtbr13_executive_summary.pdf. Accessed April 10, 2014.
- ¹⁰ Tuberculosis. World Health Organization. Available at <http://www.who.int/mediacentre/factsheets/who104/en/print.html>. Accessed April 14, 2014.
- ^{11,12} Executive Summary: Global Tuberculosis Report 2013. World Health Organization. Available at http://www.who.int/tb/publications/global_report/gtbr13_executive_summary.pdf. Accessed April 10, 2014.
- ¹³ Drug-resistant tuberculosis: Frequently asked questions. Available at <http://www.who.int/tb/challenges/mdr/tdrfaq/en/>. Accessed April 14, 2014.
- ¹⁴ The use of short regimens for treatment of multidrug-resistant tuberculosis. World Health Organization. Available at http://www.who.int/tb/challenges/mdr/short_regimen_use/en/. Accessed April 14, 2014. There have been great strides in developing shorter regimens to treat MDR-TB. However, the WHO considers these treatments to be still in their experimental phase and not guaranteed to be effective.
- ¹⁵ Drug-resistant tuberculosis: Frequently asked questions. World Health Organization. Available at <http://www.who.int/tb/challenges/mdr/tdrfaq/en/>. Accessed April 14, 2014.
- ¹⁶ TB and Me: History. Médecins Sans Frontières/Doctors Without Borders. Available at <http://blogs.msf.org/tb/files/2012/03/TB-infographic-history-final.pdf>. Accessed May 20, 2014.
- ^{17,18} Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus." Paul Farmer, Jim Yong Kim. Available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1113843/pdf/671.pdf>. Accessed April 14, 2014.
- ¹⁹ The Green Light Committee: Ensuring access to life-saving treatment for MDR-TB patients while preserving the efficacy of second-line drugs – our last line of defence against TB. World Health Organization. Available at ftp://ftp.cdc.gov/pub/nchstp/tb/WHO_CC_Latvia/present/GLC.pdf. Accessed April 14, 2014.
- ²⁰ Lilly continued producing these medicines for many years (cycloserine through 2007 and capreomycin through 2011).
- ²¹ The Lilly MDR-TB Partnership was responsible for training more than 17,000 healthcare professionals, including 85 MDR-TB hospital managers and over 1,000 nurses in 15 countries. Lilly and our partners developed and distributed more than 10 guidelines and toolkits to approximately 200,000 professionals and over 45,000 hospitals and clinics.
- ²² Pharmaceutical production and related technology transfer: Landscape Report. World Health Organization. Available at http://www.who.int/phi/publications/pharmaceutical_production/en/index.html. Accessed July 23, 2013.
- ²³ Technology Transfer: a Collaborative Approach to Improve Global Health. International Federation of Pharmaceutical Manufacturers & Associations. Available at http://www.ifpma.org/fileadmin/content/Publication/IFPMA_Technology_Transfer_Booklet_2011.pdf. Accessed April 14, 2014.
- ²⁴ WHO Global Tuberculosis Report 2013: Gains in TB fight are at huge risk. Stop TB Partnership. Available at http://www.stoptb.org/news/stories/2013/ns13_067.asp. Accessed March 23, 2014.
- ²⁵ Fluctuations in estimated MDR-TB among notified cases may reflect TB reporting activity by countries and do not necessarily imply changes over time in the true global burden of MDR-TB. For more details see: Falzon D, Jaramillo E, Wares F, Zignol M, Floyd K, Raviglion MC. "Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data." *The Lancet Infectious Diseases*. 2013 Aug; 13(8):690–7.
- ²⁶ Selection of TB Medicines and Supplies. Management Sciences for Health. Available at http://www.who.int/hiv/amds/%281.4%29Product%20Selection%20for%20TB%20Control_GDF.ppt. Accessed April 14, 2014.
- ²⁷ Generic Drugs. World Health Organization. Available at <http://www.who.int/trade/glossary/story034/en/>. Accessed April 14, 2014.
- ²⁸ The Green Light Committee (GLC) Initiative. World Health Organization. Available at http://www.who.int/tb/challenges/mdr/greenlightcommittee/faq3_what_is_glc/en/. Accessed April 14, 2014.