THE GLOBAL ALLIANCE FOR
TB Drug Development

the *economics* of TB Drug Development

new data for new research

The Economics of TB Drug Development

Global Alliance for TB Drug Development

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Foreword

A Public Health Perspective…

Tuberculosis is one of the most serious and devastating problems threatening public health worldwide. Nearly 2 billion people are infected with the TB bacterium. Every year, more than 8 million people develop an active case of TB and some 2 million people die. This mortality rate is compounded by TB's social and economic impacts. As nearly 30 years have passed since the introduction of a new compound to treat TB, the need for new drugs cannot be overstated. *The Economics of TB Drug Development* is a welcome and enormously important step in moving new R&D forward.

This study was carried out under the auspices of the Global Alliance for TB Drug Development, a public-private partnership created to further the discovery and production of new TB medicines. This organisation and the groundbreaking study presented here are some of the latest developments in the great progress stemming from the Amsterdam Conference in March 2000. At this conference, governments from the 20 countries most seriously affected by TB pledged to make it a priority on their national policy agendas. Later that year, the Group of Eight nations committed to reducing the death toll from TB in half within 10 years. With these political commitments and the leadership of the Stop TB Partnership—which oversaw the development of the Global Alliance and the Global TB Drug Facility—we can begin to envision a world without TB.

Why are new drugs needed to achieve a world without TB? Because while the DOTS strategy for supervised TB treatment is one of the most cost-effective measures available, current drugs and DOTS alone are not enough to stop TB. TB treatment needs to be shorter and/or require fewer supervised doses. It needs to be effective against multidrug-resistant strains of TB that threaten our ability to cure this deadly disease. And it must provide an effective treatment for latent TB infection to stop the spread of the disease.

An Industry Perspective…

I urge my colleagues in industry and all public health stakeholders to take a careful look at this new contribution of the Global Alliance for TB Drug Development. This comprehensive, breakthrough study will be invaluable in helping all parties interested in new drug development to better understand the potential costs and markets for future new anti-TB drugs.

Slightly more than a generation ago, the Surgeon General of the United States made the now famous comment that society could "close the book" and turn its attention away from the challenges of tuberculosis and other infectious diseases. Today, however, TB stands beside AIDS and malaria as among the most critical diseases to be addressed by increasing access and research. Clearly, new TB drugs are needed, and this report represents one of the more important steps towards undertaking that effort.

Estimating the market from $316 million and $432 million, the report goes on to explore the costs of development of a new TB drug and to discuss recent trends in the market and its environment.

Perhaps the most important new trend for the industry to consider is the Global Alliance itself. Along with the Global Alliance for Vaccines and Immunization (GAVI) and the Medicines for Malaria Venture (MMV), as one of the premier new public-private partnerships tackling health outcomes in developing countries, the Global Alliance represents an important opportunity for the industry and the global health community at large. Acting as a virtual incubator, it will speed the process of discovery and/or development of cost-effective new TB drugs. It aims to be a new partner for the pharmaceutical industry, with an important contribution to make, beginning with this one—an authoritative study of the market.

Beyond research, political commitment and adequate local and international funding of people's access to health care will be required to lift the bar that has prevented industry involvement in TB drug development research. It is important to engage countries and multilateral financial institutions now on how they plan to upgrade their health effort and

We must remember, as the report highlights, that in addition to the obvious public health benefits provided by a new TB drug with a shorter treatment regimen lie tremendous social and economic benefits. Furthermore, such a drug will allow public health agencies to redirect their scarce resources away from the costly and labour-intensive observed treatment and toward, for example, buying more drugs.

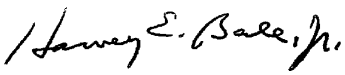
This report not only provides key information on the global burden of TB today and over this decade, but also outlines the potential market for and costs of developing a new TB drug. And it presents some of the other trends that are changing the R&D climate so that all parties can make informed decisions about supporting and pursuing TB drug development.

I strongly invite all those invested in public health outcomes to build on the foundation provided by this report. We cannot afford to ignore the opportunities outlined here. Sustaining the fight against TB is essential for our health and socio-economic future.

Dr. Gro Harlem Brundtland
Director-General
World Health Organization

infrastructure to fight the spread of this disease. That means living up to the commitment to accelerate action against TB—made in Amsterdam last year by countries representing 80% of the global TB burden—so that a majority of the afflicted population will receive treatment. This would lift the last bar to development and provide the industry additional incentive to investigate the opportunity detailed in this report.

The Economics of TB Drug Development report provides a very useful discussion of key factors in making a decision to undertake the risks of TB drug development. It enables a better understanding of the potential costs and markets for future new anti-TB drugs. While a few of the assumptions in the study may be challenged (e.g., on the costs of drug development), the Global Alliance has made a major contribution in identifying and estimating the key variables important to additional industry investment in TB drug discovery and development. I hope this report receives the close attention it rightfully deserves and generates a healthy dialogue among all stakeholders about taking the next steps.



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Preface

The millions of people stricken with tuberculosis (TB), the large number of family and community members indirectly affected by the disease, and all of the people that will be similarly affected in the future compose a group in dire need of help. Although the scientific community and the pharmaceutical industry have provided them with drugs that, in some places and under certain conditions, can cure the existing cases, poverty and poor health infrastructures limit the effectiveness of these drugs. The human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) and multidrug-resistant strains of TB (MDR-TB) will make matters far worse in the future.

Within the pharmaceutical industry, serious drug development for treating TB virtually stopped some 30 years ago, in part because it was perceived that TB was defeated. The Global Alliance for TB Drug Development believes that activity remains low, at least in part, because the real size of the market and costs for drug development are insufficiently appreciated by industry.

This report presents data that sponsors—be they pharmaceutical companies, private foundations, or other investors—need to make an informed decision about investing in drug discovery and development for a new anti-TB treatment:

- The summary of report findings presents an overview of the key data discussed throughout this document.
- The introduction summarises the current treatments available for TB and discusses the need for new therapies.
- *Chapter 1* presents up-to-date, conservative estimates of the number of TB cases in 1999 and projected cases in 2010, the estimated trends for latent TB infection (LTBI), and average public sector health system costs for TB diagnosis and treatment.
- *Chapter 2* presents data on the market for anti-TB drugs, focusing on sales of anti-TB drugs between 1997 and 2000. A projected market for 2010 is estimated as is the potential market for a new anti-TB drug.
- *Chapter 3* presents the costs associated with developing a new anti-TB drug, including drug discovery efforts, preclinical development, pharmaceutical development, and clinical trials.
- *Chapter 4* discusses the potential return on investment, based on the data presented in the previous chapters. The social benefits of a new anti-TB drug also are presented.
- *Chapter 5* discusses other essential trends that should further encourage investment in TB drug development. These trends include public-private partnerships, developments in public policy and philanthropy, and the increasing role of the private sector in treating TB.

A new drug that enables less frequent or, most importantly, shorter duration treatment would be expected to capture a significant portion of the market for anti-TB drugs. Furthermore, health officials in industrialised countries have developed plans for TB elimination; treatment of persons with LTBI is an important component of these plans. A highly effective new drug stands to enable a cost-effective extension of this approach to those developing countries with reasonable infrastructure and thereby multiply its earnings several fold.

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Acronyms

ADME	absorption, distribution, metabolism, and elimination
AIDS	acquired immune deficiency syndrome
API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
BCG	Bacillus of Calmette and Guérin
BUN	blood urea nitrogen
CAPM	capital asset pricing model
CDC	U.S. Centers for Disease Control and Prevention
CGMP	current good manufacturing practices
C_{max}	peak serum level
CMC	chemistry, manufacturing, and controls
CPT	current procedural terminology
CRA	clinical research associate
CRF	case report form
CTM	clinical trial material
DOTS	directly observed treatment, short-course
EBA	early bactericidal activity
FDA	U.S. Food and Drug Administration
G8	Group of Eight nations
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GDF	Global TB Drug Facility
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IND	investigational new drug application
IRR	internal rate of return
IUATLD	International Union Against Tuberculosis and Lung Disease
LFT	liver function test
LTBI	latent tuberculosis infection
MBC	minimum bactericidal concentration
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
MMV	Medicines for Malaria Venture
NCDDG	National Cooperative Drug Discovery Groups
NCE	new chemical entity
NDT	nondrug treatment
NGO	nongovernmental organisation
NIAID	U.S. National Institute of Allergy and Infectious Diseases
NIH	U.S. National Institutes of Health
NNT	number needed to treat
NTP	national TB programme
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	principal investigator
PLWH	people living with HIV/AIDS
PP	private provider
PPD	purified protein derivative
R&D	research and development
RC	research coordinator
RFLP	restriction fragment length polymorphism
RTI	Research Triangle Institute
S&P	Standard and Poor's
SAMRC	South African Medical Research Council
TB	tuberculosis
TBTC	TB Trials Consortium
TBRU	TB Research Unit (Case Western Reserve University)
TDR	Special Programme for Research and Training in Tropical Diseases (UNDP–World Bank–WHO)
VCT	voluntary counseling and testing
WHO	World Health Organization

Summary of Report Findings

Summary of Report Findings

The Economics of TB Drug Development is a rigorous, authoritative source of information on the epidemiology of tuberculosis, potential market for new anti-TB drugs, costs of drug development, the potential return on investment, and options for funding and conducting drug development. Prepared by a variety of TB experts at public health agencies, research organisations, private pharmaceutical companies, and nongovernmental organisations (NGOs), under the auspices of the Global Alliance for TB Drug Development, this report provides essential data required for informed investment decisions by industry, foundations, government organisations, and world health and financial organisations.

This study was conducted because new and more effective drugs would greatly facilitate treatment and control of the TB epidemic. Current drugs impose long treatment durations (at least 6 months) and complex regimens for the internationally recommended DOTS strategy (directly observed treatment, short-course) that are hindering the progress of TB control. For the same reasons, patient compliance often is poor, leading to multidrug-resistant strains of TB against which most drugs are ineffective. And new drugs with shorter regimens are needed for those most at risk of having their latent TB infection develop into active TB.

New drugs that (1) shorten the duration of treatment of TB to 2 months or less, (2) better treat MDR-TB, and (3) offer a shorter regimen to prevent progression from infection to disease would address the needs of millions, accelerate global control and elimination of the disease, and dramatically reduce the overall costs of treating TB.

Yet, no new class of anti-TB drug has been developed in over 30 years, and TB patients worldwide still are treated with the same drugs that were discovered 40 years ago. Research and development (R&D) for new drugs has suffered from the pharmaceutical industry's perceived lack of need and sufficient market. The prevailing wisdom is that costs of drug development far outweigh the potential global market for anti-TB drugs, and thus a sufficient return on investment could not be guaranteed. This study examines these issues to fully understand the economics of TB drug development.

This report discusses the following key findings. All monetary values are in U.S. dollars.

TB Epidemiology

In 1999, an estimated 8.4 million people around the world developed active TB.[1] If current trends continue, this figure is expected to reach an estimated 10.2 million cases in 2005 and 11.6 million cases by 2010.

The number of people starting treatment for LTBI each year in countries with a high HIV prevalence might reach 1 million to 2 million by 2010. In established market economies, this figure is expected to be at least 150,000 and could reach as high as 1.25 million per year.

The average public sector health care costs of treating a single case of infectious TB are estimated to range from $51 in Indonesia to more than $25,000 in the United States. The majority of these costs are to pay for health care services; drug costs make up only a small fraction of the per-patient total costs for TB treatment. Furthermore, the costs should be considered lower bound estimates because costs that might remain fixed as treatment duration is reduced (e.g., programme supervision) were not included in the analysis.

Market for Anti-TB Drugs

Two major markets exist for anti-TB drugs: the private market and the public/tender market. The private market is composed of traditional pharmacy and hospital sales. The public/tender market comprises (1) government purchases of anti-TB drugs at the federal, regional, and/or local level, depending upon the country, and (2) international donors with an interest in TB control strategies that supply drugs to countries with developing economies and/or a high TB burden.

According to the analysis conducted in this report, the current (2000) global market for anti-TB drugs is estimated to be between approximately $412.5 million and $470.5 million per year. This total includes an estimated annual $275 million to $318 million worldwide private market, an estimated annual $125 million to $140 million public/tender market, and an estimated annual $12.5 million market for drugs to treat MDR-TB.

This global market is estimated to increase to between $612 million and $670 million per year by 2010.

At a minimum, a new anti-TB drug that enables a 2-month treatment regimen might be able to capture a market of between $316 million and $345 million per year. This estimate is based on several assumptions, as discussed in the report.

Some markets might be willing to pay a premium for a new anti-TB drug that enables a shorter treatment regimen than is allowed by current pharmaceuticals. This premium would be more than offset by the overall health system savings as a result of the shortened treatment period. Depending on which markets pay a premium and how high the premium is, the market for a new anti-TB drug might expand to an estimated $396 million to $432 million per year.

Costs to Develop a New Anti-TB Drug

This report focused on estimating the total development costs (past the discovery stage) for a new anti-TB drug. Using an approach to include the costs of unsuccessful projects, the total costs of developing a new chemical entity (NCE)—including the costs of

failure—are estimated to be approximately $76 million to $115 million (depending on total development time and discount rate) for preclinical development through Phase III clinical trials and regulatory approval. The actual costs—without factoring in the costs of failure—would total between approximately $36.8 million and $39.9 million (assuming that all development work takes place in countries with established economies):

- The preclinical studies expected to be required to support registration of an NCE are estimated to cost between approximately $4.9 million and $5.3 million.
- The overall costs for the chemistry, manufacturing, and controls (CMC) portion of a pharmaceutical development programme are estimated to be at least $5.3 million. Parexel's 1999 *Pharmaceutical R&D Statistical Sourcebook* suggests that these costs could be as high as $8 million.[2]
- A full programme of clinical development (Phase I through Phase III trials) for a new anti-TB drug is estimated to cost about $26.6 million in a country with an established economy. Comparable studies conducted in a country with a developing economy are estimated to cost approximately $9.9 million.

As for discovery costs, these are estimated to range from $40 million to $125 million (including failure costs). As suggested by the breadth of this range, discovery costs are difficult to estimate. Even so, one can use these rough estimates of discovery and the estimated costs of preclinical through clinical development calculated for this report to project a total cost of between $115 million and $240 million to discover and develop a new anti-TB drug (including the costs of failure). However, it generally is accepted that discovery and development of a new drug to treat TB will require an international, collaborative effort among governments, academic institutions, foundations, NGOs, and pharmaceutical companies. In this way, costs can be shared by multiple organisations, ultimately lowering the investment burden borne by a single agency or company.

Return on Investment: Financial and Social

According to analyses using standard formulas and the above data, the internal rate of return for a new anti-TB drug is estimated to range from 15% to 32%, depending on the pace of development, where the clinical trials are conducted, and the size of the revenues. This range is calculated on the basis of development costs from preclinical research through regulatory approval and includes TB-specific probabilities of success. The range indicates that investing in development of a lead compound is an attractive commercial venture.

The social benefits of a new anti-TB drug that meets the criteria outlined at the beginning of this summary will be significant. In most countries for which data are available, drug costs make up less than half of total costs to diagnose and treat TB. Reducing the duration of treatment by two-thirds (from 6 months to less than 2 months) will significantly reduce the number of sputum smears, X-rays, hospital days, DOTS visits, and clinic visits required. Consequently, even if drug costs under a 2-month regimen are the same as under the 6-month regimen, the per-patient treatment costs will be substantially reduced. Such improvements will enable health systems to treat more

patients without an increase in expenditures and will help DOTS programmes expand more quickly.

The public health benefits of a shorter regimen include improved compliance, resulting in reduced resistance, transmission, morbidity, and mortality. A 2-month treatment for TB also will reduce the heavy price that TB exacts on patients and their families, who incur significant direct nonmedical costs (e.g., travel and special food during treatment) and indirect costs (e.g., lost income).

Essential Trends and Opportunities

Public-private partnerships are providing opportunities to share and balance the risks and investments. For example, the Global Alliance for TB Drug Development is bringing together public and private sector resources and expertise to ensure the provision of new medicines with equitable access for the improved treatment of TB. Its R&D partners include pharmaceutical and biotechnology industry firms, public research organisations involved in TB and/or anti-infectives R&D, and academic institutions conducting TB research.

Furthermore, a number of developments are occurring on the public policy agenda and in philanthropic circles that might transform the context of TB control and R&D for anti-TB drugs. Pledges have been made by donors and high-burden countries alike to accelerate action against TB—one of three major infectious diseases threatening global health (HIV/AIDS and malaria are the other two). Mechanisms are being designed to expand TB control programmes, procurement of anti-TB drugs, and TB research. Meanwhile, several foundations have placed global health as a central or key priority and are actively supporting innovative strategies to fight the disease.

In addition, the private sector is playing an increasing role in TB treatment. Studies investigating TB patients' health-seeking behaviour in many high-burden countries, such as India, Pakistan, the Philippines, Viet Nam, and Uganda, indicate that a large proportion of patients with symptoms of TB first approach a private provider. Thus, perceptions that anti-TB drugs are sold only in the public/tender market in these countries are misplaced.

Conclusion

The analyses in this report provide information needed for a pharmaceutical company, foundation, public agency, or other investor to make a sound decision concerning investment in the development of a lead compound for TB. Indeed, the findings point to a sizable TB market, relatively controlled costs, and attractive expectations in terms of return on investment and social benefits.

These findings, and the new trends and opportunities for TB R&D, ought to reinvigorate interest in developing lead compounds into new, faster acting, more effective, and affordable TB treatment by the end of this decade. Such a new drug will go a long way toward winning the battle against a disease that not only is a tremendous burden to the poorest countries but also is a threat to all nations.

Introduction

Introduction: Overview of TB and its Treatment

Tuberculosis is one of the most deadly infectious diseases in the world, and it is projected to remain so even in the year 2020.[3] Although TB thrives in areas of poverty, its reach extends to all economies and affects all age groups. In 1999, an estimated 8.4 million people around the world developed active TB.[1] The disease is estimated to claim the lives of approximately 2 million people worldwide every year.[4] Next to AIDS, TB kills more young and middle-aged adults than any other disease.[5] Approximately 50% of those with active TB will die of the disease if they are not treated. Because of a powerful interaction between TB and HIV, the number of TB cases has risen rapidly in sub-Saharan Africa and Asia. Multidrug-resistant TB has been reported at alarming rates in a number of countries throughout the world.[6]

TB is an airborne disease that is spread easily through coughing and sneezing. Most people with TB have pulmonary TB (which can be infectious or noninfectious), although some have extra-pulmonary disease (which is always noninfectious).

As a disease, TB is the result of two distinct steps. An individual first must become infected with *Mycobacterium tuberculosis*, most commonly by close exposure to persons with infectious TB. This step leads to latent TB infection, which is not associated with symptoms and is not infectious. Approximately 10% of infected individuals then develop active TB months to years after initial infection, and some of these cases will be infectious. However, this rate is much higher for those who are coinfected with TB and HIV. Because HIV suppresses the immune system, individuals who are coinfected with TB and HIV are 30 to 50 times more likely to develop active TB than those who are HIV-negative.[7]

Existing Approaches to Diagnose and Treat Active TB

TB began to be effectively controlled in countries with established economies in the 1960s and 1970s, leading to a significant reduction in TB cases in industrialised countries.[5] However, inadequate control practices in countries with developing economies, which tended to focus on case-finding rather than effective treatment, actually worsened the TB problem. Moreover, the anti-TB vaccine (Bacillus of Calmette and Guérin [BCG]), although widely used, did not effectively reduce pulmonary TB incidence in adults.[8] Ensuring that effective TB control is provided demands that the health care infrastructure be functioning adequately and can support well-organised TB diagnostic and treatment services.

Diagnosis

Pulmonary TB is most commonly diagnosed by microscopic examination of stained smears of expectorated sputum using the acid-fast technique. If the sputum smear is positive, then the TB case is infectious. However, acid-fast microscopy detects only those patients with relatively advanced pulmonary TB. The technique is arduous and time-consuming and requires continued training and supervision of microscopists to maintain effective performance. A recent expansion of research activities in this field is expected to lead to more accurate and more easily performed routine diagnostic tests within 3 to 5 years.[9]

Treatment and Control: DOTS

Control of TB depends on new vaccinations and/or effective treatment, in part because treating TB prevents transmission of the contagious disease. New, more effective vaccines are unlikely to be available for widespread use for the next 20 years or more.[10] Drug treatment has had the most effect in controlling TB over the last 50 years.[11] The drug regimens for treating TB currently recommended by the World Health Organization (WHO) are presented in Exhibit 1. These regimens include a 2-month "intensive phase," during which four drugs usually are administered, and a "continuation phase" of two drugs for 4 to 6 months.

Only during the past 20 years have effective systems of TB control been developed in low-income countries. Building on the groundbreaking work of the British Medical Research Council and the International Union Against Tuberculosis and Lung Disease (IUATLD), WHO developed detailed guidelines for TB management in developing countries, including standardised drug regimens, diagnostic algorithms, and guidelines for programme management from drug procurement to patient registration materials.[12] This treatment policy is called DOTS, which stands for directly observed treatment, short-course. The main components of DOTS are as follows:

- Government commitment to TB control
- Diagnosis by smear microscopy for sputum acid-fast bacilli (and by culture where resources permit)
- Standardised short-course chemotherapy using rifampicin-based regimens with directly observed treatment at least for the first 2 months
- A secure supply of safe, high-quality drugs and diagnostic supplies
- Recording and reporting systems with individual patient evaluation at end of treatment

WHO has adopted DOTS as the mainstay of its global TB control strategy. The strategy has been shown to be both efficacious and cost-effective in several countries.[13–15] According to the World Bank's *World Development Report*, DOTS compares favourably with infant vaccination, oral rehydrations for childhood diarrhoeal disease, and protection of blood supply (for HIV).[13] Cure rates of up to 95% for cases of smear-positive pulmonary TB have been achieved using the DOTS strategy.[1]

Exhibit 1: Current WHO-Recommended Drug Regimens for Treatment of Drug-Susceptible TB

TB Patients	Drug Regimen	
	Intensive Phase (no. of months of drug combination)	Continuation Phase (no. of months of drug combination)[a]
New Sm+ pulmonary TB; new Sm– pulmonary TB with extensive parenchymal involvement; new cases of severe forms of extra-pulmonary TB	2 of EHRZ or 2 of SHRZ	4 of HR
	2 of EHRZ or 2 of SHRZ	4 of H_3R_3
	2 of EHRZ or 2 of SHRZ	6 of HE
Sm+ relapse; treatment failure; treatment after interruption	2 of SHRZE and 1 of HRZE	5 of $H_3R_3E_3$
	2 of SHRZE and 1 of HRZE	5 of HRE
New Sm– pulmonary TB (other than in category I); new less severe forms of extra-pulmonary TB	2 of HRZ	6 of HE
	2 of HRZ	4 of HR
	2 of HRZ	4 of H_3R_3

[a] Subscript 3 indicates that this is a 3 times/week regimen. All others are daily regimens.

H = isoniazid: daily at 5 mg/kg/day or 3 times/week at 10 mg/kg/day

R = rifampicin: daily at 10 mg/kg/day or 3 times/week at 10 mg/kg/day

Z = pyrazinamide: daily at 25 mg/kg/day or 3 times/week at 35 mg/kg/day

S = streptomycin: daily at 15 mg/kg/day or 3 times/week at 15 mg/kg/day

E = ethambutol: daily at 15 mg/kg/day or 3 times/week at 30 mg/kg/day

Sm+ = sputum smear-positive Sm– = sputum smear-negative

The rate at which the DOTS strategy has been adopted by high-burden countries initially was rapid. According to the latest WHO *Global Tuberculosis Control* report, only 10 countries used DOTS in 1990; by the end of 1999, 127 had adopted it, including the 23 countries that make up 80% of the world's TB burden.[1] In 1999, 45% of the global population had access to a DOTS programme, and 23% of diagnosed smear-positive cases were being treated in these programmes.

However, the pace of DOTS expansion in recent years has been deemed too slow. The WHO report acknowledges that, if current trends hold steady, the goal of having DOTS detect 70% of cases by 2005 will not be met—in fact, estimates suggest that this level of coverage will not be achieved until 2013. Some of the delay in DOTS expansion stems from its being cumbersome and labour intensive throughout the minimum 6 months of treatment.

The introduction of a shorter, simplified treatment with fewer doses needed under supervision would likely facilitate DOTS expansion.

Diagnosing and Treating LTBI

Diagnosis

The current standard technique for diagnosing persons with latent TB infection is to measure the induration produced in the skin of the forearm through a delayed hypersensitivity reaction following intradermal injection of a standardised preparation of tuberculous proteins. The goal of the "tuberculin skin test" is to identify tuberculin-positive individuals at high risk for developing active TB. High risk can be defined as the following:[16]

- Recent infection with *M. tuberculosis* (especially for young children), including recent contact with infectious TB cases
- The presence of clinical conditions that are associated with an increased risk of progression of LTBI to active TB (e.g., HIV infection, organ transplant, silicosis, leukemia, diabetes mellitus)
- Those with lung scars from remote, untreated TB

Because of their extremely high susceptibility to TB, treating LTBI in people living with HIV/AIDS (PLWH) is quite important. However, detecting *M. tuberculosis* in PLWH is not straightforward. Criteria for determining when to consider the tuberculin skin test positive (and indicative of LTBI) have been modified to allow both for BCG vaccination (to which there is cross-reactivity, as BCG itself is a member of the same complex of organisms as LTBI) and for HIV status (which through its immunosuppressive effects, reduces the hypersensitivity reaction). Despite these modifications, rates of skin test positivity remain higher among people who are HIV-negative than among people who are HIV-positive with similar background exposures, even among those who are not deeply immunosupressed.

The use of antigens derived from genes that are absent in BCG but present in wild strains of *M. tuberculosis* has led to tests for LTBI that are more specific than the tuberculin skin test. Whether such tests will prove sufficiently sensitive and practical to detect a greater proportion of PLWH who also have LTBI remains an important question.

Treatment

The mainstay of treatment for LTBI has been isoniazid for 6 to 12 months. Recent studies have shown that rifampicin-based regimens lasting for only 2 to 4 months are as effective as isoniazid.[16,17]

Guidelines for treatment of LTBI vary. According to the U.S. Centers for Disease Control and Prevention (CDC) guidelines, persons with recently acquired infection (e.g., contacts with infectious patients and recent immigrants from countries with high TB rates) and those with medical conditions that increase the likelihood of progressions to active TB (e.g., HIV infection) should be considered for LTBI therapy if their tuberculin test is positive, their chest X-rays are normal, and no symptoms consistent with active TB are present.[18] WHO and IUATLD recommend that individuals coinfected with TB and HIV be given preventive therapy.[19] Under some circumstances, it might not be feasible to perform purified protein derivative (PPD) testing, and WHO has recommended that it is reasonable to treat LTBI in PLWH even in the absence of a skin test result, if the background prevalence of LTBI is high (>30%) in the population being treated.

Limitations of Current Control and Treatment Methods

As DOTS coverage has expanded, it has become apparent that the current TB treatment regimens, although highly effective, are far from ideal. For every success story (e.g., Peru, Viet Nam, parts of India and China), there are many others far less optimistic, and the TB epidemic continues to grow.

O'Brien and Nunn succinctly summarise the limitations of currently available drugs:[5]

> Using the optimal combination of available drugs, the duration of treatment required for curing patients cannot be reduced below 6 months. In most low-income countries, an 8-month regimen is used. When used under suboptimal program conditions, these regimens are associated with high rates of patient nonadherence, with the consequence of increased mortality and the creation of chronic, infectious drug-resistant cases.[20] Furthermore, all four of the most effective oral drugs—isoniazid, rifampicin, ethambutol, and pyrazinamide—must be taken together during the first 2 months of treatment. Although rates of serious adverse reactions are low, many patients experience unpleasant side-effects when taking 10 or more tablets/capsules at one time.

Side effects range from frequent nausea, vomiting, diarrhoea, liver toxicity, and potentially fatal rash to hearing damage and kidney damage to hepatitis, fever, and hypothyroidism to neurological changes and psychosis to severe abdominal pain and skin colour changes. O'Brien and Nunn also note that second-line drugs are more expensive, more toxic, and/or less effective.[5] For example, ethambutol can be replaced with streptomycin, but this introduces the disadvantages of an injectable drug—namely, the need for sterile needles, syringes, and water for injection.

In addition, having treatment directly observed by a health care provider is cumbersome, labour-intensive, and expensive. Development of drug resistance is far more likely when supervised treatment is not given, when recommended regimens are not used, and when drugs with poor bioavailability are used.

Rates of MDR-TB have increased in countries such as the Russian Federation, where MDR-TB has spread in prisons and to the general population.[21] To address this problem, WHO and others have advocated the strategy of DOTS-plus, a combination of effective control practices and the provision of second-line anti-TB drugs in a systematic way.[22]

In addition, the cost of these second-line drugs can be prohibitive. White and Moore-Gillon estimated that the costs of treating MDR-TB in the UK are approximately 10 times the costs of treating the drug-susceptible disease,[23] though it can be up to 50 times more expensive (see *Section 2.3*).

Properties of a New Anti-TB Drug*

As discussed in the *Scientific Blueprint for TB Drug Development*, treatment and control of TB has three urgent needs:[24]

- Improve current treatment by shortening the total duration of treatment and/or by providing for more widely-spaced intermittent treatment
- Improve the treatment of MDR-TB

* It should be noted that new drugs alone will not solve the TB problem. Introducing new drugs into a poorly run program only accelerates the development of new strains of MDR-TB.

- Provide for more effective treatment of LTBI in programmes that are able to implement this practice

New drugs to improve current treatment by enabling regimens that facilitate patient and provider compliance would have the greatest impact on TB treatment. Shorter regimens and those that require less supervision are the best way to achieve this. Most of the benefit from treatment comes in the first 2 months, during the intensive, or bactericidal, phase when four drugs are given together; the bacterial burden is greatly reduced, and patients become noninfectious.[25] The 4- to 6-month continuation, or sterilising, phase is required to eliminate persisting bacilli and to minimise the risk of relapse. A potent sterilising drug that shortens treatment to 2 months or less would be extremely beneficial. Drugs that facilitate compliance by requiring less intensive supervision also are needed. Obviously, a compound that reduces both the total length of treatment and the frequency of drug administration would provide the greatest benefit.

Exhibit 2 presents the minimum and desired product profile for a new anti-TB agent to make it substantially better, compared with currently available medications.

Exhibit 2: Product Profile for a New Anti-TB Drug

	Minimal Product Characteristic	Added-Value Product Characteristic
Route of administration	Oral	
Likelihood of resistance developing	Spontaneous mutation rate similar to that for existing anti-TB drugs	Spontaneous mutation rate less than that for existing anti-TB drugs
Early bactericidal activity		EBA activity as a single entity
Activity against latent TB		Active
Activity against MDR strains	Active *in vivo* against all TB isolates including MDR strains	
Dosing schedule	Once daily	Once weekly or less
Length of administration	6 months as part of combination chemotherapy	Entire regimen is 4 months or less (combination chemotherapy)
Clinical safety	Safety profile in clinic not significantly worse than existing first-line anti-TB agents in terms of incidence and seriousness of adverse reactions when given in combination for desired length of administration[a]	No significant toxicity
Clinical efficacy	Relapse rates at 6 months post-treatment similar to current regimen (when new agent is used in combination for desired length of administration)	Relapse rates at 6 months shown to be significantly better than standard therapy with four drugs given for 6 months (when new agent is used in combination for desired length of administration)
Clinical use in TB regimen	New agent can replace one of four drugs used in current 6-month regimen	New agent can replace two or more of four drugs used in current 6-month regimen
Drug-drug interactions	No serious interactions with companion anti-TB medications[b]	None, including other anti-TB and anti-HIV agents
Drug–comorbid disease interactions	No serious drug-comorbid disease state interactions (e.g., thiacetazone and HIV)	

[a] Side effects of current regimens include red-orange discoloration of urine and feces, hepatoxicity, arthralgias, ototoxicity, visual impairment, vertigo, gastrointestinal intolerance, and hypersensitivity.

[b] Drug-drug interactions include interactions with medications that induce the cytochrome P450 system.

Source: Global Alliance for TB Drug Development[24]

1.0 The Global Burden of Tuberculosis

1.0 The Global Burden of Tuberculosis

To understand the economics of TB drug development and the potential return on investment, one first must understand the epidemiological and economic burden of the disease. This chapter examines the current and future burden of TB using estimates of the following:

- The number of TB cases in 1999 and the predicted number in 2010
- The health care costs of treating drug-susceptible disease

According to the World Health Organization, an estimated 8.4 million people around the world developed TB in 1999.[1] If recent trends continue for the rest of the decade, the projected global number of new cases will increase to an estimated 10.2 million in 2005 and an estimated 11.6 million in 2010. The number of new MDR-TB cases arising in 2000 worldwide currently is estimated to be roughly 273,000 per year. [26]

Treating individuals with latent TB infection could prevent transmission of TB within a community. Although LTBI treatment has been minimal, the rising burden of HIV-related TB in poor countries and the increasing relative importance of imported TB in rich countries provide opportunities for more widespread treatment of LTBI. It is expected that the number of people starting treatment for LTBI each year in high-HIV-prevalence countries might reach 1 million to 2 million by 2010. In established market economies, this figure is expected to be at least 150,000 and could reach as high as 1.25 million per year.

The health care costs of treating drug-susceptible disease vary widely from country to country and region to region. Estimates suggest that the public sector costs per treated smear-positive case might range from as low as $51 per patient in Indonesia to more than $25,000 per patient in the United States (all monetary figures are in $US). It should be noted that these cost estimates exclude any costs that might remain fixed even when treatment duration is reduced (e.g., programme supervision, training). The majority of the treatment costs pay for health care services such as sputum smears, X-rays, hospital days, DOTS visits, and clinic visits. Drug costs make up only a small fraction of the per-patient total costs for TB treatment.

Taken together, these findings, which are discussed in detail in this chapter, suggest that the market for anti-TB drugs is large and likely to expand. For more information on the market for anti-TB drugs, see *Chapter 2*.

Exhibit 3: Estimates of TB Cases and the Incidence Rate in 23 High-Burden Countries (1999)

Country (ranked by burden)	Population (1,000s)	All TB		Smear-Positive TB	
		Cases (1,000s)	Rate per 100,000 pop.	Cases (1,000s)	Rate per 100,000 pop.
1 India	998,056	1,847	185	827	83
2 China	1,266,838	1,300	103	584	46
3 Indonesia	209,255	590	282	265	127
4 Nigeria	108,945	327	301	142	130
5 Bangladesh	126,947	306	241	138	108
6 Pakistan	152,331	269	177	121	79
7 Philippines	74,454	234	314	105	141
8 Ethiopia	61,095	228	373	96	157
9 South Africa	39,900	197	495	80	201
10 Russian Fed.	147,196	181	123	81	55
11 DR Congo	50,335	151	301	65	130
12 Viet Nam	78,705	149	189	67	85
13 Kenya	29,549	123	417	51	173
14 Brazil	167,988	118	70	53	31
15 UR Tanzania	32,793	112	340	47	145
16 Thailand	60,856	86	141	38	62
17 Mozambique	19,286	79	407	33	169
18 Myanmar	45,059	76	169	34	76
19 Uganda	21,143	72	343	31	146
20 Afghanistan	21,923	71	325	32	146
21 Zimbabwe	11,529	65	562	26	226
22 Cambodia	10,945	61	560	27	251
23 Peru	25,230	58	228	26	102
High-burden total	**3,760,358**	**6,700**	**178**	**2,969**	**79**
Global total	**5,975,045**	**8,417**	**141**	**3,724**	**62**

Source: WHO[1]

1.1 Estimated Number of TB Cases in 1999 and 2010

The latest information on the number of cases of TB worldwide is presented in *Global Tuberculosis Control: WHO Report 2001*.[1] The fifth of a series of annual reports, this document presents and analyses data on 1999 case notifications and treatment outcomes supplied by national TB control programmes. Of the 211 countries surveyed, 171 (81%) responded, including nearly all of the 23 countries (not Mozambique) with the highest burden of TB and all countries with populations exceeding 10 million except Canada, Yemen, Madagascar, and Niger.

1.1.1 Global Distribution and Trends

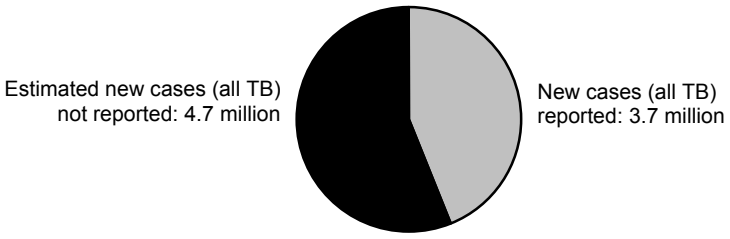
According to WHO, the estimated number of new TB cases worldwide in 1999 was 8.4 million.[1] However, TB incidence varies dramatically around the world. The 23 countries with the highest TB burden accounted for 80% of the world's new cases in 1999 (Exhibit 3).

Exhibit 4: Number of New Smear-Positive TB Cases by Region (1999)

Region	Notified Smear-Positive Cases	Estimated Smear-Positive Cases	Case Detection Rate
Africa	321,260	863,782	37%
Americas	133,363	178,822	75%
Eastern Mediterranean	67,135	277,397	24%
Europe	86,271	213,017	41%
South-East Asia	485,790	1,348,194	36%
Western Pacific	391,964	842,956	47%
Total	**1,485,783**	**3,724,168**	**40%**

Source: WHO[1]

Exhibit 5: Proportion of Estimated New Cases (all TB) Actually Notified Worldwide (1999)



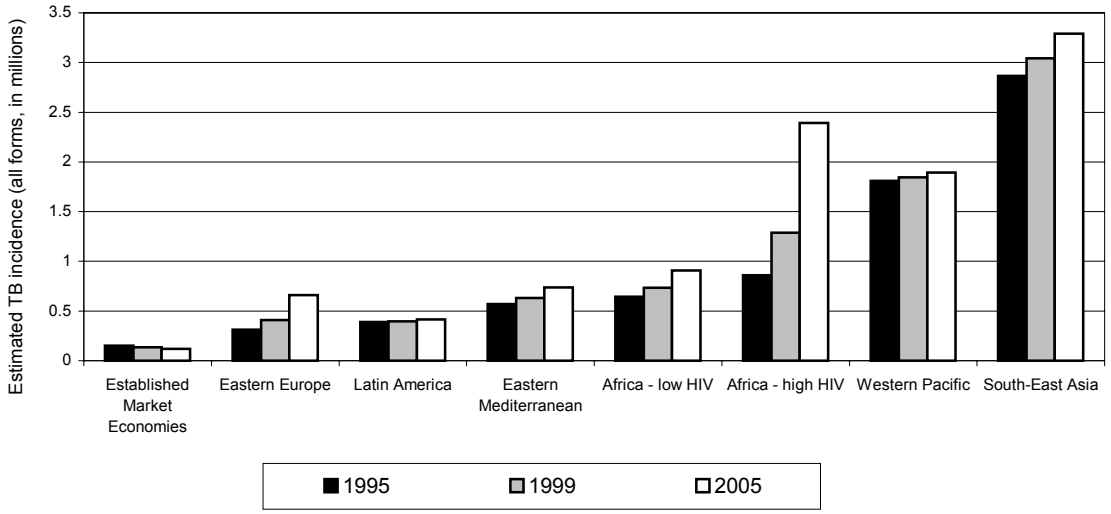
Source: WHO[1]

By far the largest number of estimated cases were in India (1.8 million) and China (1.3 million), which together represent more than one-third of the world's TB cases. It should be noted, however, that the estimated incidence (i.e., the rate of new cases per 100,000 people) for all TB cases in India and China was not the highest. Sixteen high-burden countries had an estimated TB incidence greater than India's, and only one high-burden country (Brazil) had an estimated TB incidence lower than China's.

Exhibit 4 presents an overview of how the TB burden is distributed around the world. The data presented are the number of **notified** sputum smear-positive (i.e., infectious) cases in 1999. As might be expected, the South-East Asia region and Western Pacific region, which include India and China, respectively, had the highest numbers of notified cases. However, it is believed that many cases of TB are not reported. As shown in Exhibit 5, WHO estimates that approximately 56% of all TB cases worldwide were not reported in 1999. The proportion of smear-positive cases of TB not reported in 1999 was an estimated 60%.[1]

WHO projections indicate that the number of TB cases will increase worldwide except for countries with established market economies.[1] Exhibit 6 presents estimated numbers of TB cases for 1995, 1999, and 2005 for groups of epidemiologically similar countries.

Exhibit 6: Estimated Number of New TB Cases by Region: 1995, 1999, and 2005



Source: WHO[1]

It illustrates the impact of HIV infection on the TB incidence in Africa, where African countries with a high HIV prevalence show a steep rise in the number of new cases.

For all countries combined, the rate of increase in the number of new TB cases is about 3% per year. **If this trend continues for the rest of the decade, the projected number of new TB cases worldwide will increase to 10.2 million in 2005 and to 11.6 million in 2010.** These projections should be viewed only as gross approximations; however, to the extent that the historical trends will continue, the projections do provide reasonable estimates of future incidence.

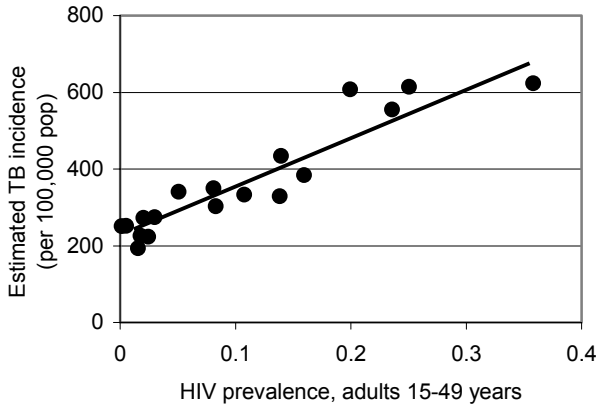
1.1.2 Drug-Resistant TB

In addition to the projected global increase in the number of new TB cases, several countries also are experiencing increases in the proportion of cases of drug-resistant TB. The number of new MDR-TB cases worldwide in 2000 is estimated to be roughly 273,000.[26] WHO and the IUATLD conducted surveys of 58 geographic sites.[6] These surveys found that among new cases, the median proportion that were resistant to at least one drug was 10.7%. The median proportion of TB cases with multiple drug resistance was 1.0%. In Estonia, the prevalence of drug-resistant TB increased from 28% of all TB cases in 1994 to 37% in 1998. Of the sites with data available for at least 2 years, additional countries that showed a significant increase in the proportion of new cases with resistance to at least one anti-TB drug included Denmark, Peru, New Zealand, and Germany. Although significant increases in the proportion of MDR-TB cases did not occur in countries that had a high prevalence of MDR-TB, the prevalences remained high.

In many parts of the world, including the Americas, Western Europe, and Africa, drug resistance apparently is not a serious problem. However, the problem of drug resistance persists in several Eastern European countries, and newly surveyed areas of Iran and parts of China have revealed a high proportion of MDR-TB cases. Unfortunately, of the countries with the highest number of TB cases (Exhibit 3), only half have relevant data available regarding drug resistance,[6] so the magnitude of the problem is unclear.

1.2 Estimating Trends of LTBI over the Next Decade

Exhibit 7: Association between Estimated TB Incidence and HIV Prevalence among Adults in 18 African Countries (1999)



Source: WHO[1]

Part of the substantial increase in TB is due to its collision with the HIV epidemic. Individuals who are HIV-positive are highly susceptible to TB and, in turn, active TB disease boosts HIV levels in the blood. Exhibit 7 presents the estimated incidence of TB compared to HIV prevalence in the 18 African countries that report TB cases consistently. As the graph shows, TB incidence is highly correlated with the estimated prevalence of HIV infection among adults.

As stated earlier, treating individuals with LTBI could prevent transmission of TB within a community. However, since the number of people in poor countries with LTBI is huge (sometimes more than half the adult population), and the large majority of these will never progress to active TB, it has not been thought practical or efficient to establish programmes to treat them. In such countries, treatment of LTBI usually is included in TB guidelines only as preventive treatment for young children (typically under 5 years) who are living in close contact with an infectious case. Despite appearing in programme manuals, such contact tracing and preventive therapy often is applied poorly or not at all, and the priority continues to be placed on detecting the active cases and treating them to prevent transmission of infection.

1.2.1 LTBI and People Living with HIV

Recent developments have changed the outlook for treatment of LTBI. The rising burden of HIV-related TB in poor countries and the increasing relative importance of imported TB in rich countries provide opportunities for more widespread treatment of LTBI.

The HIV epidemic has led to devastating rises in TB cases, particularly in Africa but also in specific regions of countries in Asia where HIV prevalence rates have risen. In these

countries, more than half of the adult population may already have LTBI. HIV is the strongest risk factor yet identified for progression from LTBI to active TB;[27] therefore, it is not surprising that many PLWH develop active TB. Recent estimates of TB incidence in countries with varying prevalence of HIV among adults have demonstrated that the scale of the HIV epidemic remains the most important determinant of the rising burden of TB in Africa.[28] An attractive possibility to reduce the impact of HIV on the burden of TB is to treat PLWH before they develop active TB.

Current estimates are that about 12 million adults are living with HIV-TB coinfection and that 35 million people are living with HIV infection only. The number of people who know their HIV status is probably fewer than 5%—around 600,000 coinfected persons and 1.8 million HIV-only persons. The number of people currently given treatment for LTBI is estimated to be very small—probably fewer than 5% (30,000) of those who are coinfected and even fewer (e.g., 3.3%) of those whose HIV status is unknown.

A new initiative in sub-Saharan Africa—ProTest—promotes voluntary counselling and testing (VCT) for HIV as an entry point for a range of HIV and TB prevention and care interventions.[29] The populations served by the pilot sites are hard to quantify because people from other populations might enter the site specifically to access the services. Nonetheless, estimates indicate that testing has now increased as high as 365 per 100,000 adult population per month in some parts of Africa (e.g., the East London area in South Africa). Many other VCT initiatives are beginning to scale up. If such activities were scaled up considerably, the proportion of people who know their HIV status could rise substantially. In Uganda, the AIDS Information Centre has tested more than 600,000 adults during the past 10 years through its network of VCT centres. The contribution of the private sector also is hard to estimate as data are not collated or published.

If the momentum for ProTest and other VCT expansion continues, it seems plausible that 15% to 25% of PLWH in 2010 will know their status and around 50% of these might be coinfected with *M. tuberculosis*. This might lead to approximately 5 million coinfected adults knowing their HIV status.

The experience in the ProTest pilot studies and other sites offering treatment of LTBI is that fewer than 50% of those eligible for screening actually start treatment. Reasons for not starting treatment include previous or current active TB, symptomatic disease that requires investigation, and a variety of other logistic or personal reasons. Many VCT services that are established in the next decade will start off delivering antiretrovirals to prevent transmission from mothers to their babies. Thus, even if adherence to treatment could be improved, it is hard to imagine that more than 25% (around 1.25 million) of coinfected individuals would be started on treatment through these sorts of sites. In addition, some people still would be started without proof of infection with *M. tuberculosis*, although the proportion of those treated blindly might fall as tests for LTBI improve.

Another mechanism that has been proposed for some high-prevalence situations (e.g., industrial settings) is to use a mass treatment approach. In these situations, treatment for LTBI would probably be offered without HIV testing. There is no experience yet of the acceptability or efficacy of such an approach in a high-HIV-prevalence setting, although

it has been used in the past in other settings. If this approach is developed and researched over the next few years, it could lead to large numbers of people (either HIV-positive or -negative) starting treatment.

The number of people starting treatment for LTBI in high-HIV-prevalence countries could grow gradually from around 50,000 per year at present to a maximum of around 1 million to 2 million per year over the next decade.

1.2.2 LTBI in Established Market Economies

The past decade has seen an awakening of enthusiasm for treatment of LTBI as a control strategy in established market economies, particularly the United States. Since the risk of infection with *M. tuberculosis* has fallen considerably over the past 50 years in these countries, the oldest age cohorts have the highest prevalence of infection. Active disease now occurs most commonly among older people or among specific population groups, such as immigrant communities, homeless people, and intravenous drug users (sometimes in association with HIV). One treatment approach that has been advocated to reduce rates of TB in these settings is to target such population groups for detection of LTBI and to treat them.[30] Several studies have demonstrated that short-course-combined regimens including 2 months of rifampicin, given daily or intermittently, provide effective protection from the development of active TB.[16,17]

According to WHO, around 110,000 cases of TB are currently detected each year in established market economies.[1] Perhaps 50,000 of these arise in immigrants and other high-risk populations. Given continued population mobility, this number might remain rather stable over the next years.

The "number needed to treat" (NNT) is a parameter derived from clinical trials and meta-analyses that allows an estimate of how many people need to be treated to prevent one outcome event. For treatment of LTBI, the outcome event would be active TB. The NNT depends on the efficacy of the treatment and the frequency of the outcome. Since many people in established economies who are infected with LTBI will never develop active TB, the NNT is expected to be at least 10, even if the efficacy of treatment is rather high. (For example, if the treatment has a 66% efficacy and 15% of those with LTBI are expected to develop active TB in the absence of treatment, then for every 10 people given treatment one case would be prevented.) If the NNT is high, the risks and costs of treatment will outweigh the benefits.

Thus, if treatment of LTBI is to be delivered on a sufficient scale to reduce the burden of TB among the 50,000 immigrants and other high-risk populations by 30%, it would need to be given to approximately 150,000 people per year—that is, 10 (the estimated NNT) x 15,000 (the estimated number of cases prevented). An upper boundary for this estimate might be 1.25 million people treated per year—that is, an NNT of 50 x an impact of 50% (25,000 cases).

1.2.3 Implications

These numbers for the use of treatments for LTBI in HIV-endemic areas and established market economies are based on order-of-magnitude estimates that should be considered with caution. Nonetheless, they suggest that the number of cases of HIV-related LTBI treated each year by the year 2010 could be 1 million to 2 million in countries with a high HIV prevalence. At present, most authorities seem reluctant to use rifamycin derivatives or other new products in this area for fear of losing drugs effective in the treatment of active TB, which still is the priority. In addition, a further 150,000 to 1.25 million cases of LTBI might be treated in settings with a lower prevalence of active disease, where there will be less reluctance to use shorter rifampicin-containing regimens or new products. *Chapter 2* discusses in detail the potential drug costs for treating LTBI.

1.3 Average Public Sector Health System Costs for TB Diagnosis and Treatment per Treated Case

Estimates of health care expenditures associated with a TB diagnosis are based on two major sets of inputs:

- The unit costs of services required to diagnose and treat TB
- The numbers and types of these services for different types of TB cases (i.e., smear-positive, smear-negative, and retreatment cases)

These data then can be used to estimate the costs for each diagnosed and treated case (see *Appendix A* for methodology). The estimated unit costs and health care use data presented in this section were made using the data available:

- Published costing studies[16,17,23,31–36]
- Unpublished cost data from recently completed and ongoing projects by WHO and the Royal Tropical Institute that are considered to be of high quality
- Interviews with national TB programme staff
- Interviews with WHO country and regional office staff
- Review of national plans and guidelines

Drug costs represent the prices paid by the public market. (For more information on the public versus the private markets, see *Chapter 2*.)

The number and types of specific services included in diagnosing and treating TB vary from region to region; however, they often include various diagnostic tests, hospital bed days, and DOTS visits and out-patient visits to clinics for collection of drugs or sputum-smear monitoring. The unit costs for each of these items, including recurrent (e.g., staff, supplies) and capital (e.g., buildings, equipment) items, are presented in Exhibit 8 for 15 countries around the world.

By estimating the extent to which these services are used in each country and multiplying these estimates by the unit cost information presented in Exhibit 8, one can estimate per-patient total costs in each country. Exhibit 9 presents these estimated public sector health

Exhibit 8: Estimated Public Sector Unit Costs for Health Care Services Related to TB for Selected Countries (in $US)

	Smears	X-rays	Fluoroscopy	Hospital Days	DOTS Visits	Clinic Visits
Africa						
Ethiopia	$0.4	$5.5	$1.0	$3.6	$0.3–$0.6	$0.3–$0.6
Kenya	$0.4	$5.5	$1.0	$4.3-$8.2	$1.6	$1.6
South Africa	$1.8–$2.9	$6.6–$12.8	$1.0	$32.3	$3.9	$3.9
Uganda	$0.4	$5.5	$1.0	$6.4–$7.7	$0.03	$0.7
Zimbabwe	$0.4	$5.5	$1.0	$14.1	$0.2	$2.0–$2.4
Americas						
Peru	$1.5	$4.4			$0.9	
Eastern Mediterranean						
Egypt	$3.4–$18.0	$4.6–$25.0		$13.0	$1.5–$5.0	$5.0
Syria	$3.0–$4.0	$26.0–$65.0			$3.0–$24.0	$8.5
Europe						
Russia	$0.2	$6.6	$0.5	$4.0	$1.0	$1.0
South-East Asia						
Bangladesh	$0.4	$5.5	$0.4–$1.0	$3.6–$8.2	$0.3–$2.4	$0.6–$2.4
India	$0.4	$5.5	$1.0	$3.6–$8.2	$0.6–$2.4	$0.6–$2.4
Indonesia	$0.4	$5.5	$1.0	$3.6–$8.2	$0.1–$0.4	$0.6–$2.4
Myanmar	$0.4	$5.5	$1.0	$3.6	$0.1–$0.3	$0.6
Thailand	$1.8–$2.9	$6.6–$12.8	$1.0	$32.3	$0.6	$3.9
Western Pacific						
China	$1.0	$5.5	$1.0	$3.6–$8.2	$0.2	$0.6–$2.4

Sources: Published costing studies;[16,17,23,31–36] unpublished cost data from WHO and the Royal Tropical Institute, interviews with national TB programme staff, interviews with WHO country and regional office staff, and national plans and guidelines.

system costs (with drug costs identified) for the 15 countries presented in Exhibit 8 and the United States and the United Kingdom. As expected, the U.S. and U.K. have the highest costs per case.

Upon considering the per-patient treatment costs presented in Exhibit 9 and the extent to which the disease is being treated, one can begin to comprehend the magnitude of the public sector health care costs for treating TB. Estimates derived from the treatment costs presented here and the number of TB cases reported to WHO for 1999 suggest that the annual total public sector costs in the United States range from $182 million to $447 million; in the United Kingdom, approximately $56 million; in India, $57 million to $197 million; and in China, $30 million to $40 million.

For several reasons, the per-country health system costs discussed in this section should be considered **lower bound estimates**:

- The costs presented do not include district and national costs for the overall TB programme management and supervision, training, health promotion, and operational research. In most countries, dedicated personnel at the district and national level are responsible for implementing the TB programme.

Exhibit 9: Estimated Public Sector Health System Costs per Treated Case for Selected Countries (in $US)[a]

	New Smear Positive		New Smear Negative		Retreatment	
Africa						
Ethiopia	Total:	$71–$94	Total:	$62–$85	Total:	$95–$138
	Drugs:	$33	Drugs:	$25	Drugs:	$66
Kenya	Total:	$345–$579	Total:	$71–$315	Total:	$483–$835
	Drugs:	$43	Drugs:	$25	Drugs:	$86
South Africa	Total:	$1,350–$1,486	Total:	$1,343–$1,474	Total:	$1,913–$1,925
	Drugs:	$55	Drugs:	$55	Drugs:	$118
Uganda	Total:	$430–$541	Total:	$77–$117	Total:	$646–$764
	Drugs:	$32	Drugs:	$25	Drugs:	$64
Zimbabwe	Total:	$148–$164	Total:	$130–$146	Total:	$182–$199
	Drugs:	$43	Drugs:	$25	Drugs:	$86
Americas						
Peru	Total:	$189	Total:	$163–$169	Total:	$217
	Drugs:	$30	Drugs:	$27	Drugs:	$104
U.S.	Total:	$10,376–$25,117	Total:	$9,972–$24,714	Total:	$11,806–$26,547
	Drugs:	$797	Drugs:	$393	Drugs:	$2,227
Eastern Mediterranean						
Egypt[b]	Total:	$164–$981	Total:	$164–$981	NA	
	Drugs:	$75	Drugs:	$75		
Syria[b]	Total:	$183–$353	Total:	$183–$353	NA	
	Drugs:	$73	Drugs:	$73		
Europe						
Russia	Total:	$1,115–$1,395	Total:	$1,114–$1,394	Total:	$1,115–$1,162
	Drugs:	$83	Drugs:	$83	Drugs:	$83
U.K.	Total:	$9,029	Total:	$8,940	Total:	$9,950
	Drugs:	$200	Drugs:	$111	Drugs:	$1,121
South-East Asia						
Bangladesh	Total:	$64–$319	Total:	$37–$69	Total:	$98–$417
	Drugs:	$33	Drugs:	$25	Drugs:	$66
India	Total:	$57–$201	Total:	$38–$127	Total:	$45–$162
	Drugs:	$7	Drugs:	$7	Drugs:	$7
Indonesia	Total:	$51–$111	Total:	$47–$107	Total:	$86–$149
	Drugs:	$33	Drugs:	$25	Drugs:	$66
Myanmar	Total:	$68–$82	Total:	$48–$63	Total:	$105–$128
	Drugs:	$43	Drugs:	$25	Drugs:	$86
Thailand	Total:	$219–$280	Total:	$199–$256	Total:	$217–$304
	Drugs:	$43	Drugs:	$25	Drugs:	$86
Western Pacific						
China	Total:	$61–$75	Total:	$57–$71	Total:	$66–$86
	Drugs:	$18	Drugs:	$18	Drugs:	$36

[a] Drug costs are conservatively estimated using tender prices for the public market. (See *Chapter 2* for a discussion of the public/tender vs. the private market.)

[b] The data source for Egypt and Syria did not distinguish between per-patient costs for treating smear-positive and smear-negative cases.

Sources: Totals were calculated based on estimates of health care usage and the unit cost data presented in Exhibit 8.

- The drug costs used are the costs of the drug bought in the public/tender market for use in the public health system. Private market drug prices are higher (see *Chapter 2*).
- The costs per treated case for MDR-TB have not been estimated, and these costs are considerably higher than those for drug-susceptible disease. For example, in the UK, the costs of treating MDR-TB are approximately 10 times the costs of treating drug-susceptible disease.[23]

- The costs per treated case for LTBI are not included, which are expected to be quite high in the United States, where an average eight individuals are identified during investigations as coming in contact with infectious cases.[37]
- TB suspects sometimes receive treatment before a final diagnosis is made. For example, it is estimated that, for every person in the United States with a confirmed diagnosis of TB, 3.22 people are suspected, started on therapy, and ultimately determined not to have active disease.[34] The costs for each of these cases are estimated to be $358 in total and $169 for drugs.[34,36]
- The costs discussed in this section do not include various significant costs incurred by the patient. These costs include direct nonmedical costs (e.g., travel, lodging, special food) and indirect costs (e.g., income lost due to sick leave).

For a discussion of how the health system and other costs might be impacted by a new anti-TB drug that enables the duration of treatment to be reduced to 2 months, see *Section 4.2*.

1.4 Summary

The information presented in this chapter shows that the number of new TB cases each year is high and is projected to increase substantially at a rate of 3% per year. The 1999 estimated figure for new cases of TB per year is 8.4 million, and this figure is expected to increase to 10.2 million in 2005 and 11.6 million in 2010—assuming previous trends hold steady. Clearly, the burden of TB is high and will continue to grow.

Moreover, because of the HIV epidemic, the number of people who have LTBI and are HIV-positive is likely to increase significantly in regions with a high burden of HIV; this change will increase the pool of people eligible for treatment of LTBI. It is estimated that the number of people per year who will start treatment for LTBI might reach 1 million to 2 million in countries with a high prevalence of HIV. In established market economies, this figure is estimated to become at least 150,000 and could reach as high as an estimated 1.25 million per year.

Also presented were estimates of the average total costs and drug costs associated with diagnosing and treating drug-susceptible TB in the public sector (drug costs per patient are higher in the private sector). These cost estimates for diagnosing and treating a case of smear-positive TB range widely within and across regions—from a low of approximately $51 per patient in Indonesia to more than $25,000 per patient in the United States. The total health system costs per TB patient are high and unlikely to change over the next 10 years. With the projected increase in TB incidence, global expenditures for TB treatment will show corresponding increases. If the proportion of cases who become aware of their HIV or LTBI status increases, then the health system costs for treating LTBI also could increase substantially over the next decade. All of these increases would lead to a growing market for anti-TB drugs.

Apart from the costs incurred for provision of health care services, patients and their families and friends bear other costs of the disease, including travel, lodging, and special food while the patient accesses health care (i.e., direct nonmedical costs) as well as lost

income due to time spent in care (i.e., indirect costs). *Section 4.2.2* explores these costs in depth and the benefits that will be reaped if a new anti-TB drug is introduced that reduces the treatment regimen from 6 months to 2 months.

Chapter 2 focuses on the markets for anti-TB drugs, examining the public/tender and private (i.e., pharmacy and hospital) sales of anti-TB drugs in various regions, as well as in the 23 countries with the highest TB burden.

2.0 Market for Anti-TB Drugs

2.0 Market for Anti-TB Drugs

This chapter details the global market for anti-TB drugs (including those to treat MDR-TB) and drugs to treat latent TB infection. Also discussed are projections for the market for a new anti-TB drug.

Two major market segments exist for anti-TB drugs: the private market and the public/tender market. **The private market** is composed of traditional pharmacy and hospital sales. **The public/tender market** comprises (1) government purchases of anti-TB drugs at the federal, regional, and/or local level, depending upon the country, and (2) international donors with an interest in TB control strategies that supply drugs to developing and high-burden countries. Such donors include WHO, the Canadian Agency for International Development, and the Stop TB Partnership. This chapter presents market information according to these two markets. All monetary values are in U.S. dollars.

The current (2000) total global market for anti-TB drugs is estimated to be between $412.5 million and $470.5 million per year. This figure includes the following:

- An estimated annual $275 million to $318 million worldwide private market (based on 2000 sales data for anti-TB drugs); this includes approximately $17 million to treat LTBI
- An estimated annual $125 million to $140 million public/tender market (as projected by experts at the World Bank, WHO, and Partners in Health)
- An estimated annual $12.5 million market for drugs to treat MDR-TB

As detailed in this chapter, this market is expected to increase to between $612 million and $670 million per year by 2010.

In order to calculate the potential market for a new drug to treat TB, one must make several assumptions, as described in this chapter: (1) the new drug would hit the market in 2010 and would be administered along with the current drug regimens for various forms of TB, (2) the new drug would reduce the duration of treatment for standard drug-resistant TB from 6 months to 2 months, (3) the new drug would be active against MDR-TB and would shorten its treatment from an average 18 months to 6 months, (4) the new drug would be used to treat LTBI and would reduce its treatment duration from 3 months to 1 month or less, and (5) the total costs for the drug regimen would remain the same. Under these five assumptions, the potential market that might exist for such a new drug is estimated to range from $316 million to $345 million per year. If some markets are

Exhibit 10: Global Private Market Sales of Anti-TB Drugs (by WHO region): Dollar Volume and Unit Volume 1997–2000 (in thousands of $US and in units)

	1997		1998		1999		2000	
Region	**$000**	**Units**	**$000**	**Units**	**$000**	**Units**	**$000**	**Units**
AFR	$6,486	110,122	$5,350	75,720	$7,445	106,159	$9,347	113,005
AMR	$60,556	103,914	$56,727	94,674	$58,998	96,557	$57,227	102,593
EMR	$15,512	261,701	$14,054	277,159	$13,616	276,872	$13,097	273,116
EUR	$58,230	410,273	$40,152	360,428	$35,452	279,400	$37,059	311,421
SEAR	$117,127	1,427,688	$100,427	1,432,891	$100,584	1,462,967	$100,996	1,484,352
WPR	$55,773	475,296	$47,751	447,119	$56,298	456,822	$57,167	464,355
Total	**$313,684**	**2,788,994**	**$264,461**	**2,687,991**	**$272,393**	**2,678,777**	**$274,893**	**2,748,842**

AFR=Africa EMR= Eastern Mediterranean SEAR=South-East Asia
AMR= Americas EUR=Europe WPR= Western Pacific
Source: IMS Health

willing to pay a premium of at least 35% for the new drug (see *Section 2.6*), then the market might expand to between $396 million and $432 million per year.

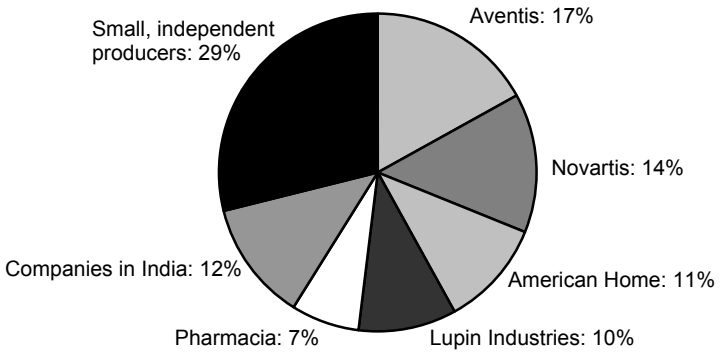
It should be noted that the above figures for the current market and the potential market for anti-TB drugs are **only estimates**. Calculating the size of the market for anti-TB drugs is problematic for a number of reasons. First, control strategies for TB, and thus markets for anti-TB drugs, are highly dependent upon national economies and medical infrastructure. Second, estimates of current and past anti-TB drug sales are incomplete. Specifically, data on sales in the private and public/tender markets are not available for a number of countries, including many of the 23 countries with the highest burden of TB. Third, the market for anti-TB drugs is highly dynamic, as the demand for drugs is affected by the TB epidemic and political commitment to providing the funds needed to combat it. Therefore, current and past sales for these drugs might not reflect changes in the number of TB cases nor the true societal demand for anti-TB drugs. However, although they are imperfect, estimates of total worldwide sales of anti-TB drugs provide the best available data for estimating the size of the market.

2.1 Private Market for Drugs to Treat Active TB

As noted above, private markets generally are traditional pharmacy and hospital sales and usually are found in highly industrialised countries. Information for the private market for anti-TB drugs was provided by IMS Health* as audited sales data for the period 1997 to 2000. Total sales are calculated in current U.S. dollars. IMS Health also provided data on the total number of units (i.e., number of doses).

* IMS Health is an information provider for the pharmaceutical and health care industries. IMS Health tracks volume, growth trend, and market share information for ethical/prescription drugs in health care markets around the world. More information is available online (http://www.imshealth.com).

Exhibit 11: Market Share of the Private Anti-TB Drug Market (1998)



Source: IMS Health

2.1.1 Global Private Market Sales

Exhibit 10 summarises total dollar-volume and unit-volume sales in the private market for anti-TB drugs by region from 1997 to 2000. When measured in terms of the number of units sold, the global private market for anti-TB drugs appeared to be stable. Unit volume remained relatively constant—at about 2.7 billion units—between 1997 and 2000. Annual dollar volume of sales worldwide decreased slightly from more than $313 million in 1997 to nearly $275 million in 2000.

According to 1998 data from IMS Health, the majority (59%) of the private market for anti-TB drugs was shared by Aventis, Novartis, American Home Products, Lupin Industries, and Pharmacia. Indian producers of generic formulations made up about 12% of the private market, while the remaining 29% of the private market was shared by a number of smaller, independent producers worldwide. These private market shares are presented in Exhibit 11. More than 40% ($113 million) of private sales in 2000 were in industrialised countries, as detailed in Exhibit 12.

Falling dollar-volume sales combined with constant unit-volume sales suggest that the unit price of anti-TB drugs has decreased over the past 4 years. This finding is not surprising given that all of the drugs in the WHO-recommended regimen are generic drugs, resulting in greater competition among drug producers that has caused unit prices to fall. In addition, raw material production in India, China, and Korea has increased. In India, this increase has contributed to lower production costs and a substantial decrease in the price of anti-TB drugs. Substantial improvement in TB control during the past 10 years in many high-burden countries also might have contributed to stable unit-volume sales.

As shown in Exhibit 10, private market sales in dollars and units declined in every region between 1997 and 2000 except Africa, where the incidence of TB increased and the WHO DOTS initiative expanded during this period. However, it is important to note that overall unit-volume sales held constant during this time period.

By far, the largest private market for anti-TB drugs can be found in South-East Asia, and data were available for all countries in this region with the exception of Myanmar. In 2000, this region, which includes high-burden countries such as Bangladesh, India, Indonesia, Myanmar, and Thailand, accounted for nearly 37% of worldwide private market sales ($101 million) and 54% in unit volume (1.5 million units). Within South-East Asia, India accounted for nearly 85% of dollar-volume sales ($85.3 million) and more than 75% of unit-volume sales (1.1 million units) in 2000. In terms of dollar-volume and unit-volume sales, India by far has represented the largest private market in the world.

During 2000, the Americas region was the second largest private market in the world in dollar volume ($57 million) but had the lowest unit-volume sales (less than 103,000 units). This finding is tied to exceptionally high unit prices in the United States. The second largest private market in unit-volume sales was the Western Pacific region, with more than 464,000 units sold in 2000. Leaders in this region included Japan and the Philippines. Even with more than four times the unit sales, this region essentially matched the Americas region in dollar volume. The European region came in third with sales of about 311,000 units. Within this region, the Russian Federation represents the largest single market in unit-volume sales, with nearly 137,000 units sold in the private market in 2000. Dollar-volume leaders in the region are Germany ($7.9 million), the Russian Federation ($7.0 million), the United Kingdom ($5.9 million), and France ($5.4 million).

Exhibit 12: Private Sales of Anti-TB Drugs in Industrialised Countries: Dollar Volume and Unit Volume 2000 (in thousands of $US and in units)

Country	$000	Units
Australia	$1,041	3,093
Austria	$880	1,927
Belgium	$651	2,417
Canada	$603	2,899
Finland	$760	993
France	$5,401	19,112
Germany	$7,867	15,033
Greece	$403	4,151
Ireland	$92	417
Israel	$24	41
Italy	$1,001	9,031
Japan	$28,475	144,375
Korea, Rep.	$4,895	118,615
New Zealand	$400	1,005
Norway	$61	56
Portugal	$5	173
Spain	$2,032	18,967
Switzerland	$657	1,375
United Kingdom	$5,885	14,532
United States	$52,076	84,545
Total	**$113,209**	**442,757**

Source: IMS Health

2.1.2 Private Market in High-Burden Countries

As discussed in *Chapter 1*, 23 countries account for nearly 80% (6.7 million) of the estimated 8.4 million annual new TB cases worldwide.[1] Recent private market sales data are available for 11 of these 23 high-burden countries (Exhibit 13). Private market sales of anti-TB drugs in 2000 for these 11 countries accounted for over 53% of estimated worldwide private market dollar-volume sales—$148 million of $275 million—and more than 80% of worldwide unit-volume sales—2.2 million units out of 2.7 million units. Among these high-burden countries, India has the largest number of new TB cases per year, the largest private market dollar-volume sales, and the largest unit-volume sales for

Exhibit 13: Private Sales of Anti-TB Drugs in High-Burden Countries: Dollar Volume and Unit Volume 1997–2000 (in thousands of $US and in units)

Country (Region)[a]	Estimated 1999 New TB Cases (000)	1997		1998		1999		2000	
		$000	Units	$000	Units	$000	Units	$000	Units
India (SEAR)	1,847	$98,784	1,143,630	$91,731	1,193,174	$86,275	1,127,857	$85,336	1,121,624
China (WPR)	1,300	$654	42,949	$723	42,351	$1,494	46,491	$2,008	54,239
Indonesia (SEAR)	590	$12,901	178,327	$4,659	153,847	$11,089	263,289	$12,347	289,095
Bangladesh (SEAR)	306	$3,864	57,582	$2,974	46,212	$2,012	31,588	$2,296	36,577
Pakistan (EMR)	269	$13,490	244,382	$12,220	260,946	$12,109	265,079	$11,672	262,291
Philippines (WPR)	234	$22,141	159,269	$17,866	152,607	$19,150	148,130	$16,655	135,495
South Africa (AFR)	197	$6,486	110,122	$5,350	75,720	$7,445	106,159	$9,347	113,005
Russian Fed. (EUR)	181	$15,010	188,209	$5,619	119,902	$2,714	89,029	$6,972	136,709
Brazil (AMR)	118	$14	71	$12	29	$12	35	$11	21
Thailand (SEAR)	86	$1,578	48,149	$1,063	39,658	$1,208	40,233	$1,017	37,056
Peru (AMR)	58	$641	4,201	$454	3,579	$258	2,668	$231	2,269
Total	**6,700[b]**	**$175,563**	**2,176,891**	**$142,671**	**2,088,025**	**$143,766**	**2,120,558**	**$147,892**	**2,188,381**
% of worldwide private market		**55.97%**	**78.05%**	**53.95%**	**77.68%**	**52.78%**	**79.16%**	**53.80%**	**79.61%**

AFR=Africa EMR= Eastern Mediterranean SEAR=South-East Asia
AMR= Americas EUR=Europe WPR= Western Pacific

[a] Data were not available for the following high-burden countries: Afghanistan, Cambodia, DR Congo, Ethiopia, Kenya, Mozambique, Myanmar, Nigeria, Uganda, UR Tanzania, Vietnam, and Zimbabwe.

[b] Total estimated TB cases for 1999 includes the caseload in the countries for which sales data were not available (i.e., those listed in note a).

Source: IMS Health

anti-TB drugs. Only China and South Africa saw an increase in both dollar-volume and unit-volume sales since 1997. Indonesia and Pakistan experienced a reduction in dollar-volume sales and an increase in unit-volume sales during this same period. Each of the remaining seven countries for which data were available—Bangladesh, Brazil, India, Peru, Philippines, Russian Federation, and Thailand—saw a drop in both dollar-volume and unit-volume sales.

In an effort to better estimate anti-TB drug sales in the private market in all 23 high-burden countries, one can use data on the estimated incidence of TB. In 1999, the 11 countries for which sales data exist accounted for 77% of new TB cases among the 23 high-burden countries. Therefore, it is conceivable that the $148 million in 2000 private market sales understated the true total by nearly 23%. Thus, the 2000 private market in the 23 high-burden countries might have totalled $191 million (a $43 million increase) and as many as 2.8 million units. These figures could be reasonably interpreted as upper bound estimates of the size of the private market in high-burden countries, making the upper bound estimate for the worldwide private market in 2000 approximately $318 million. However, it is important to note that it is not known to what extent, if any, private sales are restricted in the 12 countries for which private market sales data are not available.

2.2 Public/Tender Market for Drugs to Treat Active TB

The public/tender market is made up of national, regional, and local government purchases of anti-TB drugs along with contributions to drug acquisition from donor agencies and organisations. In order to better understand the size of the public/tender market for anti-TB drugs and the supply challenges faced by ministries of health throughout the world, the WHO Communicable Diseases Cluster is pursuing a survey of national TB programme authorities in Ministries of Health in 123 low- and middle-income member states. Designed to obtain information on experiences acquiring anti-TB drugs in recent years, the survey instrument includes questions regarding drug need, budget forecasting, drug regimens and packaging, financing for drug supply, procurement, distribution, local production, and quality control. The survey is still in progress, and a complete analysis of the data is not yet available. However, WHO published interim data from the survey for the purpose of estimating the potential size of the public market for anti-TB drugs in 2000.[38]

Survey respondents reported that in 2000 anti-TB drug purchases through various public/tender sources specified in the survey were $78 million; however, the data are far from complete. As of May 2001, 75 out of the 123 countries responded to the WHO survey, and data were not collected on local and provincial purchases because national TB programme authorities could not easily compile this information. Data from Russia are not included among the survey responses. For China, federal authorities could provide information on the World Bank–financed TB programme reaching half of the country but did not include information on purchases made by provinces and local authorities in the rest of China. Of the $78 million in public/tender worldwide purchases, approximately

$54 million occurred in 17 high-burden countries.* For those nations that responded to the survey, approximately 25% of anti-TB drug purchases were reported to be financed with external donor resources (including development bank loans), while the remaining three-fourths were governmental purchases. In high-burden countries, donor organisations played an even larger role, funding one-third of public/tender purchases of anti-TB drugs.

Although many data are still outstanding for the WHO survey, conservative estimates suggest that the public/tender market was at least between $125 million and $140 million.** It is believed that approximately $40 million to $60 million of this total is being provided by international donors. This donor estimation stems from data indicating that, international donors provided approximately $190 million for TB control in 2000.[39] While the survey was not able to determine what portion of the donation was for drug purchases, it is estimated that 25% to 40% was allocated to the purchase of anti-TB drugs. A new donor initiative that is expected to provide additional funds for the public/tender market in the future is the Global TB Drug Facility (GDF). The GDF is projected to spend an estimated $50 million per year to finance DOTS expansion, ensuring universal, uninterrupted provision of quality-assured anti-TB drugs.

Currently the majority of anti-TB drugs in the public/tender market are provided by producers of generic pharmaceuticals. The portion of the public/tender market available to research-based pharmaceutical companies is very small.

2.3 Market for Drugs to Treat MDR-TB

The number of new MDR-TB cases worldwide in 2000 is estimated to have been roughly 273,000.[26] Although the MDR-TB estimate is small compared to the estimated 8.4 million drug-susceptible TB cases, the costs of treating MDR-TB cases are substantially higher. Exhibit 14 presents the costs of drugs for treating MDR-TB cases as a function of the degree of drug resistance for countries with various average incomes. These estimates are based on 2000 cost data from the national TB programmes of about a dozen countries that purchased second-line drugs on a large scale. The average costs worldwide for drugs alone range from about $7,000 for organisms resistant to two drugs to $15,000 for organisms resistant to six drugs. In the United States, the estimated drug costs for treating a single patient with drug-resistant TB range from nearly $38,000 to more than $54,000—or between 47 and 67 times the approximately $800 needed to treat drug-susceptible TB (see Exhibit 9).

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* In addition to half of China and all of the Russian Federation, data are missing for Indonesia, Pakistan, Mozambique, Myanmar, and Zimbabwe.

** These estimates were provided by Diana Weil (WHO/World Bank) and based on personal communication in April 2001 with Katherine Floyd (WHO) and Olivier Appaix (consultant to Partners in Health and WHO). While data from all high-burden countries were not available, Dr. Floyd estimated the budgeted public expenditures in countries with 40% of the total number of cases reported to be detected and cured total $50 million to $60 million per year. From this number, Dr. Floyd estimated total public expenditures to be in the range of $125 million to $150 million annually. Dr. Appaix estimated that the total public/tender market expenditures for first-line anti-TB drugs will total $620 million to $700 million in low- and middle-income countries between 2001 and 2005. From this, annual expenditures are estimated to be $125 to $140 million. Dr. Weil concurs with these estimates based on extrapolation of the survey data.

Exhibit 14: Estimated Drug Costs per Treated Case of MDR-TB (in $US)

	2-Drug Resistance	4-Drug Resistance	6-Drug Resistance
United States	$37,897	$51,341	$54,363
High-income country average	$10,068	$16,576	$18,988
Low-income country average	$1,840	$4,711	$7,054
Global average	$7,074	$12,759	$15,266
GLC 2001	$1,073	$1,321	$1,782
GLC 2010	$441	$605	$876

GLC = Green Light Committee, which approves projects for WHO-supported drug supply to treat MDR-TB. The cost projections for 2010 are lower than 2001 costs assuming future reductions in the costs of drugs. However, the market includes patented drugs, nonpatented drugs under monopoly production status, and other drug classes with different costs, so these projected costs are highly speculative.

Source: 2000 cost data from 12 national TB programmes that purchased second-line drugs on a large scale

The 2000 market for drugs to treat MDR-TB is estimated to be approximately $12.5 million. Out of this total, approximately $4.9 million is in the United States. Because the $12.5 million market estimate assumes that MDR-TB organisms are resistant to only two drugs, one can assume that the market would be substantially higher if these patients were treated with the more expensive regimens to treat four- and six-drug resistance.

2.4 Market for LTBI Drugs

Approaches to treating latent TB infection recently have received increased attention. An estimated 2 billion people—one-third of the world's population—are infected with the TB bacillus, and an estimated 100 million to 200 million will develop active disease. Individuals developing active disease will infect an additional 10 to 15 other people each year while untreated.[40] These numbers provide a clear rationale for the treatment of LTBI to control the growing problem of TB infection around the world.

In particular, people living with HIV/AIDS are considered to be at very high risk of developing active TB. According to the Joint United Nations Programme on HIV/AIDS, patients coinfected with HIV and the TB bacterium are 30 to 50 times more likely to develop active TB than people who are HIV-negative. TB is responsible for the death of one out of every three people with HIV/AIDS worldwide.

Despite the demonstration of efficacy, treatment of LTBI among PLWH has not yet become a common intervention and is still limited to a few pilot sites and districts in Africa and Asia. There are several reasons for this. First, it has proved difficult to establish robust systems to find people who are willing to have HIV testing; to be certain that they do not already have active TB (which would be a strong contra-indication to giving treatment for LTBI, as it would select for drug-resistant organisms); and to maintain adherence through a 9-month course of treatment with isoniazid. Although shorter courses based on rifampicin have been shown to be effective, national

programmes still are reluctant to introduce these for fear of promoting rifampicin-resistant TB.

The second disappointment has been that the efficacy observed in the randomised trials gradually wanes so that, within a few years of starting preventive therapy, no benefit from having received active treatment rather than placebo is detectable. An obvious next step would be to try longer regimens or intermittent treatment (e.g., giving a course of treatment once every 2 or 3 years). Trials of such approaches are being promoted, but given the demonstrated efficacy of the regimens for the first year or two, they will need long follow-up times to test their hypotheses.

Finally, the pressure to provide antiretroviral drugs at affordable prices may reduce the need for specific treatment aimed at LTBI. There is already some evidence that PLWH who take highly active antiretroviral therapy are less likely to develop TB than those who are not on antiretrovirals.

HIV testing is becoming more acceptable, and there is considerable pressure to provide more voluntary counselling and testing services. The pressure is particularly strong when linked to other medical interventions, such as preventing transmission of HIV from mothers to their babies and providing specific HIV-related prophylaxis (e.g., cotrimoxazole) or treatment (e.g., antiretrovirals). The proportion of people who know their HIV status therefore is likely to rise during the next decade. However, in much of the region most severely affected by HIV, health services are stretched beyond the breaking point. Considerable investment in training, infrastructure, and financial resources will be necessary to allow many people to take advantage of new approaches to treatment. In addition, rapid, accurate ways to determine who is infected with *M. tuberculosis* would increase the attractiveness of targeted treatment among PLWH.

As described in *Chapter 1*, the growing burden of HIV-related TB in many developing countries and the increasing concern for controlling TB in established market economies have stimulated increasing interest in drugs to treat LTBI. In countries with high HIV prevalence, the challenges to treating LTBI include the large numbers of the population infected with TB (sometimes more than half of the adult population), the high probability of reinfection after LTBI treatment, the costs for treating large segments of the population, and the limited testing available for HIV or TB. Currently, TB guidelines in developing countries include treatment of LTBI only in young children living in close contact with an infectious case. As cited in *Chapter 1*, the number of people currently starting treatment for LTBI in high-HIV prevalence countries is approximately 50,000 per year. Continued experience with new approaches, such as treating LTBI in high-prevalence areas, could increase the number of people treated for LTBI in these countries to a maximum to 1 million to 2 million over the next 10 years.

Current treatment for LTBI usually consists of isoniazid daily (300 mg for adults) for 9 months or a combination of rifampicin and pyrazinamide for 3 months.[30] Costs for these treatments in the U.S. are shown in Exhibit 15.

In countries with established economies, increased population mobility and immigration have heightened concerns for controlling TB. In the United States, an average eight individuals are identified during investigations as coming in contact with infectious cases

Exhibit 15: Regimens for Treatment of LTBI

Regimen Characteristics	Isoniazid	Rifampicin + Pyrazinamide
Interval and Duration	1/day x 9 mo.	1/day x 3 mo.
No. of Doses	270	90 of each
Adult Dose (max)	5 mg/kg (300 mg)	10 mg/kg (600 mg) rifampicin 15–20 mg/kg (2.0 g) pyrazinamide
Cost/Dose ($US)	$0.017	$1.21 rifampicin $2.50 pyrazinamide
Total Drug Costs/Course ($US)	**$4.59**	**$333.90 ($108.90 + $225.00)**

of TB.[37] According to WHO, the number of detected smear-positive cases of TB in the U.S. totalled 6,000 in 1999, leading to the treatment of about 48,000 people with LTBI. In addition, an estimated 50,000 people in established economies are being treated for LTBI due to their HIV status, being immigrants, or other high-risk individuals (e.g., health care workers). Assuming that half of these LTBI treatments receive the 9-month isoniazid treatment and the other half receive the 3-month rifampicin-pyrazinamide treatment, the 2000 market for drugs to treat LTBI is estimated to be approximately $17 million; however, this total is included in the total sales of anti-TB drugs in the private market.

2.5 The Estimated Market for Anti-TB Drugs in 2010

Anti-TB drug sales appear to be stable. In addition, as evidenced in *Chapter 1*, the number of people afflicted with TB is again on the rise. According to WHO, the estimated number of new TB cases worldwide rose from 8.0 million in 1997 to 8.4 million in 1999.[1] Furthermore, WHO and the Joint United Nations Programme on HIV/AIDS estimate that, due to the increased spread of HIV/AIDS, the number of new TB cases in Africa will double to 4 million per year soon after 2005.[7]

As explained in the sections above, the current market for anti-TB drugs is estimated to be approximately $412.5 million to $470.5 million. Exhibit 16 shows the projections for the market in 2010 to be between $612 million and $670 million. These projections are based on four assumptions:

- The private market in 2000 will remain the same to 2010, except for the treatment of LTBI (see fourth assumption).
- The public/tender market will increase as DOTS coverage continues to expand, enabled in part by the GDF's expected annual contribution of approximately $50 million.
- In 2000, the number of MDR-TB patients was estimated to be 273,000 but only about 7,000 of these received treatment. It is assumed that the total number of MDR-TB patients will not change over the decade; however, it also is assumed that a large percentage of MDR-TB patients will be treated in 2010. Thus, the market for drugs to treat MDR-TB will increase.

Exhibit 16: Estimated Market for Anti-TB Drugs in 2000 and 2010 (in $US)

Market	2000	2010
Private (excluding LTBI)	$258M–$301M	$258M–$301M
Public/Tender	$125M–$140M	$175M–$190M
MDR-TB drugs	$12.5M	$120M
LTBI	$17M	$59M
Total	**$412.5M–$470.5M**	**$612M–$670M**

Assumptions

– The private market in 2000 will remain the same to 2010, except for the treatment of LTBI (see fourth assumption).

– The public/tender market will increase as DOTS coverage continues to expand enabled in part by the GDF's expected annual contribution of approximately $50 million.

– The total number of MDR-TB patients will not change over the decade; however, it also is assumed that a large percentage of MDR-TB patients will be treated in 2010. Thus, the market for drugs to treat MDR-TB will increase.

– The market for drugs to treat LTBI will increase to include 2 million people receiving the 9-month isoniazid regimen (vs. 100,000 in 2000) and 150,000 people receiving the 3-month rifampicin-pyrazinamide regimen (vs. 48,000 in 2000).

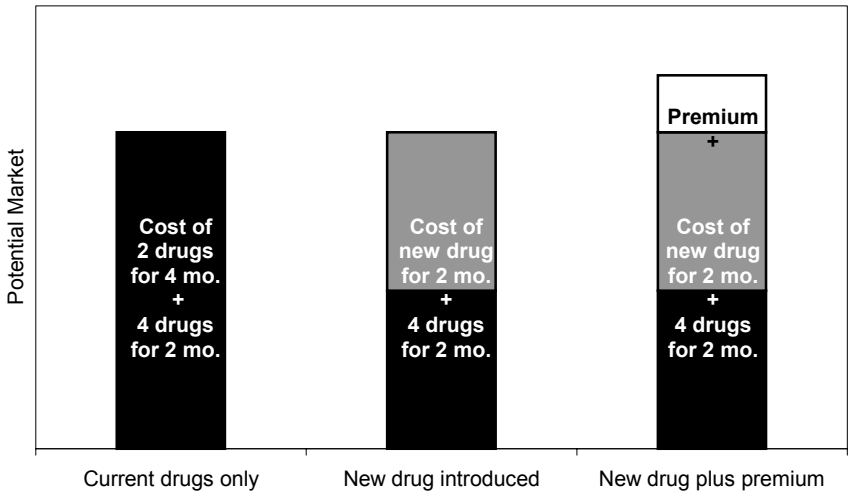
- The market for drugs to treat LTBI will increase to include 2 million people receiving the 9-month isoniazid regimen (vs. 100,000 in 2000) and 150,000 people receiving the 3-month rifampicin-pyrazinamide regimen (vs. 48,000 in 2000).

2.6 The Potential Worldwide Market for a New Anti-TB Drug

As discussed above, estimating the size of the market for anti-TB drugs is a difficult undertaking that is subject to much uncertainty. Therefore, projecting the size of the market for a new anti-TB drug is an even more daunting exercise. However, the potential market can be considered making several assumptions of how a novel agent introduced in 2010 and used with current drugs to treat and cure TB might affect annual expenditures for anti-TB drugs:

- The total costs for the full drug regimen (i.e., the total anti-TB drug market) do not decrease.
- The new drug reduces the duration of treatment for standard active TB from 6 months to 2 months, thus reducing the purchase of current drugs by 50%.
- The new drug is active against MDR-TB and shortens its treatment from an average 18 months to 6 months, thus reducing the purchase of current drugs by at least 50%.
- The new drug is used to treat LTBI and reduces its treatment duration from 3 months to 1 month, reducing the purchase of current drugs by two-thirds.
- Some markets (e.g., the private market) might be willing to pay a premium of at least 35% for the new drug due to its advantages and potential for substantial reduction in overall health care costs. This 35% is a conservative estimate that represents the minimum premium likely to be used. In addition, in certain countries the exact percentage of the premium will need to be negotiated with government agencies.

Exhibit 17: How a New 2-Month Drug Regimen Might Impact the Relative Distribution of the Market for Anti-TB Drugs



To understand how these assumptions work together, consider Exhibit 17. The first column represents the total costs for the currently used drugs. If the new drug's 2-month regimen means that half as much money is needed to buy the currently used drugs (because no continuation phase drugs are needed), the remaining half can be used to purchase the new drug without an increase in total drug costs. And if some markets are willing to pay a premium for the improvements afforded by the new drug, then the market available to the new drug will grow accordingly.

With the above assumptions, the potential market for a new anti-TB drugs is estimated to be at least between $316 million and $345 million per year, as detailed in Exhibit 18. If a 35% premium is charged for the new drug in all but the public/tender market, the estimated potential market increases to between $396 million and $432 million per year. It is important to note that these estimates are highly sensitive to the size of the current market and the assumptions discussed above. However, the estimates do indicate that, under a reasonable set of assumptions, the market for a new anti-TB drug might be substantial.

In addition to its dependence on the estimates of the current market and the assumptions made, the potential market also can be affected by many other factors. For example, future markets for a drug used to treat LTBI will be influenced by results of research on treatment alternatives in areas with a high TB prevalence, policy changes regarding treatment in established and developing economies, and the availability of a shorter course of therapy that would improve the difficult compliance problem of long-term therapy in asymptomatic patients.

Exhibit 18: Estimated Potential Market for a New Anti-TB Drug Introduced in 2010 (in $US)

Market	Market Available for Current Drugs If No New Drug Is Introduced	Market Available for New Drug (per assumptions)	Market Available for New Drug If Some Markets Pay Premium
Private (excluding LTBI)	$258M–$301M	$129M–$150.5M	$174.2M–$203.2M
Public/Tender	$175M–$190M	$87.5M–$95M	$87.5M–$95M
MDR-TB drugs	$120M	$60M	$81M
LTBI	$59M	$39.3M	$53.1M
Total	**$612M–$670M**	**$315.8M–$344.8M**	**$395.8M–$432.3M**

Assumptions

– The total costs for the full drug regimen (i.e., the total anti-TB drug market) does not decrease.

– The new drug reduces the duration of treatment for standard active TB from 6 months to 2 months, thus reducing the purchase of current drugs by 50%.

– The new drug is active against MDR-TB and shortens its treatment from an average 18 months to 6 months, thus reducing the purchase of current drugs by at least 50%.

– The new drug is used to treat LTBI and reduces its treatment duration from 3 months to 1 month, reducing the purchase of current drugs by two-thirds.

– A 35% premium is assumed in the private, MDR-TB, and LTBI markets. No premium will be charged in the public/tender market for active TB. (As indicated on p. 33, 35% is a conservative estimate representing the minimum premium that is likely to be used.)

Note: Market estimates are only a projection based on the assumptions. Different assumptions would yield a different potential market.

2.7 Summary

The current (2000) private market for anti-TB drugs is estimated to be between $275 million and $318 million per year (including $17 million for drugs to treat LTBI). The public/tender market is estimated to range from $125 million to $140 million per year. The current market for drugs to treat MDR-TB is estimated to be $12.5 million per year. Therefore, the annual global market for anti-TB drugs is estimated to be at least $412.5 million and could be as high as $470.5 million. The makeup of the total market is complex and difficult to evaluate.

The size of the global public/tender market is difficult to determine primarily due to the lack of good tracking data. WHO currently is conducting a survey that should enable an improved understanding of the public/tender market for anti-TB drugs, particularly in developing nations.

Overall, national governments appear to fund approximately 75% of the public market purchases, with about 25% of purchases funded by international donors. In the high-burden countries, national governments fund about 67% of public market purchases, relying on international donors for the remaining 33% of funding. This implies that international donor organisations are playing a substantial role in the current public/tender market for anti-TB drugs. Furthermore, the Global TB Drug Facility is expected to contribute an additional $50 million from the international donor community to finance the drugs needed for the expansion of DOTS.

Given various assumptions, the market for anti-TB drugs is estimated to grow to between approximately $612 million and $670 million per year by 2010. Within this estimated

market, a new 2-month treatment for TB could potentially yield annual revenue of between $316 million and $432 million; however, the assumptions underlying this estimate are numerous and far reaching, particularly given the fact that the market for anti-TB drugs is a function of the spread of the disease and local, national, and international efforts to control it.

3.0 Estimating Drug Development Costs

3.0 Estimating Drug Development Costs

The costs of developing a new chemical entity to treat TB include the value of the purchased resources plus the value of company-owned resources employed in the effort. These resources will be utilised over a many-year period beginning with discovery, through preclinical studies, and culminating in clinical trials and submission to regulatory agencies for marketing approval.

The value of company-owned resources devoted to NCE discovery and development will vary from company to company depending on the alternative uses each company has for those resources. For this reason, the approach taken in this chapter is to develop all cost estimates based on the assumption that all components of the drug discovery process are contracted out. In practice, drug developers will use a combination of self-owned and purchased resources based on their individual circumstances.

Without considering the costs of failure (see below), the costs of successfully developing an NCE for TB have been estimated to total approximately $36.8 million to $39.9 million (U.S. costs). This estimated range covers preclinical development ($4.9 million and $5.3 million), pharmaceutical development (at least $5.3 million), and Phases I through III of clinical development ($26.6 million). These efforts are designed to reach regulatory approval.* The investment required depends on the extent to which the sponsor of the development effort partners with other organisations. Forms of cost-sharing might be available wherein governments and nongovernmental agencies incur some of the costs. For example, organisations such as the Global Alliance for TB Drug Development have mechanisms for sharing discovery and development costs as well as revenue if the effort is successful (see *Section 5.1*). Further, the costs will be affected by the venue where the development activities occur. Specifically, if some of the clinical trials are conducted in Africa, the costs likely will be less than expected in the United States.

Finally, these costs will be spread out over a period of years, requiring the use of discounting as shown in *Chapter 4*. Discounting requires consideration of the specific timing of the outlays (and revenues) and the firm's cost of capital.

* For more information on overcoming the regulatory hurdles associated with anti-TB drugs, see the Global Alliance's *Scientific Blueprint for TB Drug Development*.[24] It should be noted that there is a history of fast-track approval for anti-TB drugs, as seen in the case of rifapentine.

Drug discovery and development is an intrinsically uncertain and long endeavour and process, typically with many failures for each success. A given effort may be judged a failure and the initiative terminated at any point in the process. The costs estimated in this chapter do not cover the costs of failed efforts. However, an alternative approach to include the costs of failure (i.e., the costs of unsuccessful projects) provides estimates of total development period costs. This estimation method depends on the costs of each phase of drug development, assumptions of the attrition rates across phases (i.e., the rates/probabilities at which compounds successfully move to the next stage of development), and development and regulatory review times.[41] Phase attrition, time in each phase, total development time (normal vs. rapid), and where the development activities will be conducted (i.e., studies conducted in developed and/or developing countries) are important sources of variability in estimating the total costs of drug development.

Estimates of the costs of developing an NCE based on this method to include the costs of failure are approximately $76 million to $115 million* for preclinical development through Phase III trials and regulatory approval. These estimates do not include the costs of discovery, which are estimated to range from $40 million to $125 million (including the costs of failure). As suggested by the breadth of this range, discovery costs are difficult to estimate. Even so, one can use these rough estimates of discovery and the estimated costs of development calculated for this report to project a total cost of between $115 million and $240 million to discover and develop a new anti-TB drug (including the costs of failure). However, it generally is accepted that discovery and development of a new drug to treat TB will require an international, collaborative effort among governments, academic institutions, foundations, NGOs, and pharmaceutical companies. In this way, costs can be shared by multiple organisations, ultimately lowering the investment burden borne by a single agent.

3.1 Estimating Discovery Costs

R&D costs for lead discovery and optimisation can vary widely and are difficult to estimate. Discovery costs are tied to many factors, including the level of difficulty of synthesis or extraction, the desired characteristics of the drug, the capacity of the company's research facilities, and the availability of advanced technologies that may reduce the cost and time required for discovery of a promising lead compound. The Pharmaceutical Research and Manufacturers of America estimates that, on average, about one-fourth of total drug development costs (including failure costs) cover drug discovery efforts.[42] This ratio and this report's high-end estimate of $115 million for preclinical through clinical development costs can be used to calculate an estimate of $40 million for discovery costs. Alternatively, one can estimate discovery costs using the one-fourth ratio and industry's average total of $500 million for discovery and development costs across all therapeutic areas,[42] yielding estimated discovery costs of $125 million. However, given the scarcity of TB drug R&D in recent years, it is difficult to confirm the relevance of the average discovery-to-development ratio of one-fourth cited above.

* Depending on total development time (normal or rapid) and discount rate (0% or 3%).

Furthermore, it is generally accepted that discovery and development of a new drug to treat TB will require an international, collaborative effort among governments, academic institutions, foundations, NGOs, and pharmaceutical companies. In this way, discovery costs can be shared by multiple organisations, ultimately lowering the investment burden borne by a single agency or company (see *Section 5.1*).

To fulfil the goal of improved drugs for the treatment of TB, the successful completion of a series of research activities leading to the selection of a drug candidate to be evaluated in advanced preclinical and clinical studies must be accomplished. In broadest terms, these steps are target selection and validation, assay development and implementation, identification of lead compounds, and optimisation of lead compounds to advanced lead or drug candidate.[24]

The selection of targets for the development of therapies for TB has been aided by the availability of the complete genome sequence of the tuberculosis organism.[43] The understanding of the molecular basis of mechanisms such as cell division, dormancy, reactivation, and drug resistance has been accelerated by the information gained through elucidation of the proteins coded for the genome. Significant progress has been made toward establishing a transcriptome map of the tubercle bacillus,[44] and approximately half of the 4,000 polypeptides expected from the genome sequence already have been detected.[45] Studies of the genome have already indicated that *M. tuberculosis* differs radically from other bacteria in that a very large portion of its coding capacity is devoted to the production of enzymes involved in lipogenesis and lipolysis.[43]

Several approaches are being used to determine which genes of *M. tuberculosis* are essential to the organism and would serve as critical targets for further exploration toward development of new therapies. Potential targets are being evaluated using techniques such as gene inactivation by means of allelic exchange using haploid or partially diploid hosts[46] or through conventional or sequence-tagged transposon mutagenesis.[47–49] Targets obtained by these means are being converted to moderate or high-throughput assays that are capable of being used to screen large combinatorial libraries of compounds.

Using recently developed techniques, researchers are uncovering and exploring additional biochemical pathways and regulatory circuits as possible targets for new drug discovery. Evidence of some rather unique features of the bacterium related to the latency and long-term persistence of the organism in the human host is being obtained. For example, it has been demonstrated that the persistence of *M. tuberculosis* in mice was facilitated by isocitrate lyase, an enzyme essential for the metabolism of fatty acids. Disruption of the gene coding for isocitrate lyase attenuated bacterial persistence and virulence in immune-competent mice without affecting bacterial growth during the acute phase of the infection.[50] Studies such as these, aided by the knowledge of the sequence of the genome, are yielding new targets for the treatment of TB infections.

A more complete review of recent advances in the drug discovery and development process has been published in the Global Alliance's *Scientific Blueprint for TB Drug Development*, which was published as a supplement to the journal *Tuberculosis*.[24]

3.2 Estimating Preclinical Costs

This section outlines the costs and duration of the preclinical studies required to advance to registration an NCE to treat TB that has not been previously evaluated in preclinical or clinical studies. Toxicology studies adequate to allow at least 6 months of clinical administration as well as to satisfy all of the requirements for regulatory approval are proposed. Pharmacokinetics and absorption, distribution, metabolism, and elimination (ADME) studies are recommended in order to select the most appropriate animal species for evaluation of activity and toxicity and to obtain pharmacokinetic/pharmacodynamic relationships. The total costs of the proposed preclinical studies required to support registration based on a clinical dosing period of 3 to 6 months range from $4.9 million to $5.3 million.

The goal of preclinical studies is to characterise the activity and toxic effects of the drug candidate to identify an initial safe starting dose for human trials and to identify parameters for clinical monitoring of potential adverse effects. Toxic effects are studied with respect to target organs, dose dependence, relationship to exposure, and potential reversibility of toxicity. Toxicokinetic data will be used to support all of the proposed *in vivo* toxicity studies by relating the exposure achieved to toxicological findings and aiding in the determination of the relevance of these findings to clinical safety.

The proposed studies are based on recommendations presented in manuscripts by Goldberger[51] and Hopewell and colleagues[52] as well as in guidance documents provided by the U.S. Food and Drug Administration[53] (FDA) and the European Agency for the Evaluation of Medicinal Products.[54] **Cost estimates have been obtained from a survey of contract research organisations specialising in microbiology, toxicology, and drug metabolism.** Although the costs of some studies might vary based on the properties of the drug candidate, the estimates reflect the costs that can be expected based on previous studies carried out by these organisations.

The number of preclinical studies required to evaluate a drug already marketed for indications other than TB could be considerably less than estimated here. However, the exact nature of the studies that would be required depends significantly on previous clinical exposure as well as on preclinical data available for the marketed product.

Although these studies are referred to as “preclinical,” not all of the proposed studies must be initiated prior to clinical studies. Studies to select a lead compound ($450,000 per compound) and to sufficiently assess toxicology and ADME ($325,000) must be conducted before beginning multiple-dose clinical studies. For more information about this, see *Section 3.2.2*.

Finally, although the development of sensitive and specific assays for the drug candidate and its metabolites are critical to the study of metabolism and drug interactions, the costs and time for assay development can be estimated only roughly. Costs and development time depend on the drug candidate as well as on the number of major metabolites.

Exhibit 19: Estimated Costs (in $US) and Duration of Microbiological Activity Studies

Study	Estimated Cost	Estimated Duration
***In Vitro* Studies**		
Evaluation of activity against *M. tuberculosis* susceptible to standard drugs as well as activity against other bacterial strains		
Broth dilution assay (1–40 compounds at two concentrations for each strain tested)	$6,000	4 weeks
MIC/MBC (1–6 compounds)	$6,500	5 weeks
Evaluation of activity at pH 5.6 and pH 6.8 (MIC of 1–3 compounds)	$6,500	4 weeks
Evaluation of activity in combination with currently used drugs	$6,000[a]	4 weeks[a]
Evaluation of activity against *M. tuberculosis* resistant to first-line therapy (MIC/MBC of 1–3 compounds)	$12,000	8 weeks
Evaluation of activity in infected macrophages	$41,200[b]	10 weeks[b]
Assessment of drug interactions and sequencing of drugs	$6,000[a]	4 weeks[a]
Determination of the frequency of emergence of drug-resistant organisms	$11,500	8 weeks
***In Vivo* Studies**		
Determination of activity as a single agent compared with that of standard drugs	$58,000	8–10 weeks
Comparison of activity in combination with a standard drug to the activity of the current best regimen, including assessment of potential synergy or antagonism with currently used therapy	$79,150	8–10 weeks
Assessment of survival and relapse rates	$173,500	12 months
Total (minimum)	**$406,350**	**c**

[a] Costs/Duration per each two-drug combination study.

[b] Costs/Duration for the evaluation of a single compound in two macrophage cell lines.

[c] Since many studies can overlap and/or be combined, a duration total is not meaningful.

MIC = minimum inhibitory concentration MBC = minimum bactericidal concentration

Source: Contract research organisations specialising in microbiology, toxicology, and drug metabolism

3.2.1 Microbiology

Selecting an anti-TB agent for clinical evaluation begins with a series of studies in culture and in animals evaluating the activity of a drug candidate as a single agent and in combination with drugs that are part of currently used therapy regimens. The major studies to be carried out for evaluation of the microbiological activity of drug candidates are outlined in Exhibit 19.

The initial screen for the evaluation of drug candidates consists of *in vitro* susceptibility testing against cultures of *M. tuberculosis* that are sensitive to isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol. This screen is conducted using agar and/or broth dilution susceptibility studies. Evaluation of activity is carried out at pH 5.6 and pH 6.8. Cross-resistance with the first-line drugs is determined using strains of bacteria that are resistant to each of these drugs.

The activity of an anti-TB agent depends on its ability to kill both extracellular and intracellular bacteria. The intracellular activity of a compound depends on its ability to penetrate into the macrophage and on the extent of its activity at the low intracellular pH of the macrophage. The negative aspects of pH-dependent activity are exemplified by

results from studies on isoniazid and streptomycin. Isoniazid was shown to be four-fold less active at pH 5.6 than at pH 6.8. Streptomycin is active only at neutral or alkaline pH and thus is likely to be active primarily on tubercle bacilli located outside the cells, where there is a neutral pH, and inactive intracellularly, where there is an acid pH. In contrast, rifampicin exhibits equal activity at both pH values.[55–58] Thus, evaluation of the activity of drug candidates in infected macrophages will yield information on both drug penetration into cells and activity at acid pH.

Using studies similar to those described by Sbarbaro and colleagues,[59] researchers also can use infected macrophages to obtain preliminary information on the bactericidal/bacteriostatic activity, drug interactions (synergy or antagonism), and sequencing of drugs in multidrug regimens. This information can be obtained prior to studies in animal models of infection.

Although the *in vitro* studies described above yield considerable information regarding the activity of compounds against *M. tuberculosis*, the results are limited because they are obtained in the absence of the contributions of ADME. Although many of the objectives of the *in vivo* studies outlined in Exhibit 19 are similar to those of the *in vitro* studies, the *in vivo* results give a more complete assessment of the expected activity in the clinical trials in humans.

In vivo models in the mouse,[60] guinea pig,[61] and rabbit[62] have been used for the evaluation of treatments for TB.* These animals have varying immunological and pathophysiological responses to *M. tuberculosis.* For some drugs, pharmacokinetic and metabolic profiles differ among species and can differ markedly from those observed in humans. Although the most appropriate animal species for the preclinical evaluation of a drug candidate depends on the nature of the compound being evaluated, the mouse is the model of choice for TB.[24]

3.2.2 Preclinical Safety Studies

The preclinical safety studies proposed here (see Exhibit 20) are based on the M3 Guidance for Industry developed by the International Conference on Harmonisation (ICH) and represent the consensus among the three ICH regions—United States, European Union, and Japan.

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* The largest number of *in vivo* studies for anti-TB drugs has been carried out with variants of the mouse model. In addition to being cost-effective and relatively easy to use, the mouse, like the majority of healthy humans, is able to generate a strong immune response to *M. tuberculosis*, and the infection is likely to recrudesce as the animals grow old.[60]

Studies of the comparative biology of the guinea pig have revealed a number of relevant similarities between this species and humans. Newborn guinea pigs possess a very mature lymphomyeloid complex. Hormonally and immunologically, guinea pigs are much more similar to humans than are other rodents. The guinea pig also is considered a corticosteroid-resistant species. The physiology of the pulmonary tract, especially the response of the lung to inflammatory stimuli, is quite similar to that of humans, as is the dermal response to both acute and chronic inflammatory mediators.[61]

Most commercially available rabbits are of intermediate resistance to *M. tuberculosis*. However, considerable variation in resistance to tubercle bacilli has been observed, due to the fact that outbred rabbits have been used in most studies. In general, rabbit models have not been as well-studied as those in mice and guinea pigs.[62]

Exhibit 20: Estimated Costs (in $US) and Duration of Preclinical Safety Studies

Study	Estimated Cost	Estimated Duration
Acute toxicity (mouse)	$12,000	12 weeks
Acute toxicity (nonrodent)	$26,000	12 weeks
28-day repeated-dose toxicity (mouse)	$80,000	16 weeks
28-day repeated-dose toxicity (nonrodent)	$95,000	16 weeks
6-month repeated-dose toxicity study with a 3-month interim sacrifice (mouse)[a]	$415,000	10 months
9-month repeated-dose toxicity study with a 3-month interim sacrifice (nonrodent)[a]	$550,000	13 months
Safety pharmacology[b]		
Cardiovascular profile (dog)	$35,000	12 weeks
Neurological screen	c	16 weeks
Respiratory effects (guinea pig)	$22,000	12 weeks
Renal function (rat)	$10,000	12 weeks
Gastrointestinal tract motility (mouse)	$7,500	12 weeks
28-day drug combination toxicity study (mouse)	$150,000	16 weeks
Genotoxicity		
Ames bacterial reverse mutation assay	$7,500	6 weeks
Structural chromosome aberration assay in human lymphocytes *in vitro*	$35,000	18 weeks
In vivo mouse micronucleus test	$35,000	18 weeks
Reproduction toxicity studies	$750,000	
Segment I: fertility and reproductive performance		22 weeks
Segment II: teratology (rat)		46 weeks[d]
Segment II: teratology (rabbit)		
Segment III: perinatal and postnatal development		38 weeks
Carcinogenicity studies		
3-month repeated dose range-finding study (rat)	$150,000	28 weeks
2-year carcinogenicity study (rat)	$1,500,000	3 years
Total (minimum)	**$3.88 million**	**e**

[a] *Scientific Blueprint for TB Drug Development* suggests 13-week, repeated dose studies in three species. If 6- and 9-month studies are done, these 13-week studies would not be necessary. However, if the new drug is intended to be given for only 2 months in humans, the 13-week studies and not the 6- and 9-month studies might be more appropriate.

[b] For a given drug candidate, it might not be necessary to carry out of all of these studies.

[c] Can be done as part of 28-day study.

[d] Includes 20 weeks for a dose range-finding study.

[e] Since some studies can overlap and/or be combined, a duration total is not meaningful.

Source: Contract research organizations specializing in microbiology, toxicology, and drug metabolism

The goals of these studies are to characterise the toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility in order to identify an initial safe starting dose for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The preclinical safety studies are important for characterising toxic effects and for determining the feasibility of continuing studies. Studies will be carried out in males and females in order to determine whether any observed toxicities are gender-dependent.

Although studies are listed individually, several studies might be combined, resulting in reduced development time and costs. In addition, not all of the safety studies must be conducted prior to entry into the clinic. Generally, toxicity in two mammalian species, appropriate safety pharmacology, and the *in vitro* genotoxicity tests should be evaluated prior to the first human exposure. Additionally, some exposure data in animals should be

evaluated prior to initiation of human trials. However, the exact study design and sequencing relative to Phase I clinical trials can be accurately determined only after a lead compound has been selected.

The duration of the repeated-dose toxicity studies—proposed here as 6 months and 9 months—depends upon the duration, therapeutic indication, and scale of the proposed clinical trials. In general, the duration of the repeated-dose animal toxicity studies should be equal to or exceed the duration of the human clinical trials. For a drug to be administered in humans for more than 3 months and up to 6 months, repeated-dose toxicity studies of 6 months in rodent and nonrodent species is required to support Phase I and II trials in the European Union and Phase I to III clinical trials in the United States and Japan. A 6-month study in rodents and a 9-month study in nonrodents would be required to support Phase III clinical trials in the European Union and registration in all regions.

In the United States, acute toxicity studies in animals can provide the primary safety data to support single-dose safety/pharmacokinetic studies in humans. In this case, the studies should be designed to assess dose-response relationships and pharmacokinetics following a single dose; animals should be observed for 14 days. Monitoring of clinical pathology and histopathology is required in these studies; however, conducting the 28-day toxicology study does not significantly delay entry of the drug candidate into the clinic, and its completion would allow single-dose pharmacokinetic studies as well as multiple dose studies in the United States, the European Union, and Japan.

An important aspect of the preclinical safety studies is determining toxicokinetics by integrating pharmacokinetics into the toxicity testing. The primary focus is on interpreting the toxicity tests rather than on characterising the basic pharmacokinetic parameters. Toxicokinetic data can be used (1) to support all of the proposed *in vivo* toxicity studies by relating the exposure achieved to toxicological findings and (2) to determine the relevance of these findings to clinical safety. Samples for generation of toxicokinetic data can be collected from the main study animals in the nonrodent studies or from satellite groups in the rodent studies.

All genotoxicity tests should be completed prior to the initiation of Phase II clinical studies. Reproduction toxicity studies are conducted as appropriate for the population that will be treated. In all ICH regions, men can be included in Phase I and Phase II clinical trials prior to the male fertility study provided that an evaluation of the male reproductive organs is performed as part of the 28-day repeated dose toxicity studies. Women not of child-bearing potential can be included in clinical trials provided that an evaluation of the female reproductive organs has been conducted in animals. Thus, gross and histopathological evaluation of male and female reproductive organs will be carried out in the 28-day repeated dose toxicity studies to allow entry of these populations into the early Phase I/Phase II clinical studies. Under most circumstances, carcinogenicity studies should be started at the time of the initiation of Phase III clinical studies.

Exhibit 21: Estimated Costs (in $US) and Duration of Pharmacokinetic and ADME Studies

Study	Estimated Cost	Estimated Duration
Single-dose rodent pharmacokinetic study (oral and intravenous dosing)[a,b]	$20,000	12 weeks
Single-dose nonrodent pharmacokinetic study (oral and intravenous dosing)[a]	$40,000	12 weeks
28-day repeated-dose rodent pharmacokinetic study (oral dosing)[c]	$80,000	16 weeks
28-day repeated-dose nonrodent pharmacokinetic study (oral dosing)[c]	$95,000	16 weeks
Tissue distribution study (rodent)	$50,000[d]	10 weeks
Drug metabolism studies *in vitro* and *in vivo*	$100,000–$375,000	1 year
Drug interaction studies	$150,000	e
Assay development and validation	$40,000–$80,000[f]	f
Total (minimum range)	**$575,000–$840,000[g]**	**g, h**

[a] Can be done in conjunction with the acute toxicity study.

[b] Might be done before the evaluation in mouse models of TB in order to choose the appropriate dosage.

[c] Can be done in conjunction with the 28-day repeated-dose toxicity study.

[d] Assumes the use of radiolabeled compound at one time point in 15 tissues.

[e] Depends on the number of studies that are done.

[f] Depends on the properties of the drug candidate as well as the properties and number of the major metabolites. Can require up to 1 year for full assay development.

[g] Depends on the properties of the drug candidate as well as the properties and number of the major metabolites.

[h] Since the duration of assay development and validation studies can vary, and some studies can overlap and/or be combined, a duration total is not meaningful.

Source: Contract research organizations specializing in microbiology, toxicology, and drug metabolism

3.2.3 Pharmacokinetics and Drug Metabolism

Because the drug candidate is to be evaluated in a multidrug combination, the route of metabolism and the potential to interact with drugs that are used as the standard therapy for TB are critical factors in the development process. The proposed pharmacokinetic and ADME studies and their costs are outlined in Exhibit 21.

Although the development of sensitive and specific assays for the drug candidate and its metabolites are critical to the study of metabolism and drug interactions, the costs and time for assay development can be estimated only roughly. Costs and development time are extremely dependent on the drug candidate as well as on the number of major metabolites. In addition, metabolism can be species-dependent, particularly if metabolism by the cytochrome P450 system is a major route. Selection of the appropriate species for these studies can be determined only after selection of a lead compound or compound class. Therefore, the wide-ranging studies proposed are quite general in nature and would be refined once a specific drug candidate has been determined.

Since the proposed route of administration is oral, one of the objectives of the single-dose studies is to determine the drug candidate's oral bioavailability by comparing the blood levels following oral and intravenous dosing. Determination of the pharmacokinetics after repeated dosing can yield information on the ADME of the drug candidate following prolonged administration. These studies, combined with *in vitro* metabolism studies, allow determination not only of its own metabolism but also its potential to

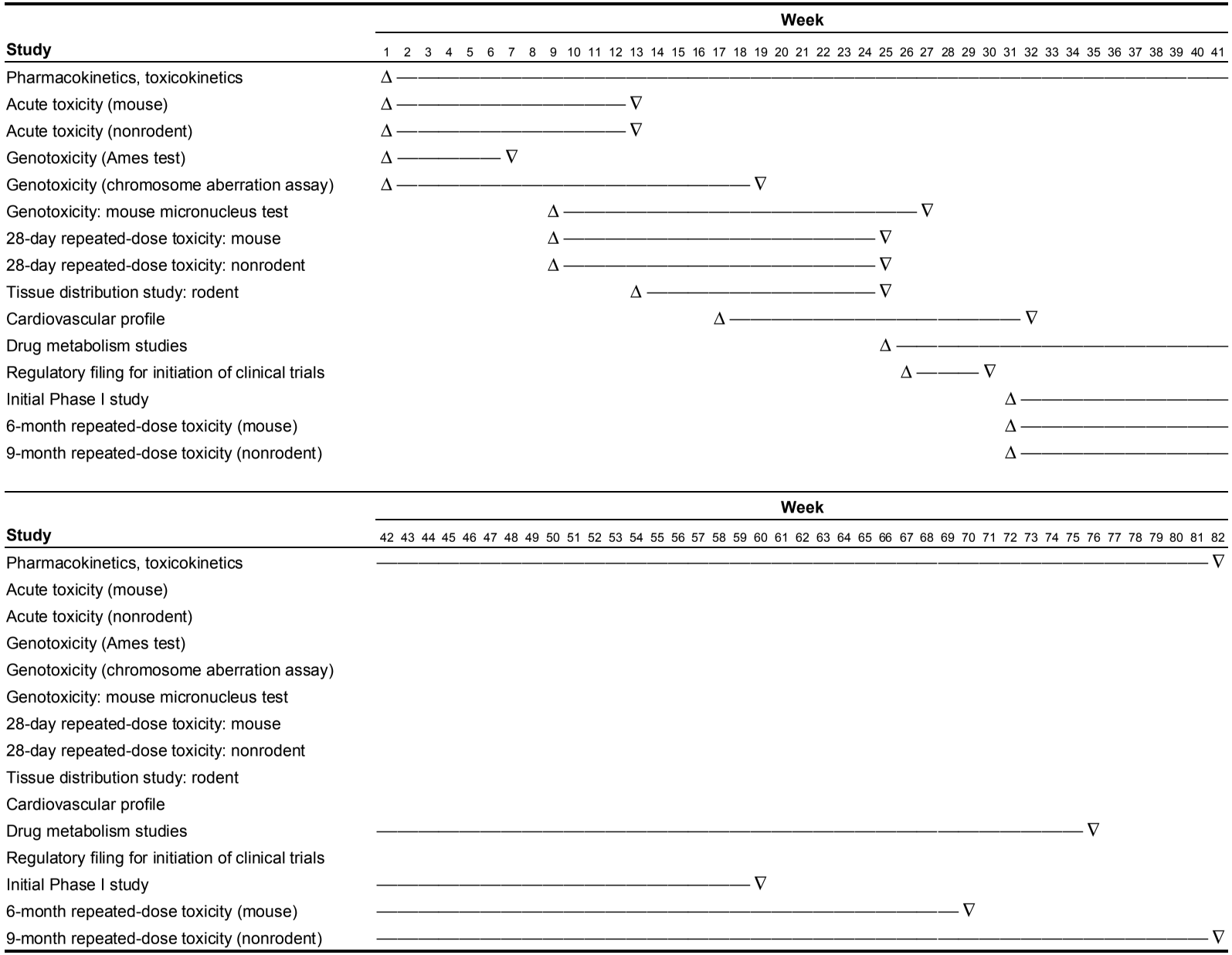
induce or inhibit the metabolism of concomitantly used drugs. The results from the pharmacokinetic studies, when evaluated in concert with the *in vivo* efficacy studies, yield information regarding the pharmacodynamics of the compound being tested. Through analysis of the pharmacokinetic/pharmacodynamic data, researchers can determine which pharmacokinetic parameters (e.g., area under the concentration-time curve [AUC], peak concentration, time over the MIC) best correlate with antibacterial activity. Results from these studies aid in the selection of doses and dosing schedules for the initial clinical studies that are least likely to result in the occurrence of adverse effects and/or the development of drug-resistant organisms.

The clinical evaluation of the drug candidate involves its use as part of a multidrug regimen with drugs accepted as the standard of care. Because of the number of drugs in the therapeutic regimen, the potential for drug-drug interactions between the drug candidate and the drugs used in the standard therapy is significant. For example, coadministration of isoniazid with rifampicin can result in a higher rate of hepatotoxicity than with either agent alone. In addition, rifampicin and rifapentine are known to induce certain hepatic microsomal cytochrome P450 enzymes, resulting in accelerated elimination of coadministered drugs metabolised by these enzymes. Rifapentine induces the cytochrome P450 enzymes CYP3A4, CYP2C8, and CYP2C9, which increases the metabolism and markedly lowers the serum concentrations of other concurrently administered drugs, such as protease inhibitors used for the treatment of HIV infections and oral contraceptives. Thus, a knowledge of the metabolism of the drug candidate and its potential for affecting the metabolism of the other drugs used in the treatment regimen is critical for the successful development of the new therapy. Moreover, *in vitro* studies comparing the metabolism of the drug candidate by human microsomes and hepatocytes to metabolism by microsomes and hepatocytes from other species can aid in the selection of the species most appropriate for conducting preclinical studies.

3.2.4 Estimating Timing of the Preclinical Studies

The sequence of studies that need to be completed prior to conducting the first Phase I multiple dose clinical trial and their estimated duration are illustrated in Exhibit 22.

Exhibit 22: Estimated Timeline for Preclinical Safety Studies for an Anti-TB Drug Candidate



3.3 Estimating Industrial and Pharmaceutical Development Costs (Chemistry, Manufacturing, and Controls)

This section outlines the steps and estimated costs associated with the development process for drug substance and drug product. In general, the overall costs for the CMC portion of a pharmaceutical development programme are estimated to be at least $5.3 million. Factors such as development timelines, the complexity of the synthetic route, costs of chemical intermediates, amounts of drug product needed for clinical testing, or other factors could significantly impact the development costs.

The proposed development plan is based on the manufacture of a solid oral dosage formulation (tablet or capsule). Individual steps within the major development stages depend upon the compound selected for advancement to preclinical and clinical testing.

The proposed chemical development plan is based in part on the CMC requirements put forth in guidance documents provided by the FDA[53] and the European Agency for the Evaluation of Medicinal Products[54] as well as on development plans previously used for marketed products and recommendations of experts in chemical development.

As in the earlier sections of this chapter, the proposed CMC development plan is for a new chemical entity that has not been previously evaluated in preclinical or clinical studies. The CMC development costs associated with a drug already marketed for indications other than TB could be considerably lower than the costs proposed herein. However, the exact nature of the required development studies depends on previous experience with the marketed product.

3.3.1 Estimated Costs for CMC Development Programme

The overall costs for the chemistry, manufacturing, and controls portion of a pharmaceutical development programme are estimated to be at least $5.3 million (Exhibit 23). The estimated costs should be considered approximations based on previous development costs for marketed drugs. Because of the large number of variables associated with the individual costs of CMC development, these estimates carry a large element of uncertainty. Factors such as development timelines, the complexity of the synthetic route, costs of chemical intermediates, amounts of drug product needed for clinical testing, and other factors could significantly alter the development costs.

Exhibit 23: Estimated Costs of CMC Development (in $US)[a]

Development Task	Estimated Cost
Chemistry evaluation	$228,000
Lab-to-pilot optimisation	450,000
Process development	1,500,000
Preparation of pilot batches	114,000
Analytical development	205,200
Analytical chemistry	182400
Analytical technology transfer	91,200
Manufacturing of clinical supplies	570,000
Safety testing for material handling	450,000
Formulation development	456,000
Technology transfer	182,400
Preliminary stability testing	91,200
Accelerated stability testing	456,000
Real time stability	300,000
Total	**$5,276,400**

[a] Estimates should be considered only as a general guide for the relative costs of the individual sections. The tasks should not be considered a complete list of the steps required, since these can only be determined once a compound has been selected.

Source: John Horton, GlaxoSmithKline, personal communication, 2000

3.3.2 Details of the CMC Development Programme

The preparation of clinical trial material (CTM) must be conducted in compliance with current good manufacturing practices (CGMP), whether the procedures are those specified in the CGMP regulations (21CFR 211) or in alternative guidelines specific to the investigational new drug. During early preclinical studies, the CGMP regulations do not apply; however, when drug products are produced for toxicology studies in animals and for clinical trials in humans, compliance with the CGMP regulations is required.

Overall, chemical process development contains the following elements:

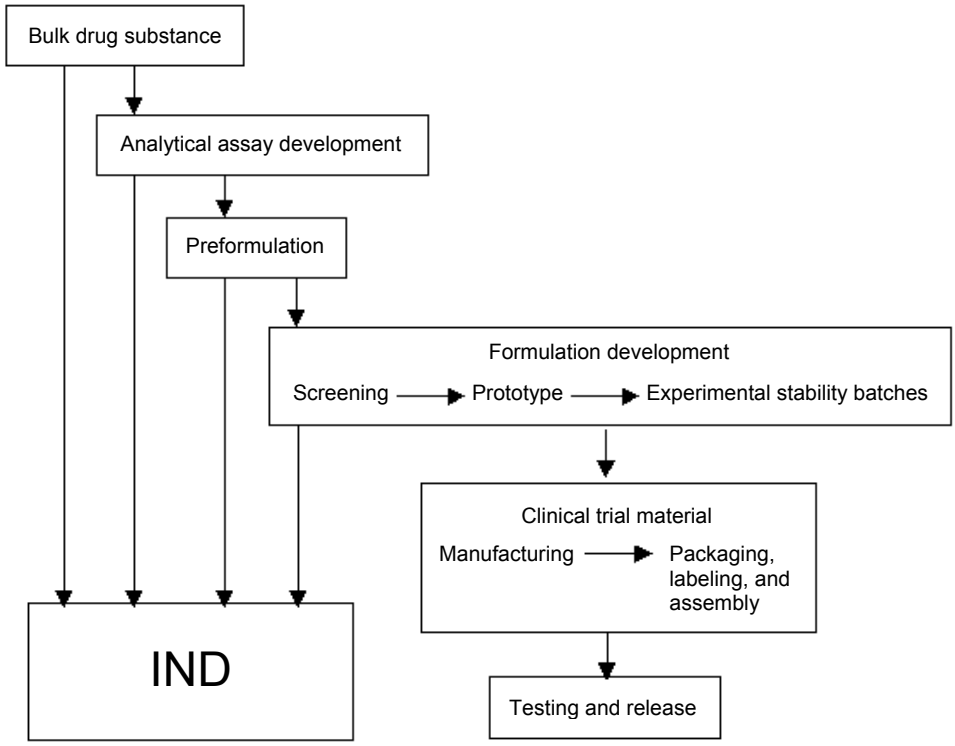
- Manufacture of bulk drug substance to produce the supply of the active pharmaceutical ingredient (API) needed to carry out the development work
- Process evaluation and improvement to solve long-term economic and proprietary considerations regarding the manufacture of the compound and the final formulation
- Sourcing of needed raw materials
- The generation of the CMC Section for registration
- The transfer of technology to the commercial manufacturing site

The CMC development plan not only must coordinate synthesis of the active pharmaceutical ingredient and analytical, preformulation, and formulation programmes but also must integrate pharmacology, toxicology, and clinical requirements. The formulation used for preclinical pharmacology and toxicology studies must be linked to the planned formulation that will be used in the initial clinical trials. If multiple formulations are used during the clinical studies, then the early formulation must be linked with its successors.

The CMC development process can be divided into two stages, although they are implemented continuously. The first stage deals with the steps to obtain sufficient and appropriate information needed to file an investigational new drug application (IND), as illustrated in Exhibit 24. The second stage centres on drug product development that is carried out concurrently with clinical testing in order to meet all CMC requirements necessary to file a marketing application.

Concurrent with toxicology testing, a portion of the API needs to be allocated to preformulation, formulation, and analytical development studies. Before CTM can be manufactured, a formulation and manufacturing process that can reliably yield a stable, bioavailable, and processable dosage form must be developed. The conceptualisation of the clinical plan and design of early clinical studies is normally conducted in parallel with bulk-drug synthesis, formulation, and analytical development efforts. Due to the length of time required for basic CMC investigations, these activities must be underway well in advance of conceptualisation of specific clinical studies. As the basic CMC, formulation, manufacturing process, and analytical database matures, study-specific product, packaging, and labelling requirements can be designed and carried out. It can take 2 to 3 months to obtain bulk drug from a manufacturing facility, 6 to 8 weeks to conduct packaging and labelling operations, and 2 to 6 weeks to test and release CTM.

Exhibit 24: CMC Activities Required for Submitting an Investigational New Drug Application



Source: David Bernstein, Cato Research, personal communication, 2000

In addition to the amount of CTM required for actual clinical use, additional quantities will be required for the following:

- In-process manufacturing samples (e.g., blend uniformity)
- Manufacturing loss
- Stability testing
- Release testing
- Packaging validation
- Packaging line start-up loss
- Final identity testing
- Retained samples

For the pivotal Phase III trials, development of a commercialisable investigational drug product will be required. The investigational product used for Phase III trials must be shown to be equivalent to the commercial product. Depending on the complexity of the manufacturing process as well as other factors, modification of the manufacturing process

used to produce investigational product for the early clinical trials to one used to produce a commercial product can easily require 6 to 9 months.

Dosage-form development normally progresses from preformulation studies to formulation and preliminary stability studies. The initial goal of the preformulation studies is to develop a comprehensive database of the physical and chemical characteristics of the API and the biopharmaceutical profile of the molecule. A knowledge of these properties will aid in the evaluation of the impact of lot-to-lot variation of these attributes on drug product performance that can result from changes in synthesis route or scale. The ultimate goal of formulation studies is to provide a rugged, stable, bioavailable, and processable formula and manufacturing procedure capable of being readily and reproducibly scaled up to commercial manufacturing. The clinical formulation might change several times between initial entry into the clinic and commercialisation.

During the early stages of the development of formulations for toxicology and Phase I studies, specifications often are selected to be broad enough to reflect the variability inherent in rudimentary formulations and analytical methods as well as narrow enough to control the product adequately. As development proceeds, specifications are tightened. However, regardless of the phase of the clinical investigation, drug product must be standardised in terms of identity, purity, strength, quality, and dosage form to give significance to the results of the clinical studies.

Reliable analytical methods must be developed to differentiate among the drug substance, impurities, and degradation products. These analytical procedures must be capable of controlling both the drug substance and drug product throughout the development programme. As development progresses, analytical methods also might need to be modified to address new excipients, new degradation products, and new impurities that arise from modifications to the synthetic procedure and scale-up of synthesis of the API. Ultimately, analytical methods must be validated and shown to be suitable for detection and quantitation of API, degradation products, and impurities. In most cases, impurities can be classified as (1) organic impurities that arise during the manufacturing process or on storage of drug substance or (2) inorganic impurities and residual solvents that are derived from the manufacturing process.

All recurring impurities at or above the 0.1% level in drug batches manufactured by the proposed commercial process will need to be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. Identification of impurities below apparent levels of 0.1% generally is not necessary. However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing pharmacologic or toxic effects at a level lower than 0.1%.

Stability testing of drug substance and drug product is required during the development of an investigational drug. The purpose of stability testing is to show how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light. Results from these studies enable recommended storage conditions, retest periods, and shelf life to be established. The design of the formal stability studies for the drug product will be based

on knowledge of the behaviour and properties of the drug substance and on experience gained from clinical formulation studies and stability studies. Stability studies must be designed to continue until the last patient has taken the last dose of medication.

3.4 Estimating Clinical Development Costs

This section addresses clinical development costs necessary to obtain drug regulatory authority approval of a new anti-TB drug. A full programme of clinical development for a new anti-TB agent, including Phase I to Phase III trials conducted in a country with an established economy, is estimated to cost about $26.6 million and to take 7 to 10 years to complete. The studies include testing a new anti-TB agent in 1,368 patients in all phases of clinical trials. Comparable studies conducted in a country with a developing economy are estimated to cost approximately $9.9 million. The costs related to the probability of failure are beyond the scope of this section and are not included in the cost estimates (see the introduction to this chapter). The costs of drug synthesis, scale-up, formulation development, and stability are discussed in *Section 3.3*.

Involving developing countries such as Uganda, India, South Africa, and/or others will be an important part of the clinical development programme. These countries have significant expertise in clinical trials and have the capabilities to conduct trials that meet the standards of the various regulatory authorities. Further, basing clinical trials in the countries with a high-burden of TB will enhance capacity building for future work in these countries.

The U.S. was the regulatory reference standard for drug approval for the design of the clinical trials because the latest anti-TB drug was registered in the United States. Although the ultimate goal for any new anti-TB therapy is to obtain worldwide regulatory approval, it is assumed that efforts to achieve regulatory harmonisation between major developed and developing countries will be successful. Thus, the studies described in this section should meet these standards for demonstrating drug efficacy and safety.

This section presents the following information:

- An estimate of the costs of conducting Phase I through Phase III clinical trials required for drug regulatory authority approval for a new anti-TB agent
- Protocol outlines for Phase I through Phase III clinical trials to develop, register, and market the new drug (Cost estimates presented in *Section 3.4.1* were based on these protocols.)
- An estimate of the timeline for conducting Phase I through Phase III clinical trials

3.4.1 Estimated Costs of Clinical Trials

A spreadsheet model was created to estimate the total costs per subject for each phase of the clinical trials and the total costs for all phases of clinical trials. Total costs for each phase of clinical trials were based on the proposed protocols described in *Section 3.4.2* and the proposed schedules discussed in *Section 3.4.3*. Total costs are estimated in 2000 U.S. dollars, but can be adjusted to various countries. The model was

Exhibit 25: Estimated Costs of Clinical Development in a Country with an Established Economy (in $US)

Trial	Subjects (per study)	Sites (per study)	Treatment Costs per Subject[a]	Total Costs per Subject[b]	Total Costs per Study[c]
Phase I Small Studies (2)	16	1	$3,770	$5,961	$95,373
Phase I Large Studies (3)	24	2	$3,770	$6,308	$151,404
Total Phase I Trial Costs	**104**	**8**	*	*	**$644,957**
Phase II EBA Study (small)	16	1	$1,798	$4,020	$64,320
Phase II EBA Study (large)	48	1	$1,798	$4,020	$192,960
Phase II Efficacy and Safety Study	200	6	$2,792	$15,652	$3,130,482
Total Phase II Trial Costs	**264**	**7**	*	*	**$3,387,765**
Administrative (personnel, travel, shipping, IRB review)					$19.1 million
Data Management (data entry clerk, programmer, statistician)					$1.3 million
Treatment (physical exam, chest X-ray, sputum cultures)					$1.8 million
Assessment (for screening; e.g., HIV screen, toxicology screen)					$0.4 million
Total Phase III Trial Costs	**1,000**	**30**	**$2,184**	**$22,601[d]**	**$22,600,924**
Total Clinical Development Costs	**1,368**	*	*	*	**$26,633,646**

*Because the Phase I and II trials encompass different populations, each incurring different study costs, average per subject costs across the entire Phase I or II clinical trials are not meaningful. Similarly, a total for the number of sites is not meaningful.

[a] Excluding overhead or administrative costs.

[b] Including fixed and variable costs.

[c] Including coordinating center costs (see *Section 3.4.1.4*) but excluding the costs of manufacturing the clinical trial drug supply (see *Section 3.3*).

[d] Including a screened population of 1,176 subjects with a 15% dropout rate at screening. For a complete discussion about the assumed dropout rate, please see *Section 3.4.2.3*.

Sources: Calculations based on proposed protocols described in *Section 3.4.2*, proposed schedules discussed in *Section 3.4.3*, cost estimates for U.S.-conducted trials, and administrative and data management costs provided by TB clinical trials experts. See *Appendix C* for spreadsheet models.

populated using cost estimates for U.S.-conducted trials because the most complete and detailed information for each cost was available for the United States. These estimates were a starting point for developing estimates for other countries (see *Section 3.4.1.6*).

In addition, several individuals were consulted to determine the administrative and data management costs.* These experts in TB clinical trials also validated previously obtained medical cost estimates and the cost models as a whole. The methodology used to determine the costs of clinical trials for a new anti-TB agent is presented in *Appendix B*.

The total costs for Phase I, II, and III trials in a country with an established market economy are presented in Exhibit 25. The spreadsheet models are presented in Exhibits C-1 to C-9 in *Appendix C*. Exhibit C-10 shows the costs for each individual item,

* Dr. Bernard Fourie of the South African Medical Research Council; Drs. Tom Kanyok and Toshiko Imamura of WHO; Drs. Andrew Vernon and Zachary Taylor of CDC; Dr. John Johnson of Case Western Reserve University; Dr. Ali Zumla of the Centre for Infectious Diseases, University College London; Dr. Carol Hamilton of Duke University Medical Center (a principal investigator for the rifapentine Study 22); and Dr. Lawrence Geiter of Sequella Foundation.

including the source, the costs incurred, the method of derivation, and assumptions associated with each cost.

In keeping with the WHO/IFPMA guidelines, HIV-positive patients are included early in the clinical evaluations to gain experience treating these patients.[63] HIV-positive patients are included in selected Phase I studies and in the Phase III equivalency/similarity study as described in *Section 3.4.2.3*. However, this raises the question of whether the sponsor of trials for an anti-TB agent should be responsible for paying for additional non-TB-related therapies such as viral load assessments and medications. Although the costs of viral load testing of HIV-positive patients in the Phase I trial are included in Exhibit 25, non-TB-related therapies to treat HIV/AIDS in Phase III trials are not included. Thus, additional per-patient costs for treating an HIV-positive patient during a clinical trial might include viral load testing four times per year (approximately $600/yr) and antiretroviral therapy, which might range from $8,000 to $16,000 per year in the western world where highly active antiretroviral therapy (HAART) is the standard of care.[64] In developing countries, HIV treatment costs will likely be much lower.

3.4.1.1 Phase I Costs

The estimated costs for conducting Phase I clinical trials, including two small studies and three large studies, total approximately $645,000, based on 104 subjects enrolled. A small Phase I study conducted at one site is estimated to cost $5,961 per subject, and a large Phase I study conducted at two sites is estimated to cost $6,308 per subject. For more information about the protocols used for Phase I trials, see *Section 3.4.2.1*.

3.4.1.2 Phase II Costs

The estimated costs of conducting the Phase II trial, including two early bactericidal activity (EBA) studies enrolling a total of 64 subjects and one pilot efficacy and safety study with 200 subjects, are $3.4 million. The estimated costs of conducting EBA studies are $4,020 per subject. The majority of the Phase II clinical trial costs can be attributed to the pilot efficacy and safety study, which is estimated to cost approximately $3.1 million ($15,652/subject). Assuming one nurse coordinator can monitor approximately 32 to 42 patients,[65] six sites were selected (one nurse coordinator per site monitoring about 33 patients at each site). Conducting a study in multiple clinical sites adds substantially to the total costs of the trial because administrative costs are duplicated, although patient accrual costs are somewhat reduced. For more information about the protocols used for Phase II trials, see *Section 3.4.2.2*.

3.4.1.3 Phase III Costs

Based on 1,000 subjects enrolled across 30 sites, the estimated costs to conduct one large, international, multicentre, randomised Phase III trial total $22.6 million. The estimated costs per subject total $22,601.

Based on expert opinion, it was assumed that the Phase III trial would have a dropout rate of approximately 30%. It also was assumed that half of these dropouts would occur immediately following screening, and the remaining half would occur over the course of

the trial.[65] Thus, to enrol 1,000 subjects in the trial, 1,176 would need to be screened. The costs of screening 176 additional subjects at $345.25 per subject contribute $60,764 to the maximum Phase III trial costs of $22.6 million. As for subjects who drop out once the trial has commenced, those who drop out at the start of the trial would result in no costs, those who drop out during the trial would result in moderate costs, and those at the end of the trial would result in costs similar to those who complete the trial. Because one cannot know the distribution of the subjects who will drop out, it is assumed that the maximum cost savings would be realised when subjects drop out at the beginning of the trial. Thus, the maximum cost savings of $275,752 is based on 150 subjects dropping out at the beginning of the study, leaving 850 subjects to complete the trial and yielding minimum trial costs of $22.3 million. Cost savings will decrease as dropouts are distributed over the duration of the trial. No cost savings will occur if subjects drop out later in the trial and incur all of the treatment and monitoring costs. Assuming that the patients who drop out during the trial do so closer to the end of the study, the total trial costs will be the full $22.6 million. For more information about the protocols used for Phase III trials, see *Section 3.4.2.3*.

3.4.1.4 Clinical Trial Coordinating Center Costs

The costs for staffing and maintaining a central coordinating centre for the various clinical trials also were estimated. This coordinating centre is responsible for the administration of all clinical trials, including protocol writing, institutional review board approval, developing case report forms (CRFs), preparing the regulatory submission, acting as a liaison between the manufacturer and regulatory authorities, publishing manuscripts, and other activities. Researchers also estimated the costs for staffing the trial coordinating centre, including one monitoring physician, two epidemiologists, one statistician, one programmer, rental space of 2,500 square feet, and communication costs. See Exhibit C-10 for the complete listing of costs for the central coordinating centre. Coordinating centre costs depend on the duration of the trial and are included in the costs of each trial (Exhibit 25).

3.4.1.5 Model Validation, Assumptions, and Limitations

The cost model was validated by comparing the modelled cost estimate of approximately $22.6 million for a multicentre, international, randomised Phase III clinical trial with a total cost estimate of approximately $25 million for the CDC's rifapentine Phase III Study 22 trial, which did not include clinical trial drug supply costs.[65] The model also has content validity based on experts' review of the model structure and inputs.

In general, costs and parameter figures are conservatively estimated, so that results of the model show the upper range of the total costs of clinical trials. The spreadsheet model is adaptable to reflect changes in the number of subjects or clinical sites, thus changing total subject care costs and overhead costs dependent on the number of trial sites. Other overhead costs, including site monitors, clerical staff, and physical study management, are independent of the study population and number of clinical sites and thus do not change. (Assumptions regarding specific parameters and costs are presented in Exhibit C-10.) Other assumptions built into the model are as follows:

- Costs of drug therapy are not included. Drug therapy involves either the study drug, which is supplied by the manufacturer, or standard therapy, which often is provided by the department of public health.[66]
- Costs of treating adverse events are not included. Treatment-related adverse events requiring intervention rarely occurred in more than 5% of the patients in the rifapentine Phase III Protocol 8 clinical trial.[67] It was assumed that, if any of the treatment-related adverse events were severe, drug therapy would be stopped, incurring no or minimal costs. Because of this, and because the majority of clinical trial costs in the U.S. are due to administrative costs, the costs of treating adverse events are not expected to have a great impact on the total clinical trial costs.

Certain treatment costs (e.g., inpatient costs) are likely to be incurred by public health units as standard TB therapy, or by the National Institutes of Health (NIH) in the United States through its support of clinical trials. However, the model includes these typically subsidised costs in its conservative estimate. Thus, actual costs are likely to be lower than those estimated by the model.

3.4.1.6 Estimated Costs in Developing Countries

Because the majority of TB cases are found in countries with developing and transitional economies and many clinical trials for anti-TB agents commonly are conducted in these countries, it is important to estimate the costs of conducting clinical trials in developing areas of the world (such as India, South Africa, and other countries in Africa). Although the cost model was populated using U.S. cost estimates, the model can be modified to calculate the costs of conducting clinical trials in developing/middle-income countries by using cost inputs for the country of interest. Although aggregate cost estimates were obtained for India and South Africa, detailed estimates for each component of the cost model were not available. Disaggregated cost estimates were obtained for Uganda.

Uganda

Total costs for conducting all clinical trials for a new anti-TB agent in Kampala, Uganda are approximately $9.9 million (Exhibit 26), or approximately one-third of the $26.6 million required to conduct the same clinical trials in a country with an established economy. The cost differential is mainly attributable to the difference in personnel costs. For example, the total annual salary for the research coordinator (i.e., a nurse to track the clinical trials) was reported to be $9,600 plus fringe benefits in Uganda, compared to $50,000 plus fringe benefits in the United States. These differences in personnel costs also are seen in the costs for clinical trials conducted in other countries with developing economies.

The cost model was populated with unit cost estimates provided by John Johnson and Marla Manning of Case Western Reserve University to calculate the total costs of conducting clinical trials in Kampala, Uganda. The spreadsheet model and cost inputs are presented in *Appendix D*. The Uganda–Case Western Reserve University Research Collaboration has conducted Phase I, II, and III clinical trials of new and existing agents for TB treatment in Uganda during the past 10 years. The same assumptions used for the U.S. cost model were used for the Uganda model except as follows:

Exhibit 26: Costs of Clinical Development in Uganda (in $US)

Trial	Subjects per Study	Sites per Study	Treatment Costs per Subject[a]	Total Costs per Subject[b]	Total Costs per Study[c]
Phase I Small Studies (2)	16	1	$348	$1,434	$22,944
Phase I Large Studies (3)	24	2	$378	$1,622	$38,928
Total Phase I Trial Costs	**104**	**8**	*	*	**$162,651**
Phase II EBA Study (small)	16	1	$731	$1,881	$30,096
Phase II EBA Study (large)	48	1	$731	$1,881	$90,288
Phase II Efficacy and Safety Study	200	6	$1,164	$7,377	$1,475,346
Total Phase II Costs	**264**	**7**	*	*	**$1,595,708**
Total Phase III Trial Costs	**1,000**	**30**	**$910**	**$8,179[d]**	**$8,179,228**
Total Clinical Development Costs	**1,368**	*	*	*	**$9,937,586**

*Because the Phase I and II trials encompass different populations, each incurring different study costs, average per subject costs across the entire Phase I or II clinical trials are not meaningful. Similarly, a total for the number of sites is not meaningful.

[a] Excluding overhead or administrative costs.

[b] Including fixed and variable costs.

[c] Including coordinating center costs (see *Section 3.4.1.4*) but excluding the costs of manufacturing the clinical trial drug supply (see *Section 3.3*).

[d] Including a screened population of 1,176 subjects with a 15% dropout rate at screening (see *Section 3.4.1.3*).

Source: John Johnson and Marla Manning of Case Western Reserve University; see *Appendix D* for spreadsheet models.

- Costs of drug therapy are included in the Uganda cost model, including costs for anti-TB medications ($45 per subject) and a $15 per-subject allocation for other medications.
- Fifteen percent was added to the annual salary for all clinical trial personnel to account for fringe benefits. In the U.S. model, 23.4% was added to the annual salary for all clinical trial personnel.

The Uganda model included additional costs that were excluded from the U.S. cost model:

- Salaries for a full-time pharmacist, home visitor, counselor, full-time laboratory technician, and a driver
- Allocations for a car, insurance, fuel, and maintenance
- Additional charges for communications

Some costs were not available for the Uganda model, and the U.S. costs were substituted:

- Travel for site monitor and clinical research associate (CRA)
- Space rental
- Full-time statistician with fringe benefits
- Full-time economist with fringe benefits
- Costs for an independent bacteriologist
- Assessments, including drug levels in Phase I, bacterial cultures in Phase II and III studies, restriction fragment length polymorphism (RFLP) testing in Phase III, and visual acuity and neurological exams in Phase II and III studies

Exhibit 27: Per-Subject Costs for Selected Clinical Trials (in $US)

	U.S. Cost Estimates (per subject)[a]		Actual Costs in Developing Countries (per subject)		
Trial	No. of Subjects	$US	Country	No. of Subjects	$US
Phase I single-dose study	16	$5,961	India[b]	16	$1,812
Phase I repeated-dose study	24	$6,308	India[b]	45	$1,700
Phase II EBA study (small)	16	$4,020	South Africa[c]	13	$2,678
Phase III	1,000	$22,601	South Africa[c]	400	$3,525

[a] For the U.S., the single-dose study estimate is based on a 3-day assessment period; the multiple-dose study estimate is based on a 30-day assessment period; the EBA study estimate is based on a 7-day in-patient assessment period; and the Phase III study estimate is based on a 5-year, multicentre, international study with a 6-month treatment period and a 24-month follow-up.

[b] For India, the single-dose study estimate is based on a 10-day assessment period and costs are in 1996 U.S. dollars; the multiple-dose study estimate is based on studying amocarzine in 45 volunteers.

[c] For South Africa, the EBA study estimate is based on a 6-day in-patient assessment period; the Phase III study estimate is based on a 3-year study with a 6-month assessment period. However, these cost estimates do not include monitoring, hospitalization (Phase III), or half of the personnel costs. They do include an average indirect government or other TB service subsidy of $15 per subject per day.

Sources: U.S. cost estimates discussed in *Sections 3.4.1* to *3.4.1.4*; South Africa costs provided by Bernard Fourie of the South African Medical Research Council; India costs provided by Tom Kanyok of the WHO. See *Appendix D* for spreadsheet models.

Other Developing Countries

Aggregate clinical trial cost estimates also were obtained for South Africa and India. Exhibit 27 compares the actual costs for these countries to the estimated costs in the United States. (*Appendix E* shows costs of individual trials in these countries.)

The experience of the WHO Special Programme for Research and Training in Tropical Diseases (TDR) indicates that conducting clinical trials in developing countries costs much less than conducting comparable trials in the United States. Personnel costs, the primary cost driver of U.S. clinical trials, are much lower in developing countries. For example, in the United States, a principal investigator (PI) might earn $10,000 to $20,000 per year plus fringe benefits for participation in a Phase III trial. In Tanzania, a PI might be paid only $1,200 per year for Phase III participation, according to WHO TDR reports. All clinical trial staff are paid significantly less in developing countries than in the United States, and it is likely to remain that way for some time.[68]
Exhibit 28 provides another example where the costs of conducting clinical trials in a developing country (South Africa) are much lower than in the United States.

Clinical trials in developing countries might incur costs that are not typically budgeted for in trials held in developed countries.[69] Items associated with a vehicle (e.g., fuel, maintenance, insurance) used to send home health workers to trace subjects and maintain follow-up and to transport patients, supplies, and clinical samples are a substantial portion of the total clinical trial costs. In addition, communication costs (e.g., mail delivery, telephones, Internet access) account for more of the total trial costs in developing countries than in developed countries. Thus, costs of patient follow-up are a larger component of the total clinical trial costs in developing countries compared to developed countries.[69]

Exhibit 28: The Breakdown of Costs per Subject for Phase III Trial in the U.S. and in South Africa

	United States (N = 1,000)[a]		South Africa (N = 400)[b]	
Cost	**%**	**$US**	**%**	**$US**
Administrative	84.5%	$19,082	70%	$1,050
Data management	5.6%	$1,274	5%	$75[c]
Treatment/Assessment	9.9%	$2,184	25%	$375
Total	**100.0%**	**$22,540/subject**	**100%**	**$1,500/subject**

Sources: U.S. cost estimates discussed in *Section 3.4*; South Africa costs provided by Bernard Fourie of the South African Medical Research Council.

[a] The U.S. costs include site-specific administrative costs for 30 clinical trial sites.

[b] Total costs do not include trial monitoring, hospitalizations, or half of personnel costs. The budget applies to one site only; thus, if multiple sites are included in the trial, overhead and other site-specific administrative costs will increase.

[c] This cost figure does not include personnel costs, such as statistician or programmer salaries, and monitoring costs.

When WHO conducts a clinical trial, it typically pays a per-subject fee to the institution for all services provided, including laboratory analyses, treatment costs, support staff salary, and other expenses. WHO TDR reports that most laboratory services are conducted within the country hosting the trial. Trial monitors also are drawn from a pool of monitors from the country in which the clinical trial is being conducted. In contrast, all data management/analysis is conducted outside the host country by a contract research organisation. However, this standard might change during the next few years such that all clinical trial tasks are done in the country hosting the trial.

The authors did not have access to subsidised costs of clinical trials conducted in developing countries. However, because the clinical trial costs were estimated based on the investor's perspective, costs subsidised by governments or other organisations are not included in the total costs (because they would not be incurred by the investor).

3.4.2 Clinical Trials Protocols

The design of the clinical trials presented in this section was based on U.S. regulatory requirements and on the WHO/IFPMA regulatory harmonisation recommendations.[63] These protocol outlines are in line with the ICH's good clinical practice (GCP) standards. The design of actual clinical trials will depend on the characteristics of the NCE being tested and best clinical practice. If recognised as a treatment for TB, a new agent may be eligible for accelerated approval.

A detailed overview of the methodology for developing protocol outlines for a new anti-TB agent is presented in *Appendix B*. For the Phase I through Phase III protocol outlines, it was assumed that the trial drug was a new chemical entity for the treatment of active TB rather than therapy for latent TB infection. Although trials of an existing product might involve fewer subjects, a more streamlined structure, or lower costs, the long duration of drug therapy and the long follow-up period to treat TB lead to the assumption that the clinical trials for an NCE and for an existing product differ only modestly.

Exhibit 29: Summary of Protocols for Clinical Development

Trial	Sample Size[a]
Phase I	
Single-dose study in healthy males and females	16–24 (8–12 each)
Multiple-dose study in healthy males and females	24 (12 each)
Pharmacokinetic study in healthy male and female adolescents	16 (8 each)
Pharmacokinetic study in elderly males and females	16 (8 each)
Pharmacokinetic study in HIV-positive males and females	24 (12 each)
Phase II	
EBA study (small)	2 arms, 8[b] in each arm
2 arms to assess bactericidal activity with isoniazid as reference drug and test drug at the likely maximum therapeutic dose. If bactericidal, then progress on to larger EBA dose response study.	7-day duration
EBA study (large)	6 arms, 8[b] in each arm
6 arms to assess bactericidal activity at various doses	7-day duration
Pilot efficacy and safety study	200 with a 6-month treatment and 12-month follow-up period
Phase III	
One large, multicentre, multinational trial	1,000 with a 6-month treatment and 24-month follow-up period[c]

[a] Sample sizes for each trial are based on the sample sizes in the studies used for rifapentine approval and expert opinion. Sample size can be re-evaluated based on the study outcomes at the time of drug development.

[b] Eight patients per arm is the minimum number required for theses studies. Because of the possibility of greater than expected variability among subjects, problems in specimen collection, and patient drop-out, as many as 14 patients per arm may be needed to produce valid results.

[c] Based on expert opinion. Between 370 and 500 subjects per arm are needed to show equivalence or better. See Makuck and Simon for a discussion on power calculations for a clinical trial designed to show equivalence.[1]

The clinical trial protocol outlines presented in Exhibit 29 were based on the studies used to obtain approval of rifapentine (Priftin®), a derivative of rifamycin that was granted accelerated U.S. approval as an orphan drug for the treatment of pulmonary TB in June 1998. *Appendix B* provides an overview of the rifapentine clinical trials. Trial designs then were evaluated by TB clinical trial experts and modified according to their recommendations.

The latest FDA guidelines suggest that a single pivotal Phase III study with supporting data might be sufficient for approval if all basic safety requirements have been met, regardless of whether the drug is an analogue of a current anti-TB therapy, an NCE, or an existing antimicrobial that is being advanced for the treatment of TB.[70]

3.4.2.1 Phase I Protocol

The studies proposed represent only a general design and might have to be modified or added to once a compound is selected for clinical evaluation. Trial durations and frequency of evaluations will be based on the half-life of the compound and results from preclinical metabolism studies.

Five Phase I clinical trials are conducted in a variety of populations. The initial Phase I study determines toxicity, pharmacokinetics, and bioavailability in healthy males and females (8 to 12 each) following a single dose of the drug candidate over a range of doses. Based on the initial study, a repeated dose pharmacokinetic and bioavailability

Exhibit 30: Overview of Phase I Clinical Trials

Design	Average No. of Patients	Assessments
Open-label, single-dose study (Study 1)	16	13 total assessments: blood and urine drug concentrations, hematology and blood chemistry, LFTs, and urinalyses
Open-label, randomised, repeated dose study (Study 2)	24	13 total assessments: blood and urine drug concentrations, hematology and blood chemistry, LFTs, and urinalyses

LFT=liver function test

study will be carried out in healthy males and females (12 of each) to determine whether multiple doses will affect pharmacokinetics, metabolism, or other parameters. Exhibit 30 contains an overview of a small, generalised pharmacokinetic study and a larger Phase I clinical trial.

Additional pharmacokinetic and bioavailability studies might be necessary in populations such as HIV-positive patients or the elderly and adolescents. For example, pharmacokinetic and bioavailability studies in asymptomatic HIV-positive patients indicated that the C_{max} (peak serum level) and AUC of rifapentine were reduced and the clearance increased relative to healthy individuals. Sample sizes will range from 5 to 25 subjects per study, with an average of 16 patients in small trials and 24 patients in large trials.

Pharmacokinetic monitoring of drug candidates will be of particular importance in HIV-positive patients with TB because of the occurrence of increased drug toxicity as well as reports of altered absorption and decreased bioavailability of some drugs in these patients.[51,67]

Overall, approximately 104 subjects will be included in Phase I clinical trials. The proposed WHO/IFPMA regulatory harmonisation guidelines separate the Phase I trials into two categories: primary studies that should be completed prior to starting Phase II trials and secondary studies that should be performed as required.[63] All required primary studies have been included in the Phase I trial cost estimates. Secondary Phase I studies might include the following:

- A single-dose pharmacokinetic study in other populations
- A multiple-dose pharmacokinetic study in other populations
- An hepatic enzyme induction study in HIV-negative patients
- A body mass/metabolism study in HIV-negative patients

The secondary studies will be conducted when needed as determined by the properties of the anti-TB agent.[63] Since the need for these trials cannot be determined in advance, they are not included in the total Phase I trial cost.

Depending on the properties of the compound selected, other studies such as drug-drug interaction studies and studies in patients with hepatic impairment might need to be conducted. It also is possible that some studies could overlap or be combined, reducing both Phase I duration and overhead costs, such as personnel and facilities, depending on

Exhibit 31: Overview of Phase II Clinical Trials

	Small EBA study	Large EBA study	Pilot efficacy and safety study
Study design	2 arms (new drug and isoniazid)	6 arms (isoniazid and 5 levels of new drug)	Randomised, multicentre, 2 arms
No. of patients	16[a]	48[a]	200
Duration	7 days; drugs dosed on days 1–6	7 days; drugs dosed on days 1–6	2-month intensive, 4-month continuation therapy, 12-month follow-up
Assessments	Sputum collection and culture	Sputum collection and culture	Sputum collection and culture, chest X-ray, physical exam, urinalysis, LFTs, hematology, blood chemistry, BUN, bilirubin, serum uric acid, visual acuity
Frequency	Daily	Daily	Screening, day 1, day 2, day 14/15, day 30, day 60, day 90, day 120, day 180, 3-month, 6-month, 12-month, 18-month, and 24-month follow-ups

LFT=liver function test; BUN=blood urea nitrogen

[a] Eight patients per arm is the minimum number required for theses studies. Because of the possibility of greater than expected variability among subjects, problems in specimen collection, and patient drop-out, as many as 14 patients per arm may be needed to produce valid results.

the country where the trials are conducted. Finally, it is highly likely that Phase II dose-ranging (EBA) studies will be initiated before completion of all Phase I studies if preliminary results indicate a favourable safety profile.

3.4.2.2 Phase II Protocol

Three Phase II trials are conducted—two 7-day randomised EBA studies and one pilot efficacy and safety study—to determine whether the drug has sufficient activity to maintain a negative culture in patients after 2 to 3 months of intensive therapy and to further assess the safety of the NCE. Exhibit 31 summarises the protocol for the proposed EBA studies and the pilot efficacy and safety study.

The first EBA study consists of two arms, with eight subjects in each, to assess bactericidal activity of a new anti-TB agent at the likely maximum therapeutic dose compared to isoniazid as the control arm.[71] Subjects are hospitalised for 7 days, during which sputum is collected daily. If the new drug has bactericidal activity, a larger EBA dose-response study should be initiated.[71]

The second EBA study has a maximum of six arms, each containing eight subjects with newly diagnosed TB. The six arms include five representing various trial drug doses and one representing a control. Depending on the findings of preclinical studies and Phase I trials, it might be possible to reduce the number of drug doses, and thus the number of arms, required to complete the study. The remainder of the methodology is similar to that of the smaller EBA study.

If the results of the larger EBA study are positive, a pilot efficacy and safety study is conducted that includes 200 male and female subjects, ranging from adolescent to elderly, with clinically verified pulmonary TB. The pilot study evaluates efficacy, time to conversion, relapse rates, drug interactions, laboratory test interactions, compliance rates, and adverse events. Subjects are randomised into the study arm (new drug) or the control arm (e.g., rifampicin). Each subject also receives the remaining components of standard

Exhibit 32: Overview of Phase III Clinical Trials

	Phase III Trial
Study design	Randomised, blinded, multicentre, international, 2 arms
No. of patients	1,000
Duration	2-month intensive, 4-month continuation therapy, 24-month follow-up
Assessments	Sputum collection and culture, chest X-ray, physical exam, urinalysis, LFTs, hematology, blood chemistry, BUN, bilirubin, serum uric acid, visual acuity
Frequency	Screening, day 1, day 2, day 14/15, day 30, day 60, day 90, day 120, day 180, 3-month, 6-month, 12-month, 18-month, and 24-month follow-ups

LFT=liver function test; BUN=blood urea nitrogen

combination therapy—isoniazid, ethambutol, and pyrazinamide—for the usual 2-month intensive phase of therapy followed by the 4-month continuation phase and 12 months of follow-up. If the new anti-TB medication's therapy has a duration shorter than the 6-month standard anti-TB therapy, a placebo replacing the drug under development will be administered for the remaining months of treatment.

Although the actual duration of therapy might be shorter or longer than 2 to 3 months, the costs for clinical trials (6 months of medical care and a 12-month follow-up period) are not affected. The only potential source of cost differences lies in the drug therapy itself; however, these differences are not likely to significantly change the final cost estimates.

3.4.2.3 Phase III Protocol

Exhibit 32 summarises the protocol for the Phase III clinical trial. One pivotal, multicentre, international, randomised, comparative equivalence/similarity Phase III clinical trial is needed. Approximately 1,000 adolescent, adult, and elderly males and females with newly diagnosed, clinically verified pulmonary TB are enrolled. Individuals with asymptomatic HIV infection and subjects with AIDS also are included in the patient population for the Phase III clinical trial.[24] Assuming a drop-out rate of approximately 30%, with 15% dropping out at screening and the remaining 15% dropping out during the course of the study,[65] 1,176 subjects should be screened.

Subjects are randomised into the study arm (new drug) or the control arm (rifampicin). Each subject also receives the remaining components of standard combination therapy and/or a placebo as in the pilot efficacy and safety study in Phase II. As in Phase II, the actual duration of the new therapy has a minimal impact on cost estimates.

A 2-year follow-up period is planned; however, provisional approval should be sought once 6-month drug therapy or 6-month follow-up data are obtained for each subject. Provisional approval could be based on a promise to continue the Phase III follow-up for 24 months and to conduct an appropriate Phase IV postmarketing trial programme. The design and costs of conducting a Phase IV postmarketing study are beyond the scope of this section. However, if a postapproval Phase IV trial is necessary, it is assumed that the costs would be similar to the per-patient costs for the Phase III clinical trials.

Phase III clinical trials provide information on efficacy, safety, time to conversion, relapse rates, drug/laboratory test interactions, and compliance rates. Specifically, outcomes should include the following:

- **Primary:** 2-month sputum culture conversion rate, initial cure at the end of treatment, complete safety profile at the end of treatment
- **Secondary:** nonrelapsing cure at 6, 12, and 24 months

According to WHO/IFPMA harmonisation guidelines, the key endpoint of the Phase III trial is equivalent efficacy (not superiority). Since "early approval with a restricted indication" is the development goal,[63] regulatory approval is based on 6-month follow-up data, conditional on the submission and approval of 24-month follow-up data as soon as it is available.

Other outcomes might include drug interactions, compliance assessment, evaluation of selected surrogate markers, pre- and postsusceptibility testing, and RFLP testing of relapses.[63]

Surrogate markers, such as mRNA or specific metabolic by-products, can be assessed in the Phase III trial once the assessment methodologies have been standardised and are uniformly accepted by national drug regulatory authorities.

Pharmacoeconomic outcomes derived from the Phase III clinical trials include medical resource utilisation, lost productivity due to TB, and patient satisfaction with care.

3.4.3 Clinical Trial Timelines

Based on the rifapentine clinical trial process, all phases of clinical trials required for regulatory approval of a new anti-TB agent will take approximately 10 years, including regulatory submission, approval, and completion of follow-up trials. Exhibit 33 shows the duration of each phase of clinical trials, and Exhibit 34 shows the proposed timelines for each phase.

The Scientific Blueprint for TB Drug Development estimates that it will take 7 years from the start of clinical trials to bring a new anti-TB drug to the market.[24] The clinical trial timelines presented here are longer because they are based on a full 12-month follow-up period for the Phase II efficacy and safety trial and a 24-month follow-up period for the Phase III clinical trial. About 3 years could be eliminated from the 10-year estimate:

- Overlap the Phase I studies
- Initiate Phase II dose-ranging EBA studies before completion of all Phase I studies if preliminary results indicate a favorable safety profile
- Start the Phase III trial after obtaining positive 6-month follow-up data in the Phase II pilot efficacy and safety trial
- Decrease the required 2-year follow-up period in a Phase III trial and allowing "early approval with a restricted indication"[63] based on 6-month follow-up or at the end of the 6-month treatment phase of the study
- Decrease the 2-year recruitment/enrollment period for the Phase III trial

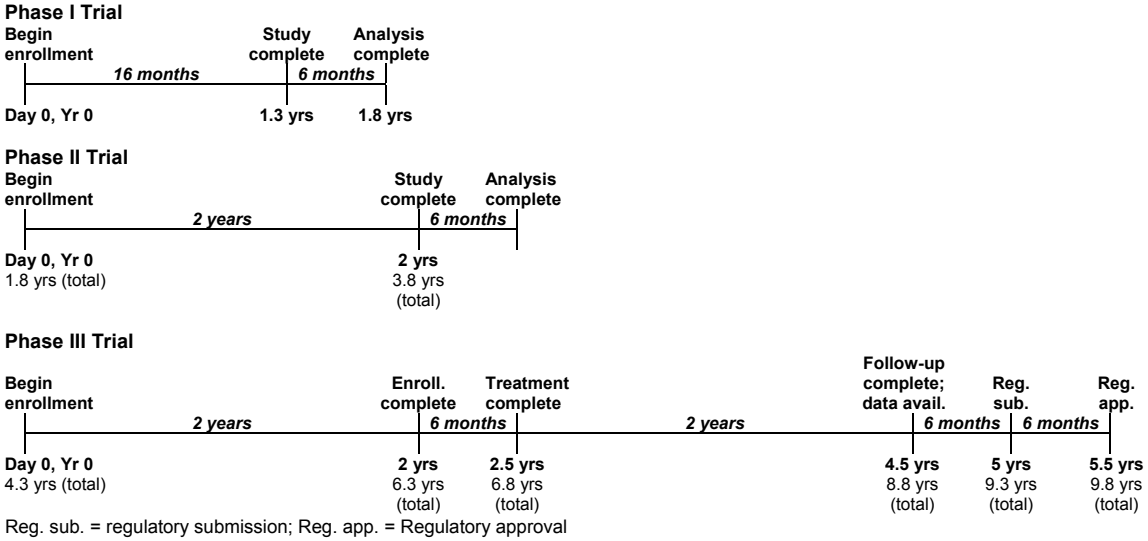
Exhibit 33: Duration of Clinical Trials

Trial	Duration[a]	Cumulative Time
Phase I	1.8 years	1.8 years
Phase II	2.5 years	4.3 years
Phase III	5.5 years[b]	9.8 years

[a] Includes time for subject recruitment/enrollment, data collection, analysis, and report preparation.

[b] Duration includes 6 months for regulatory submission and approval. Subject recruitment is assumed to take approximately 2 years to complete. If the enrollment period is decreased, the duration of the entire Phase III trial can be decreased.

Exhibit 34: Timelines for Clinical Trials



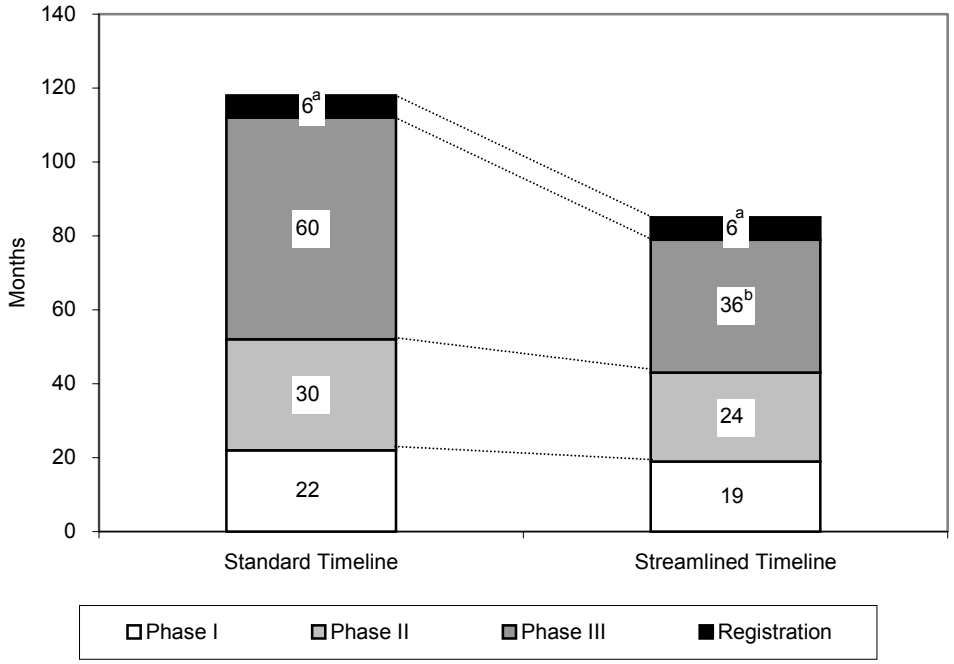
Reg. sub. = regulatory submission; Reg. app. = Regulatory approval

Exhibit 35 shows the cumulative time from the start of Phase I trials through regulatory approval under the standard approval process timeline and under a streamlined approval process, where preliminary approval after 6 months of Phase III follow-up is anticipated. Preclinical and Phase IV studies are not included in this timeline; however, Phase IV trials will be conducted postapproval.

3.5 Summary

This chapter focused on estimating development costs (past the discovery stage) for a new anti-TB drug. Using an approach to include the costs of unsuccessful projects, researchers estimate the total costs of developing (excluding discovery) an NCE to be approximately $76 million to $115 million, depending on total development time and the discount rate assumed. Actual costs—without factoring in the costs of failure—are estimated to total between approximately $36.8 million and $39.9 million:

Exhibit 35: Comparison of Clinical Trial Timelines Before and After Streamlining



[a] The 6-month time period for regulatory approval is an optimistic estimate based on the U.S. regulatory approval process. This estimate might change based on the country where approval is sought. However, regulatory harmonisation efforts should assist in providing a uniform time to regulatory approval.

[b] The 36-month estimate is based on regulatory submission for preliminary approval based on 6-month follow-up data. The study will be continued post-approval to obtain 24-month follow-up data for all subjects.

- Preclinical studies are estimated to cost between approximately $4.9 million and $5.3 million.
- The overall costs for the CMC portion of a pharmaceutical development programme are estimated to be at least $5.3 million.
- A full programme of clinical development (Phase I through Phase III trials) is estimated to cost about $26.6 million in a country with an established economy. Comparable studies conducted in a country with a developing economy are estimated to cost approximately $9.9 million.

The costs of discovery are estimated to range from $40 million to $135 million, although this range should be considered a rough estimate. Thus, the total costs to discover and develop a new anti-TB drug (including failure costs) is roughly estimated to range from $115 million to $240 million. However, it is generally accepted that discovery and development of a new drug to treat TB will require an international, collaborative effort that allows costs to be shared by multiple organisations, lowering ultimately the investment burden borne by a single agency or company.

4.0 Financial and Social Returns on Investment in Development of Anti-TB Drugs

4.0 Financial and Social Returns on Investment in Development of Anti-TB Drugs

The preceding three chapters have presented a variety of data related to the introduction of a new anti-TB drug:

- Assuming that historical trends continue, in 2010 an estimated 11.6 million people are expected to develop TB. An estimated maximum of around 1 million to 2 million people per year are expected to start treatment for latent TB infection in high-HIV-prevalence countries; in countries with established economies, this figure is estimated to be at least 150,000 and could reach as high as 1.25 million per year.
- In 2010, the total global market for anti-TB drugs is estimated to be between approximately $612 million and $670 million ($US). This estimate assumes that (1) the 2000 private market* will remain the same for the most part to 2010 (see assumption 4), (2) the public/tender market* will increase as DOTS coverage continues to expand, (3) the market for MDR-TB drugs will increase due to increases in the percentage of patients treated, and (4) the market for drugs to treat LTBI will increase due to increases in the percentage of patients treated.
- Actual costs of developing an NCE for TB—without factoring in the costs of failure—have been estimated to range from approximately $36.8 million to $39.9 million in countries with established economies. These figures cover preclinical and clinical studies and pharmaceutical development (CMC) activities. If some of the development steps were conducted in countries with developing or transitional economies, these costs will be lower.

This information—as well as a variety of other assumptions—can be used to calculate the potential internal rate of return (IRR) for a pharmaceutical company choosing to invest in the development and introduction of a new anti-TB drug. In addition, one can consider the benefits that a new, 2-month anti-TB drug would be expected to provide to health care systems and public health, as well as patients, their families, and their communities. This chapter discusses these financial and social returns.

* The private market, composed of traditional pharmacy and hospital sales, is found primarily in highly industrialised countries. The public/tender market is composed of (1) government purchases of anti-TB drugs at the federal, regional, and/or local level, depending upon the country, and (2) international donors with an interest in TB control strategies that supply drugs to developing and high-burden countries. (See Chapter 2.)

4.1 Internal Rate of Return

Internal rate of return is defined as the rate of return that equates the discounted stream of income to the discounted stream of costs generated by an investment.[72] In their analysis of the internal rate of return for new drug introductions in the first half of the 1980s, Grabowski and Vernon found that the mean IRR was 11.1%.[73,74] This is consistent with the implied rate of return from a study undertaken by the U.S. Office of Technology Assessment for new drug introductions between 1981 and 1983.[75]

The IRR for a new anti-TB drug is estimated to range from 15% to 32%, depending on where the clinical trials are conducted, the pace of development, and the size of the revenues. These rates are calculated on the basis of development costs from preclinical research through regulatory approval and indicate that investing in development of a lead compound is an attractive commercial venture. This section discusses these calculations.

4.1.1 Calculating IRR: An Overview

If the internal rate of return (r) is greater than the firm's cost of capital or its hurdle rate, then the investment should be undertaken. The firm's cost of capital (r^*) is a weighted average of its cost of capital on its debt and equity capital. This can be expressed as the following equation:

(1) $$r^* = r_D(1 - T_C)(D/V) + r_E(E/V)$$

where r_D = expected rate of return on assets of comparable riskiness for the firm's debt securities

r_E = expected rate of return on assets of comparable riskiness for the firm's equity securities

T_C = corporate tax rate

D/V = proportion of firm's market valuation represented by debt securities

E/V = proportion of firm's market valuation represented by equity securities

The debt component of the cost of capital is multiplied by $(1–T_C)$ because interest on debt obligations is tax deductible, while earnings on equity shares are not. For most major pharmaceutical firms, debt securities account for less than 10% of market valuation, so that the equity cost of capital is the dominant economic component of the firm's cost of capital for firms in this industry.

Myers and Shyam-Sunder[76] and Myers and Howe[77] used the capital asset pricing model (CAPM) to examine the cost of capital for equity financing for the pharmaceutical industry during the period 1980 to 1994. In the CAPM, investors require a risk premium for holding equity in a particular company. This premium is based on the company's assets' relative riskiness or contribution to the variance in the return of a diversified portfolio of equity shares. The CAPM assumes that investors hold well-diversified portfolios. In particular, the CAPM implies that the expected return on an asset is equal to

the risk-free rate plus a risk premium that is positively related to its risk relative to other stock market assets:[74]

(2) $$r_E = r_f + \beta(r_m - r_f)$$

where r_f = risk-free rate (the return in Treasury bills is typically used as a proxy)

r_m = rate of return for a market basket of common stock (usually the Standard and Poor's [S&P] index)

β = relative riskiness of a firm (based on a regression analysis that provides its covariance with the overall S&P index)*

Using the CAPM, Myers and Shyam-Sunder estimated the relative riskiness of 17 major pharmaceutical firms and then applied equations (1) and (2) to compute average pharmaceutical industry cost-of-capital values for 1980, 1985, and 1990.[76] Myers and Howe performed a similar analysis for 1994.[77] Their cost-of-capital estimates were relatively stable over 1980 to 1994. The estimated cost-of-capital values for pharmaceuticals for 1994 were about 14% nominal and 11% real. (Real values are adjusted for inflation.)

Myers and Shyam-Sunder also examined the cost of capital for seven smaller biotechnology and pharmaceutical firms.[76] These firms had higher relative riskiness and costs of capital than the major pharmaceutical firms. The greater riskiness was consistent with the fact that the smaller biotechnology firms had fewer commercialised products and proportionately more early-stage R&D projects. The average cost of capital for the small firm sample in 1989 was about 19% nominal and 14% real.

Financial economists stress that the risk and cost of capital of an individual R&D project will depend on the stage of the project and, correspondingly, on the amount and timing of follow-on investments required to achieve commercial success. By contrast, the estimates derived from corporate financial data by Myers and Shyam-Sunder,[76] by Myers and Howe,[77] and by other authors represent an average cost of capital for a firm's aggregate portfolio of R&D projects, as well as its complementary capital investments in manufacturing and marketing assets.

Some analyses of the pharmaceutical industry have used a higher cost of capital for early-stage R&D projects based on cost-of-capital estimates from firms at various stages of the life cycle. For example, the U.S. Office of Technology Assessment suggested a 14% real cost of capital might be appropriate for the earlier preclinical stages of R&D, based on Myers and Shyam-Sunder's biotechnology and small firm sample.[76] This value then could be adjusted downward as an individual project proceeds through its life-cycle and approaches commercialisation. This approach generally is consistent with the analysis of Conroy and colleagues, who found that the β measure of equity risk for specific firms is positively related to the firm's research intensity.[78] In particular, their analysis indicates

* Company-specific values for β, which are updated periodically, can be found in ValueLine's Investment Surveys and other security analyst publications.

Exhibit 36: Estimated Clinical Trial Development Costs and Timeline (assuming each step is successful)

Trial	Costs		Duration	
	Established Economy	Developing Economy	Normal	Rapid
Phase I[a]	$644,957	$162,651	22 months	19 months
Phase II[a]	$3,387,765	$1,595,708	30 months	24 months
Phase III[a]	$22,600,924	$8,179,228	60 months	36 months
Phase IV[b]	$25,000,000[b]	$9,000,000[c]	60 months	36 months

[a] Source: *Section 3.4*

[b] Source: CDC's rifapentine Phase III Study 22 trial, excluding clinical trial drug supply costs[65]

[c] 36% less than established economy by assumption

that firms with higher R&D sales ratios have greater market riskiness. Their analysis was based on a sample of firms from four industries including pharmaceuticals.

An analysis of the average cost of capital in the pharmaceutical industry for more recent time periods indicated that moderately higher values compared with the numbers derived by Myers and Shyam-Sunder[76] and by Myers and Howe.[77] For example, a cost-of-capital analysis for December 1999, using an approach comparable to these studies, yielded a 15% nominal and a 12% real cost of capital for pharmaceuticals. This reflects primarily an increase in the equity premium for the full basket of stock market securities during the 1990s (i.e., higher overall market returns) rather than an increase in the riskiness of pharmaceutical R&D portfolios relative to other investments.[79] Discussions with a few of the leading pharmaceutical firms suggest that a nominal cost of capital—12% to 15%—currently is being used by many large pharmaceutical firms.[80] Given a 3% rate of inflation, this would imply a 10% to 12% real cost of capital for major pharmaceutical firms. This is roughly consistent with estimates of the cost of capital derived from the CAPM and provides a plausible range or benchmark for evaluating internal R&D projects.

4.1.2 IRR Calculations for a New Anti-TB Drug

The internal rate of return computed below is the discount rate that gives a net present value of zero for a hypothetical new anti-TB drug. Net present value is the difference between the discounted expected net revenue and the discounted net expected costs.

The calculations assume that the new compound is entering development and do not include the costs of discovery. This scenario is appropriate at the point that a decision is made about clinical development for a compound that is already approved for another indication or for a compound for which the discovery work was completed using government or foundation funding.

The expected costs (Exhibit 36) include the clinical development costs presented in *Section 3.4* as well as Phase IV postmarketing trials. Exhibit 36 also presents the estimates of the time spent in each phase of development assuming first a normal pace development and then a rapid development, as described in *Section 3.4.3*. The clinical development costs are assumed to be spread uniformly throughout the time period for each development phase.

Exhibit 37: Estimated Other Development Costs

Development	Costs	
	Established Economy	Developing Economy
Preclinical development costs (assuming success)	$5.3 million[a]	$3.98 million[b]
Manufacturing stability testing and scale up costs (assuming success)	$8.0 million[c]	$6.0 million[b]
Prelaunch and launch period additional marketing and sales costs[d]	100% of Year 1 sales 50% of Year 2 sales 25% of Year 3 sales	100% of Year 1 sales 50% of Year 2 sales 25% of Year 3 sales
Marketing and sales costs[d]	$350,000/$1 million revenue	$350,000/$1 million revenue
Cost of good sold[d]	$200,000/$1 million revenue	$150,000/$1 million revenue

[a] Source: *Section 3.2*

[b] 25% less than established economy by assumption

[c] Sources: Parexel's 1999 *Pharmaceutical R&D Statistical Sourcebook*[2]

[d] Assumption

Exhibit 38: Estimated Revenue at Peak Sales

Forecast Compared to Current Sales*	Forecast Annual Revenue
Low (50% of current sales)	$222.5 million
Medium (75% of current sales)	$333.75 million
High (100% of current sales)	$445 million

*As outlined in *Chapter 2*, the current global market for anti-TB drugs is estimated to range from $412.5 million to $470.5 million per year. For the purposes of calculating IRR, an annual sales total of $445 million is assumed.

Exhibit 39: Other Assumptions

Variable	Value
Model time horizon after entering Phase I	25 years
Time to peak sales after launch	3 years
Decrease in sales revenue after 5 years	20%
Decrease in sales revenue after patent expiry	90%

Other development and selling cost assumptions are shown in Exhibit 37. These include the costs associated with preclinical development; manufacturing, including stability testing and scale-up activities; and the launch of a new product. In addition, annual costs per million dollars of revenue are estimated for both cost of goods and for sales and administration costs.

Exhibit 38 presents assumptions for peak sales revenues, based on the total current private and public/tender sales estimates for anti-TB drugs taken from *Chapter 2*. Exhibit 39 presents other assumptions used to compute annual revenues and costs.

Finally, the probabilities of progressing through the phases of development must be assumed to compute the expected costs and revenues for the new drug. To determine probabilities that are appropriate for a new drug to treat tuberculosis, researchers consulted with experts in TB R&D and adjusted more generic probabilities, developing estimated probabilities that are specific to TB. These are presented in Exhibit 40.

Exhibit 40: Estimated Probability of Transitioning between Phases

Transition	Probability
Preclinical to Phase I	0.1
Phase I to Phase II	0.3
Phase II to Phase III	0.5
Phase III to launch	0.65

Source: Boston Consulting Group, 2000

Exhibit 41: Internal Rate of Return for a New Anti-TB Drug

Scenario			
Economy in Country Conducting Drug Development	Pace	Revenue	Internal Rate of Return[a]
established	normal	low	15%
established	normal	medium	18%
established	normal	high	21%
established	rapid	low	17%
established	rapid	medium	21%
established	rapid	high	24%
developing	normal	low	21%
developing	normal	medium	25%
developing	normal	high	28%
developing	rapid	low	25%
developing	rapid	medium	29%
developing	rapid	high	32%

[a] The IRR shown here is based on many assumptions, as outlined throughout *Section 4.1.2* and elsewhere in this report. Changes in any of these assumptions will affect the IRR. For example, more general probabilities of success[81] were used instead of the TB-specific probabilities in Exhibit 40, the expected IRR would increase by an average of 20%.

4.1.3 Findings of IRR Calculations

A model was constructed using the above inputs and the internal rate of return computed for 12 scenarios based on the country where the clinical trials are conducted (established or developing economies), the pace of development (normal or rapid), and the size of the revenues (low, medium, or high). The results are shown in Exhibit 41. The IRR for these scenarios ranges from 15% to 24% for a drug developed in an established market economy and 21% to 32% for development based in a country with a developing economy. As indicated in the *Section 4.1.2*, these calculations include the development costs from preclinical research through regulatory approval. The IRR values indicate that investing in the development of a lead compound into a new anti-TB drug with the characteristics discussed in the Introduction to this report should be an attractive commercial venture.

It should be emphasised that the rates presented in Exhibit 41 are based on several variables, including the probability of success in transitioning to each new phase of development. The IRR calculation presented here uses TB-specific probabilities of success (Exhibit 40). If more general probabilities were used (i.e., probabilities across all therapeutic areas), different IRR figures would result. For example, DiMasi estimated the following probabilities of transitioning between phases: (1) Phase I to Phase II: 0.7, (2)

Phase II to Phase III: 0.4, and (3) Phase III to launch: 0.8.[81] If DiMasi's success probabilities were used instead of the TB-specific probabilities, the expected rates of return computed in Exhibit 41 would increase by an average of 20%.

4.2 Social Returns

New TB drug development will bring significant public health and economic benefits worldwide. Improvement would be tied mostly to the improved compliance likely to occur with a new drug that shortens the regimen to 2 months or less and/or requires fewer supervised doses.[5]

The potentially profound reduction in disease burden will result in the following benefits:

- Improved treatment success rates
- Reduced overall treatment costs
- Possible reduction in the number of multidrug-resistant cases
- Decreased morbidity and TB transmission in the long term
- Decreased medical and nonmedical costs for long-term TB treatment

This section discusses some of the immediate benefits to the health care system, as well as some of the expected long-term benefits to patients, their families, and the societies in which they participate.

4.2.1 Health Care System and Public Health Benefits

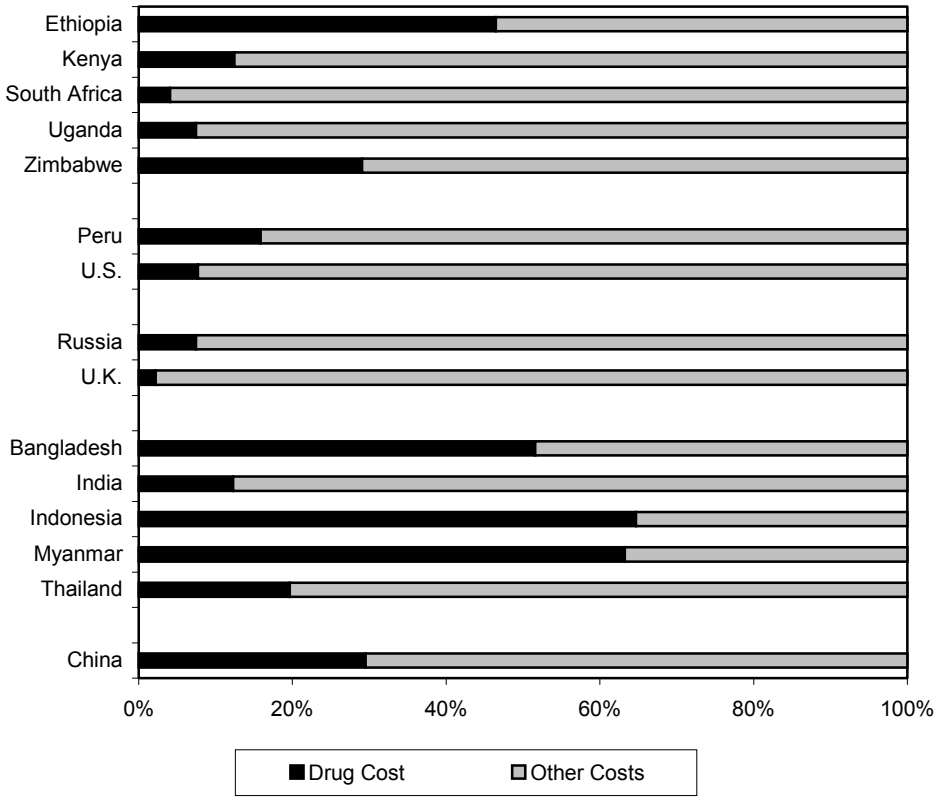
A new drug that reduces the period of treatment from 6 months to 2 months or less is likely to have a favourable impact on the health care system in several ways: (1) per-patient costs will be reduced; (2) overall health care system costs will be reduced, freeing up resources to treat more patients; and (3) DOTS coverage will be expanded. As a result, the spread of TB, and possibly the incidence of MDR-TB, will be better controlled, significantly improving public health worldwide.

4.2.1.1 Reduced Per-Patient Costs

As discussed in *Section 1.3* and presented in Exhibit 9, drug costs are only a small fraction of the total of health system expenditures related to the diagnosis and treatment of TB. As shown in Exhibit 42, even with the more conservative, low-end cost assumptions for treating a new case of smear-positive TB, drug costs in most cases make up less than half of total diagnosis and treatment costs.

Although the internationally recommended DOTS strategy is successful, the infrastructure required to implement it is cumbersome, labour intensive, and expensive.[24] The total costs per treated case mostly are composed of diagnosis and nondrug treatment (NDT) costs. NDT costs include sputum smears during treatment, hospital days, DOTS visits, and clinic visits.

Exhibit 42: Drug Costs as a Percentage of Total Public Sector Health System Costs per Treated Smear-Positive Case of TB



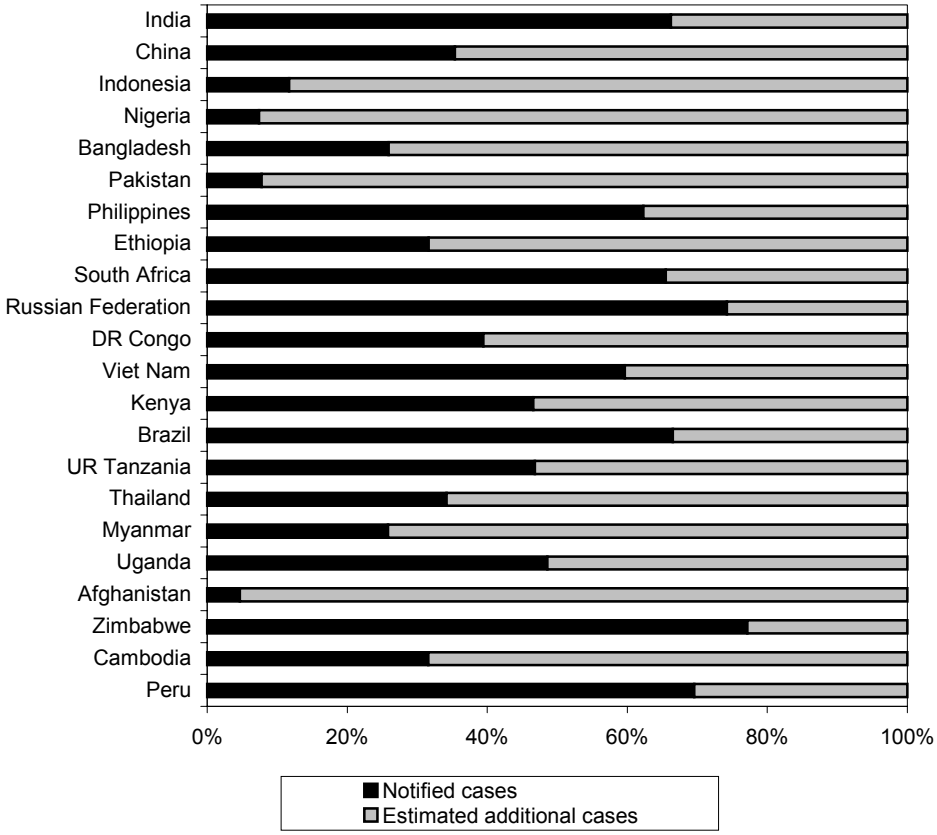
Source: Exhibit 9 (lowest estimated costs per treated case and public sector drug costs)

Reducing the treatment duration is expected to reduce NDT costs and thus the total per-patient costs. Even if total drug costs for a shorter regimen remain the same as current drug costs (see *Chapter 2*), a per-patient savings would result from the lower NDT costs. It is impossible to calculate exactly what the savings might be; however, using the same methodology used to estimate diagnosis/treatment costs (see *Appendix A*), one finds that the per-patient savings might range from more than 5% to about 65%, depending on how many hospital days, DOTS visits, and clinic visits are eliminated from the regimen with a 2-month treatment.

4.2.1.2 Expanded Health System Treatment

Reducing the per-patient costs to treat TB will provide a higher "rate of return" for the world's public health investment. This improvement will be particularly beneficial in the 23 countries with the highest burden of TB, most of which have scarce resources to allocate to their health economies. Reducing the per-patient costs to treat TB will enable health systems to treat more patients without an increase in expenditures.

Exhibit 43: Detected TB Cases as a Percentage of Total Estimated TB Cases in High-Burden Countries[a]

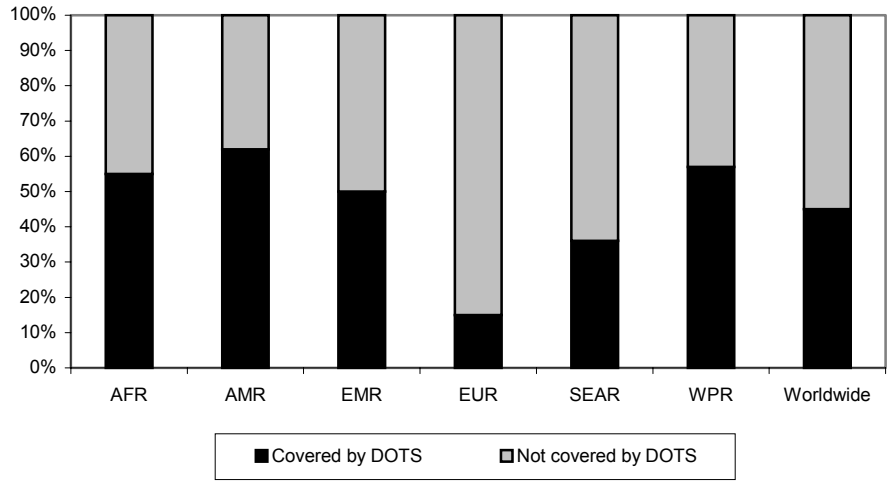


[a] Mozambique is excluded as all cases are based on estimates.
Source: WHO[1]

Similarly, reduced per-patient costs will enable international donor agencies to reap a better return on their investment in eliminating TB. As discussed in *Chapter 2*, donor agencies contributed an estimated $190 million in 2000 to control TB worldwide,[39] and it is estimated that 25% to 40% was allocated to the purchase of anti-TB drugs. Assuming that the remaining 60% to 75% was allocated to other treatment costs, donor agencies spent $110 million to $140 million on diagnosing TB cases and paying for sputum smears and other costs not tied to drugs. Even if total drug costs for a shorter regimen remain the same as current drug costs (see *Chapter 2*), the lower NDT costs will enable a portion of this $110 million to $140 million (assuming total donations remain the same) to be reallocated to diagnosing and treating additional TB patients.

Detecting and treating additional TB patients—via the use of funds previously allocated to pay for 6 months of NDT costs—will be an important improvement in TB control efforts, particularly in high-burden countries. As indicated in Exhibit 43, only a fraction of all new cases of TB are being detected in these countries. The funds made available due to the shorter regimen—assuming funding levels are not decreased—could be used to detect and treat some of these additional TB cases.

Exhibit 44: DOTS Coverage in 1999 by Region



AFR=Africa
AMR= Americas
EMR= Eastern Mediterranean
EUR=Europe
SEAR=South-East Asia
WPR= Western Pacific
Source: WHO[1]

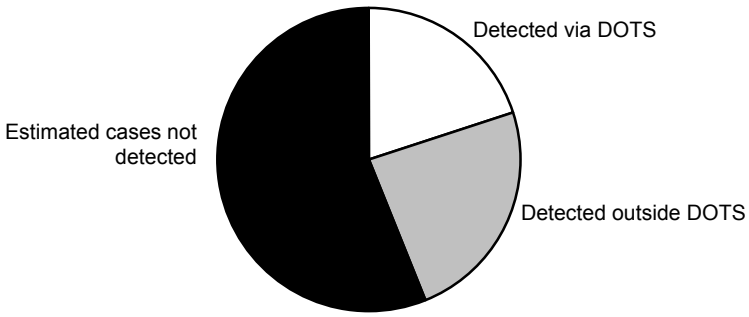
4.2.1.3 Expanded DOTS Coverage

In the same way that a shorter TB treatment would allow health systems to use their NDT funds more efficiently, such improvements also would help the DOTS programme to expand more quickly. According to WHO, 127 out of 211 countries had implemented (at least partially) the DOTS strategy by 1999.[1] This level of coverage means that approximately 45% of the world's population had access to DOTS (Exhibit 44). This global figure represents an increase over the coverage in 1998, which was only 43% of total population.

The progress in DOTS implementation in the 23 countries that contain most of the world's TB burden has been steady but slow.[1] Approximately 46% of the population of high-burden countries is covered by DOTS. For a few countries—including Kenya, Tanzania, Uganda, Cambodia, and Peru—coverage is complete. However, only two (Indonesia and Bangladesh) of the five countries with the highest TB burden had coverage exceeding 65% in 1999. In India, DOTS coverage is only 14% of the country's population, and the majority (90%) of TB case notifications are made outside of DOTS programmes.

In 1999, the proportion of all detected TB cases that were reported to DOTS was 45%, and for detected smear-positive TB cases this figure was 58%. However, the proportion of total **estimated** TB cases that were reported to DOTS was only 20%, and for estimated smear-positive TB cases this figure was 23%. Although thousands of TB patients are detected outside of DOTS programmes, Exhibit 45 shows that more than 50% of the estimated 8.4 million TB cases are not detected at all.

Exhibit 45: TB Cases Detected by DOTS and Non-DOTS Programmes as a Percentage of Total Estimated TB Cases Worldwide



Source: WHO[1]

If current trends hold steady, the WHO report shows, DOTS coverage will not expand quickly enough to reach the goal of 70% case detection by 2005. In fact, such coverage would not be attained until 2013.

The per-patient cost benefits provided by a new anti-TB drug that requires a duration of 2 months or less are expected to facilitate the expansion of DOTS coverage. Because the amount of NDT funds needed to treat the same number of cases will be reduced, the proportion of funding available to expand DOTS programmes will increase.

4.2.1.4 Improved Public Health

As discussed in the sections above, a shorter regimen to treat TB will enable various control programmes to expand their reach, resulting in an increased detection rate for TB patients. High rates of detection and cure in Cuba, Lebanon, the Maldives, Nicaragua, Oman, and Uruguay are linked to an apparent decline in TB incidence rates.[1] Thus, it may be inferred that improving detection and cure rates is the key to controlling TB. Among the additional TB patients detected, it is expected that between 40% and 44% would be smear-positive (i.e., infectious).* Treating more infectious patients will help to reduce the incidence of TB. Furthermore, if the new drug is a powerful sterilising agent, the time to convert patients who are smear-positive to smear-negative could be shortened, further reducing the chances of transmission of infection during treatment and ultimately slowing the spread of the disease.

The public health benefits of a shorter regimen include improved compliance, resulting in reduced resistance, transmission, morbidity, and mortality.

* These percentages were calculated using data from WHO.[1]

4.2.2 Patient and Societal Benefits

4.2.2.1 Economic Benefits to Patients

Apart from the costs incurred for treatment services, patients and their families bear other costs from the disease, including travel, lodging, and special food while the patient accesses health care. These **direct nonmedical costs** can be significant:

- In India, a study estimated that direct nonmedical costs paid by TB patients made up 42% of the total direct costs for treating TB.[82]
- In Zambia, researchers estimated that direct nonmedical costs incurred by patients were more than twice the medical costs they incurred.[83]

Since many of these direct nonmedical expenses to the patients are tied to the length of treatment, a new anti-TB drug with a shorter treatment programme will reduce these costs. In the same way that health care system costs will drop due to reductions in NDT costs (see *Section 4.2.1.1*) under a 2-month regimen, so too will patient costs be reduced for the travel and lodging associated with these visits.

Patients also incur **indirect costs** during the lengthy regimen currently used to treat TB. Active TB disease causes prolonged periods of sick leave from work and has been a frequent excuse for premature termination of employment. These indirect costs borne by TB patients and their families are substantial and can be two to three times greater than the costs to the health care system.[84] The following specific studies have been conducted on these indirect costs:

- On average, TB patients in developing countries lose 3 to 4 months of income, representing 20% to 30% of the household annual income.[84]
- When TB patients die, their families lose an average of 15 years of income.[84]
- In India, researchers found that TB patients lost an average of 83 work days, including 48 days before treatment and 35 days during treatment. Indirect costs represent 65% of these Indian families' expenditures for TB disease.[82]

Some studies have estimated the combined impact of direct nonmedical and indirect costs:

- In South Africa, direct and indirect costs borne by the patient have been estimated as 12% to 13% of total costs of treatment.[31]
- The percentage of total costs (direct and indirect) borne by patients or their families is 47% to 55% in Kenya and 36% to 69% in Malawi.[85]
- In rural Uganda, 70% of the total costs of treating TB are borne by the patient, most of which are tied to absence from work or decreased productivity.[84,86]

If current treatment for an infectious disease is a criterion for sick leave, then shortening the period of TB treatment could substantially reduce time off work and costs of health insurance and related benefits.

People working in the informal employment sector frequently lack any form of job security or sickness benefits. As a result, periods of ill health have a profoundly negative

impact on their employment and economic security. Long periods of treatment and frequent relapses of disease—both of which are all too common with current TB treatments—are clearly important for the self-employed or those working in the informal sector. New drugs shortening the period of treatment, increasing the likelihood of cure, and reducing the chance of relapse would clearly be of great benefit.

Finally, the losses suffered by TB patients' families often are underestimated since the reduced income suffered by TB patients' families might trigger responses that can profoundly affect their future. These responses include selling family assets or incurring debt to make up for lost income.[84,87] The effects of these reactions might last well beyond the length of the illness as families recover from the loss of productive assets, repayment of loans, and reduced productivity as the patient recovers from acute illness. Thus, a new anti-TB drug that offers an improved treatment programme will have many economic benefits for patients and their families.

4.2.2.2 Long-Term Benefits to Society

The costs borne by patients, as described above, have a long-term penalty for the families affected by TB and, ultimately, for society. The benefits of a new, shorter TB treatment not only will have an immediate economic impact for TB patients and the health care system but also will offer many societal benefits that will reveal themselves in the long term.

Several studies have been conducted on the impacts of TB, which have long-term implications. Families who have reduced income during the currently lengthy TB treatment might reduce their food consumption by 20%.[87] Reduced caloric intake during childhood might have long-term consequences for the future health and earnings of the family's children. Several studies showed that children also might be removed from school to avoid the costs of education and/or to find work to help make up for lost income, further impacting their future earning power.[84,87] A shorter TB treatment will help to mitigate these negative impacts on child development.

TB also exacts a high long-term price from women. Women with TB have reported a 50% reduction in household work, and two-thirds reported not being able to adequately care for their children.[84] A study in India reported that, although both men and women suffered losses due to their illness, women were more concerned than men about losing their jobs since men were more likely to be self-employed.[88] Women often attempt to hide their illness for fear of rejection and abandonment by their husbands and harassment from their in-laws.[88,89] Married women feared that their husbands will divorce them or take an additional wife, while single women feared that they will be unable to marry.[84,88,89] Either outcome can have devastating economic consequences for women in many countries.

In addition to the pain and suffering resulting from the disease, persons with TB often suffer from discrimination and fear rejection and social isolation.[84,89] These intangible costs result in depression, anxiety, and lower life satisfaction, further adding to the burden of TB. The availability of a cure for TB already has reduced the stigma associated with this disease in many communities. However, this issue remains an important barrier to health-seeking behaviour in some communities, particularly among women and other

disadvantaged groups. Reducing the duration of treatment would contribute to further destigmatising the disease. This reduction in stigma would further increase access to diagnosis and treatment, and contribute to accelerated disease control.

4.3 Summary

As discussed in this chapter, many benefits are expected as a result of investment in developing a new drug to fight TB:

- The internal rate of return for a new anti-TB drug is estimated to range from 15% to 32%, depending on where the clinical trials are conducted, the pace of development, and the size of the revenues. This range is based on development costs from preclinical research through regulatory approval and TB-specific probabilities of success. The range indicates that investing in development of a lead compound is an attractive commercial venture.
- Because drug costs are only a small fraction of the total of health system expenditures related to the diagnosis and treatment of TB, reducing the 6-month treatment duration to 2 months or less is expected to yield a reduction in total per-patient treatment costs, even if total costs for the drug regimen remain the same. This reduction is tied to the number of hospital days, DOTS visits, and clinic visits eliminated under a 2-month treatment.
- Reducing the per-patient costs to treat TB will enable health systems to treat more patients without an increase in expenditures. Such improvements also will help the DOTS programme to expand more quickly.
- The public health benefits of a shorter regimen include improved compliance, resulting in reduced resistance, transmission, morbidity, and mortality.
- A 2-month treatment for TB might reduce the heavy price that TB exacts on patients and their families. With a shorter treatment, patients will reduce their significant direct nonmedical costs as well as their indirect costs, such as income lost due to sick leave and costs from selling family assets and incurring debt to make up for lost income.
- A shorter TB treatment is expected to offer many long-term societal benefits, such as reductions in poor nutrition for family members due to patients being out of work, improvements in women's economic and social security, and reductions in depression and anxiety.

The final chapter of this report explores the essential trends that provide additional incentives for pharmaceutical companies, public health agencies, global financial organisations, and foundations to invest in TB drug development.

5.0 Essential Trends and Opportunities for TB Drug Development

5.0 Essential Trends and Opportunities for TB Drug Development

For over three decades, the private sector has dedicated limited resources to researching new classes of compounds to fight the growing tuberculosis problem despite recent promises of new science, particularly the genome sequencing of *M. tuberculosis*. The public sector is increasingly investing in TB basic sciences and operational research but lacks the infrastructure and know-how for R&D, which private industry has mastered in the past century. The need for collaboration is self-evident.

The fact that TB still presents a significant unmet medical need despite the existence of current drugs has not been sufficiently recognised until recently. In a February 2000 meeting in Cape Town, South Africa, leaders in health, science, philanthropy, and private industry acknowledged that, although an optimal strategy (i.e., DOTS) has been identified to treat TB with current drugs, the treatment and control of the disease is hindered by the complexity and long duration (i.e., 6 to 9 months) of treatment regimens imposed by these drugs. While DOTS certainly is the most important advance in TB treatment of the last 10 years, its wide implementation for the control of the disease worldwide clearly requires a simplification of the treatment regimen.

New drugs for TB that allow a shorter treatment will meet an unmet medical need and yield significant benefits both in the treatment of patients and in the control of the disease.

The fact that a regimen of off-patent drugs currently exists ensures downward pressure on drug prices. However, this is compensated by the large size of the market and the potential for some market segments to pay a premium for a new anti-TB drug with a shorter regimen, as discussed in *Chapter 2*.

This chapter describes the following trends and recent developments that are changing the characteristics of the anti-TB drug market and the context for TB R&D:

- Public-private partnerships are providing opportunities to share and balance the risks and investments.
- TB is a growing priority for public policy and philanthropic initiatives worldwide, suggesting an increasing interest in and possibly funding for TB drug development.

- The role of the private sector in TB control is increasing, representing a significant private market in many countries (including countries with a high TB burden).

5.1 Public-Private Partnerships for Drug R&D and the Global Alliance for TB Drug Development

As demonstrated in previous chapters, the market and social benefits clearly warrant investment in the development of new anti-TB drugs. Yet, not much effort has been made to bring new anti-TB compounds along the full R&D chain in the past 30 years. Although a single industry player might hesitate to pursue actively a single-handed development effort for TB anti-infectives, the existence of the Global Alliance for TB Drug Development—and the opportunities for partnering that the new organisation and its stakeholders offer—constitutes a new incentive for industry to revisit its TB market strategy.

This section reviews how public-private partnerships are changing the economics of drug development, how the Global Alliance for TB Drug Development can alter the risks and cost-benefit equation for its public and private investors and partners, and how the Global Alliance's stakeholders and other partners can contribute to the TB R&D value chain.

5.1.1 Public-Private Partnerships

As discussed by Widdus, public-private partnerships can combine their resources and strengths to help improve the health of the poor, particularly in R&D for neglected diseases.[90] Working with the private sector allows public agencies to complement their capabilities in certain areas (e.g., preclinical development, production process development, manufacturing, marketing/distribution). Analyses have highlighted that partnerships can be successful when the health problem can be characterised as follows:

- The problem has not been fully solved using traditional, independent efforts.
- Potential collaborators agree upon the goals.
- Each sector has relevant, complementary experience.
- Each member of the partnership stands to benefit or has its long-term goals met.
- Expertise and resources are contributed by each member of the partnership.

The generic concept of public-private partnerships applies to any combination of expertise and means across the public, private, and philanthropic sectors.

The specific concept of public-private partnerships for R&D concerns a new breed of R&D ventures structured as not-for-profit organisations that aim to employ the practices and dynamism of the private sector in pursuit of a social mission involving the discovery and development of new therapeutic tools (e.g., drugs, vaccines, diagnostics) in partnership with public and private sector research labs.

As discussed below, one such public-private partnerships for R&D—the Global Alliance for TB Drug Development—seeks to accelerate the development of anti-TB drugs, and some of its stakeholder organisations and other partners already have pledged or committed some of their capacities to the effort.

5.1.2 The Global Alliance for TB Drug Development

The Global Alliance for TB Drug Development (http://www.tballiance.org) is an international nonprofit organisation whose vision is the provision of new medicines with equitable access for the improved treatment of TB. Its mission is to accelerate the discovery and/or development of cost-effective new anti-TB drugs that will shorten or simplify treatment of TB, provide a more effective treatment of multidrug-resistant TB, and improve the treatment of latent TB infection. The Global Alliance seeks to have a new drug that achieves these improvements registered by 2010.

The Global Alliance for TB Drug Development will bring together public and private sector resources and expertise and will give preference to joint ventures involving institutions in TB-endemic countries. It will act as a guarantor of the public sector investment to ensure equitable access and to guarantee transparency and accountability and will follow high standards of confidentiality.

With an unwavering commitment to global public good, the Global Alliance will adopt the best practices of the private sector. It will function as a lean, virtual R&D organisation that outsources projects to public or private partners.

Based on a survey of TB drug development activities in the public and private sectors, the Global Alliance will selectively intervene when its actions will help move a drug candidate towards registration and use in therapy. It will build a portfolio of projects with varying levels of funding, management, and ownership. Acting as an "incubator," it will provide staged funding, expert scientific and management guidance, and some limited infrastructure (e.g., project management, legal support). It will keep a laser sharp focus, actively managing its portfolio along the R&D value chain.

Intellectual property rights are likely to be a strategic element of project deals, a means to balance two complementary goals: (1) retaining the ability to deliver new drugs cost-effectively to those who need them most and (2) providing some incentives for private industry contribution to the R&D process. For example, to secure low prices in countries with less developed economies while retaining incentives for industry, an agreement might involve separate arrangements for developing and developed economies, offering marketing independence in the wealthier markets. Agreements also might consider various conditions for patented technologies when addressing other therapeutic indications.

5.1.3 Partners in TB Drug Development

The R&D partners of the Global Alliance for TB Drug Development include pharmaceutical and biotechnology private industry firms, public research organisations

Exhibit 46: Sample Organisations that Have Pledged Support to the Mission of the Global Alliance for TB Drug Development

National Institute of Allergy & Infectious Diseases
http://www.niaid.nih.gov/dmid/tuberculosis/

Part of the U.S. National Institutes of Health, NIAID's resources include an extensive portfolio of research grants, cooperative agreements, contracts, and intramural laboratory projects with the goal of discovery and development of new antimicrobials to combat TB. NIAID also has a wealth of services specifically targeted to assist industry and university researchers in the evaluation and development of candidate TB drugs.

NIAID supports drug discovery through its own laboratory research and extramural support to universities and other research organizations. All groups collaborate with industry to integrate drug development expertise in the programs.

- **NIAID's Tuberculosis Research Section** supports an extensive program in drug discovery through molecular biology and target-directed combinatorial chemistry. Using the most advanced drug discovery technologies, hundreds of thousands of compounds have been evaluated as inhibitors of specific biochemical targets.
- **National Cooperative Drug Discovery Groups** (NCDDG) have conducted multidisciplinary research projects focused on TB since 1993. The NCDDG encourage collaborations with the private sector with the understanding that development of promising candidate therapies will be pursued toward licensure by the industrial participant. Advances achieved through this program for TB have included identification and characterization of new molecular drug targets. Participants in the NCDDG program include investigators from Colorado State University, the National Jewish Medical and Research Center, Albert Einstein College of Medicine, Texas A&M University, the University of Houston, GlaxoSmithKline, and Bristol-Myers Squibb.
- NIAID supports and directs the **Tuberculosis Antimicrobial Acquisition and Coordinating Facility** (http://www.taacf.org), a program providing preclinical data on the activity of chemical compounds against virulent *M. tuberculosis.* This service is provided free of charge to investigators throughout the world working at public and private institutions. The intention is to stimulate chemical research by providing biological testing data that might otherwise not be available in laboratories without biosafety facilities.
- Under the **NIAID Tuberculosis Technology Transfer Program**, Research Triangle Institute is actively facilitating partnerships for drug development preclincal and clinical testing, and commercial distribution. RTI provides market and pharmacoeconomic data on global TB trends and information on new compounds that offer potential as a new TB therapy.

NIH is a member of the Stakeholders Association of the Global Alliance for TB Drug Development. In addition, key NIAID staff members are on the Board of Directors and Scientific Advisory Committee.

TDR/UNDP–World Bank–WHO
http://www.who.int/tdr/

The Special Programme for Research and Training in Tropical Diseases (TDR) added tuberculosis to its list of targeted diseases in 1999. TDR's Product Research and Development Committee seeks to identify new drugs, vaccines, and diagnostics related to TB and other diseases and to develop them through clinical trials to regulatory approval and registration. Partnerships—especially with industry—to facilitate progress are actively promoted. Research grants are available for scientists from all countries, especially those where TDR's targeted diseases are endemic:

- **Collaborative research grants** are intended to support goal-oriented research as outlined in the workplans of TDR's various steering committees and task forces.
- **Project development grants** are designed to help scientists from developing countries to formulate technically sound, full-scale research proposals. Funds might be used to collect baseline or preparatory data, to initiate preliminary research, or to seek the advice of recognised experts in the preparation of a full-scale research proposal.
- **Director's Initiative Fund grants** are intended for projects for which rapid funding is essential, projects that might be preparatory to larger scale projects, and projects that focus on new lines of research relevant to disease control that may not fall within the current workplans.

More information is available online (http://www.who.int/tdr/about/strategy/prd.htm). In addition, a compendium of compounds in the public domain with some demonstrated activity against TB is being prepared for publication by TDR.

TDR is a member of the Stakeholders Association of the Global Alliance for TB Drug Development. In addition, key TDR staff members are on the Board of Directors and Scientific Advisory Committee.

Tuberculosis Research Unit (TBRU)
http://www.tbresearchunit.org/

The TBRU at Case Western Reserve University School of Medicine facilitates clinical trials of new drugs, vaccines, and diagnostics. Funded in part by a contract with NIAID, TBRU is a multidisciplinary program that involves 50 investigators at seven basic science sites and three clinical sites. The TBRU evaluates modalities for prevention and treatment of TB through Phase I/II clinical trials; characterises the current epidemiology of TB using molecular approaches; develops and validates microbiologic assays to monitor treatment, discover sensitive and rapid methods for diagnosis of TB, and rapidly determine drug susceptibility; and develops and validates immunologic markers of susceptibility/resistance. Current study sites are in the United States, Brazil, and Uganda. The TBRU's leadership encourages collaboration with the private sector for the evaluation of new candidates for development.

U.S. Centers for Disease Control and Prevention and the TB Trials Consortium (TBTC)

http://www.cdc.gov/nchstp/tb/tbtc/

CDC has played a major role in conducting clinical trials to evaluate new drug regimens for the treatment and prevention of TB since 1960. For example, CDC coordinated a series of multicentre clinical trials that helped to establish rifampicin-based, short-course therapy as the standard for TB treatment.

CDC's Division of TB Elimination provides approximately $5 million in funding each year to the TBTC—a collaboration of North American clinical investigators whose mission is to conduct programmatically relevant research concerning the diagnosis, clinical management, and prevention of TB. The TBTC includes the following:

- A network of 23 clinical sites in the United States (20) and Canada (3) whose principal investigators are recognised experts in TB treatment and prevention
- Experienced clinical coordinators and outreach workers at each site
- A communications system that includes semiannual meetings, conference calls, study newsletters, and frequent use of e-mail
- Close and collaborative relationships with local TB control programs to facilitate the recruitment and management of trial patients
- An expert data and safety monitoring board to review active protocols
- Coordination with the CDC's institutional review board and the boards at the 23 clinical sites
- A data and coordinating centre at CDC
- Cooperative relationships with key drug makers
- Support for training, monitoring, and protocol development
- Laboratory support from CDC's Division of AIDS, STD and TB Laboratory Research, Tuberculosis/Mycobacteriology Branch (http://www.cdc.gov/ncidod/dastlr/)

CDC is a member of the Stakeholders Association of the Global Alliance for TB Drug Development. In addition, key staff from the CDC Division of TB Elimination are on the Scientific Advisory Committee.

Coalition for TB Research and Development

http://www.tballiance.org/coalitionforTB

The Coalition for TB R&D is an interest group of stakeholders, predominantly research networks, from countries with a high-burden of TB. It seeks to mobilise researchers and investigators worldwide to share expertise and gather resources for R&D projects related to TB drugs and other TB research.

Although its coordinating office is hosted by the Global Alliance in its Cape Town offices, the Coalition for TB R&D is a worldwide network, with regional focal points in Latin America, Africa, and Asia.

Action TB

http://corp.gsk.com/community/tbprogrammes.htm

Glaxo Wellcome (now GlaxoSmithKline) launched the Action TB programme in June 1993 with the goal of developing new therapies for the treatment and prevention of tuberculosis. The programme aims to deliver a new drug that would either shorten the treatment duration or effectively tackle multidrug-resistant TB and a vaccine that provides universal protection. The strategic focus of Action TB falls into four key areas: promising drug targets, vaccine candidates, improved models of infection, and surrogate markers.

Action TB places emphasis on tractable drug targets that can move quickly into high-throughput screens to generate lead molecules. This will be coupled with structural information about the target to facilitate rational drug design. Cell wall biosynthesis targets identified during the programme's first phase are already being screened. Medicinal chemistry approaches are being explored to generate lead compounds and develop combinatorial chemistry libraries around molecules showing activity against *M. tuberculosis*. Action TB is seeking to understand the processes that allow *M. tuberculosis* to persist unscathed by drug treatment with a view to finding new drug targets or delivery systems that will rapidly eliminate all bacteria.

The Action TB programme is a global effort, supporting research groups in South Africa, Gambia, the United Kingdom, the United States, and Canada.

Senior scientific staff from Action TB are on the Global Alliance for TB Drug Development's Scientific Advisory Committee.

Sequella Global Tuberculosis Foundation

http://www.sequellafoundation.org

Operating on philanthropic funds donated by a variety of sources (including a large grant for TB vaccines from the Bill and Melinda Gates Foundation), Sequella Global TB Foundation is dedicated to helping researchers in academia, government, or industry identify and develop products for TB. Its services, which usually are provided free of charge, relate to U.S. and European regulatory strategies and to clinical trial design, execution, and site development in TB endemic areas. Services include the following:

- Assisting the preclinical development of new TB products
- Sponsoring clinical trials (e.g., a large BCG trial in the Western Cape region of South Africa)
- Screening large chemical libraries that currently exist in pharmaceutical (and biotechnology) companies and that have never been tested against *M. tuberculosis* for utility in TB
- Providing technology transfer so that useful technologies that cannot be developed fully in the parent institution can be brought to market by a suitable development or marketing and sales partner

The Sequella Global Tuberculosis Foundation is a member of the Stakeholders Association of the Global Alliance for TB Drug Development.

involved in TB and/or anti-infectives R&D, and academic institutions conducting TB research.

Private Industry Firms: Pharmaceutical companies, biotechnology companies, and contract research organisations have a critical role to play in the development of new drugs. Certain expertise and capacity is found exclusively in these private sector players, such as preclinical development, production process development, and manufacturing.

Academic Institutions: Academic institutions are a ready source of new projects. Their activity is strongest in basic research, drug discovery, and new target identification. However, due to the lack of preclinical funding from grant-making agencies, many meritorious projects are stalled in this stage. Funding academic projects through preclinical development in order move them forward to clinical trials is a possibility within a multiple-partners configuration.

Public Research Organisations: Government institutions are extremely valuable partners for the Global Alliance as well. Public health research institutes provide much of the impetus for R&D of anti-TB drugs, especially in the discovery stages. Partnerships with public research institutions also provide access to experience in coordinating large-scale clinical trials and expertise in established national and international clinical trials networks.

Researchers in TB-Endemic Countries: Working with researchers and investigators from high-burden countries provides several advantages: solid experience with TB epidemiology and therapeutics, proximity to the patients who are to benefit from the social mission, reduced costs, and facilitation of knowledge and technology transfer ultimately beneficial to the national health and TB programme.

Nongovernmental Organisations: Numerous NGOs are operating in the TB arena. Those affiliated with national TB control programmes are essential for late stages of development and market introduction of new drugs. For example, the World Health Organization and TDR are key players with significant expertise in TB and drug development and are committed to the success of the Global Alliance.

Regulatory Agencies: The various international regulatory agencies play a key role. Maintaining full regulatory transparency of the compounds and methods used to develop them, as well as respecting the input of the appropriate regulatory bodies, is essential and might enable regulatory "fast-tracking" and priority reviews while decreasing the chances of any unexpected hurdles in the approval process.

The Global Alliance for TB Drug Development will play a key role in catalysing and coordinating the participation of these players in the collaborative process of developing new drugs to fight TB.

Exhibit 46 provides an illustrative (not exhaustive) list of organisations that have pledged support to the Global Alliance's mission by signing on as stakeholders and/or providing staff to its Scientific Advisory Committee. These organisations feature some critical capacity in the field of public research and interesting initiatives in the private sector. In addition, significant expertise lies in other public and academic settings in a number of

countries in East and Southern Asia, Africa, Europe, and the Americas. The Global Alliance will capitalise on these initiatives and develop further partnerships with academic, private, and public sector researchers and investigators worldwide.

5.2 International Initiatives in the Fight against TB

Rising incidence, rising resistances and the confluence of the AIDS and HIV epidemic have brought about a renewed interest in the fight against tuberculosis. A number of developments are occurring on the public policy agenda and in philanthropic circles that ultimately might transform the context of TB control and R&D for anti-TB drugs.

5.2.1 On the Public Policy Agenda

5.2.1.1 Year 2000: Millennium Pledges

Amsterdam Ministerial Conference:
Strategy for Combating TB with the Support of International Development Partners

Develop and/or strengthen national development plans that incorporate health development and TB control as essential components

Build new international approaches towards ensuring universal access to, and efficient national systems of, procurement and distribution of TB drugs

Accelerate basic and operational research for the development and delivery of new tools, including diagnostics, drugs, and vaccines, and pay attention to the need for improved incentives for drug and vaccine development in a manner consistent with affordability and accessibility of such new products

Establish a global fund for TB to mobilise and invest new, additional resources to support the above activities

Amsterdam Ministerial Conference: At a March 2000 Ministerial Conference on Tuberculosis and Sustainable Development in Amsterdam, ministerial representatives from 20 high-burden countries comprising 80% of the global TB burden committed themselves to accelerate action against TB. They also called upon international development partners from the UN system, Bretton Woods institutions, bilateral agencies, NGOs, and foundations to increase their support to TB control efforts by contributing resources.

G8 Communiqué: Political commitment has been supported by the growing recognition of TB as both a global health threat and a socioeconomic problem. "Infectious and parasitic diseases, most notably HIV/AIDS, TB and malaria, as well as childhood diseases and common infections, threaten to reverse decades of development and to rob an entire generation of hope for a better future," stated the July 2000 Okinawa Communiqué from the Group of Eight nations (G8), underlining the relationship between health and prosperity and committing the G8 to "work in strengthened partnership with governments, the World Health Organization and other international organisations, industry (notably pharmaceutical companies), academic institutions, NGOs and other relevant actors in civil society to deliver three critical targets." One of these three targets is a 50% reduction in TB deaths by 2010.[91]

Focus in Low-Burden Countries: Even in low-endemic countries, the threat of TB is fuelled by regular outbreaks fed by the growing global exchange of people and goods. For example, in the United States, where national TB incidence has come under control after a dramatic resurgence in the late 1980s and early 1990s, TB not only is seen as a global problem but also is billed as a potential national threat. The National Intelligence Council mentions threats to international security caused by infectious diseases, the Council on Foreign Relations highlights global health as an emerging new dimension to

the foreign policy interests, and the 2000 Institute of Medicine recommends an "aggressive, multi-step strategy to short-circuit the cycle of TB resurgence in the United States" and "help put an end to a dangerous pattern in the nation's tuberculosis history—a pattern of complacency and neglect."

Global TB Drug Facility
http://www.stoptb.org/GDF/Index.htm

Among the new international initiatives to accelerate the control of TB is the Global TB Drug Facility.

The GDF is a mechanism to expand access to and the availability of current TB drugs to facilitate DOTS expansion. The GDF will enable governments and NGOs to implement effective TB control programs based on the DOTS strategy. Aiming to help treat 10 million patients by 2005, it is expected to inject $50 million ($US) per year for 5 years to TB drug purchase and procurement.

The key functions of the GDF will be to finance the purchase and provision of grants of quality TB drugs to qualifying countries and organizations that enter into agreements with the GDF. Functions will include procurement-related services, arrangements for buffer stocks, and services for quality control/inspection. The GDF will ensure monitoring, evaluation, and problem solving with Stop TB partners to achieve effective drug delivery, increased coverage, and treatment results. An independent review process of the programme results and progress will evaluate and determine continued supply of drugs.

The GDF will facilitate rapid DOTS expansion in countries. The rewards of DOTS expansion will be fewer TB patients, lower health care costs, and the social and economic benefits of improved public health.

5.2.1.2 Year 2001: Plans, Policies, and Pledges

Research and Investment Plans: In May 2001, the European Council published its resolution *Programme for Action: Accelerated Action on HIV/AIDS, Malaria and Tuberculosis in the Context of Poverty Reduction*.[92] The key elements of the programme relate to (1) improved impact, (2) affordability of pharmaceuticals, (3) R&D, and (4) participation in global partnerships. The resolution commits to strengthen and increase financial support for R&D. It agrees on the need to strengthen capacity in countries with developing economies and to provide incentives for the development of specific global public goods, such as new treatments and vaccines. The council further encourages strengthened cooperation with international R&D initiatives such as the Global Alliance for TB Drug Development.

"To combat diseases like AIDS, tuberculosis, and malaria, leading research organisations must develop comprehensive plans that bring international scientists together to launch a multi-pronged attack; improving prevention, diagnosis, and treatment of these diseases in regions where they exact the highest tolls," said Anthony S. Fauci, head of NIAID, as he introduced the NIAID *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*.[93] The global plan features an expanded focus on basic and applied research to prevent, diagnose, and treat these three diseases. Meanwhile, bills planning significant expansions of the overall NIH budget and funding of the TB projects in several government agencies were brought forth to the U.S. Congress in preparation of the FY2002 budget.

Public Policy Debates: Further attention was dedicated in public policy debates to the balancing of "push" and "pull" incentives as well as to the equilibrium between the rules on intellectual property and the challenge of providing access in countries with developing economies. The Performance and Innovation Unit of the UK Cabinet Office studied the latter and published a report titled *Tackling the Diseases of Poverty: A Package to Meet the Okinawa Millennium Targets for HIV/AIDS, Tuberculosis and Malaria*.[94] Among other recommendations, the British Cabinet report encourages investment of public funds in public-private partnerships, such as the Global Alliance for TB Drug Development, that offer an innovative model for balancing the intellectual property and the access/equity issues by negotiating the intellectual property rights up

front, in contractual arrangements with the private firms involved, as a condition of accessing public funds for research. Other recommendations call for incentives for R&D into these diseases to be strengthened and for additional policies to establish the purchasing power of the market. "This is recommended in the form of an advance commitment to purchase new, more effective products. Finally, as returns are still likely to be higher on Western health products where people have a higher willingness and ability to pay, we recognise there is a role for publicly funding additional research into these diseases. Where this is the case, public funds should be used as leverage for more attractive patent arrangements that ensure affordable prices to the poor."

Toward a Global Mechanism: A proposal for a global health fund to tackle infectious diseases had originally been instigated by Japan in 2000 when, shortly before the start of the Okinawa summit, Tokyo had announced a 5-year package totalling $3 billion to help countries with developing economies combat infectious diseases; in late April 2001, the UN Secretary General called for setting up the fund.

By July 2001, the G8 and U.N. Secretary General Kofi Annan announced the establishment of the Global Fund for AIDS and Health with total initial funding of about $1.2 billion, although a funding target of $7 billion and $10 billion a year had been discussed earlier at the U.N. special session on HIV/AIDS. The fund is aimed at tackling infectious diseases such as AIDS, malaria, and TB in developing countries. The fund is to be formally launched by the end of 2001, and its resources will be used to prevent the diseases, treat patients, and develop new medicines. At the time of this writing, governance and spending policies still are subject to extensive consultation and debate. Yet, this international initiative is undeniably a critical development affecting the prospects for dealing with the magnitude and the urgency of the AIDS, TB, and malaria epidemics.

With the rise of TB incidence figures being linked to the rise of HIV, and with TB killing one out of every three people with HIV/AIDS worldwide, these two epidemics are inextricably linked in their epidemiology and thus in the public policy measures developed in support of their control. An important test of this public policy resolve will be the response to the Global Plan to Stop Tuberculosis, scheduled to be unveiled in October 2001 by the Stop TB Partnership, a global movement to accelerate social and political action to stop the spread of TB.

A key feature of the fight against the TB epidemic is the strategic importance of therapeutics in both the prevention and the treatment of the disease. The international mobilisation that has led to these pledges, policies, and plans ought to yield tangible progress in expanding activities to treat and thus control TB. With political commitment to the sustainability of these efforts comes commitment to R&D for new drugs that will enable the expansion thanks to shorter treatment regimen for latent infection and active disease.

5.2.2 On the Philanthropic Agenda

The prominence of philanthropic actors in the field of global health was well illustrated by the leadership of such foundations as the Rockefeller Foundation and the Bill &

Melinda Gates Foundation, especially in the past 2 years. In the field of TB, these two foundations have provided the initial backing to a number of initiatives for TB control, diagnostics, and drug and vaccine development. Both foundations provided the key initial funding for the Global Alliance for TB Drug Development and—as stakeholders of the organisation—supported and guided its inception and development.

Beyond providing the impulse and seed funding for innovative ventures, these and other foundations also have risen to influence on the public policy agenda and the global initiatives:

- On the eve of the UN Special Session on AIDS, more than 130 leading international public health experts and top health officials from more than 15 countries convened to examine effective strategies to contain the HIV/AIDS pandemic. The Leadership Forum on HIV Prevention, which was sponsored by the Henry J. Kaiser Family Foundation, the Ford Foundation, and the Bill & Melinda Gates Foundation, attracted political leaders—including President Festus Mogae of the Republic of Botswana—as well as scientific researchers, senior officials of the world's most prominent health and development agencies, and officials from governments and universities in the developing countries hit hardest by AIDS.
- As the concept of the global fund for AIDS and health was introduced by UN Secretary-General Kofi Annan, a joint statement by the presidents of the Bill and Melinda Gates Foundation, United Nations Foundation (of Ted Turner), and the Rockefeller Foundation sought to highlight the need for building balanced, financed, and politically committed global programmes of prevention and treatment for AIDS. A Gates statement called "for world leaders to affirm their support for the UN call to action through new and unprecedented financial commitments." On the eve of the Genoa G8 meeting, the Bill & Melinda Gates Foundation announced a commitment of $100 million to the Global Fund for AIDS and Health.

Several of the more recently established foundations, many out of Silicon Valley and other high wealth areas, also have placed global health as a central or key priority. What many among these new foundations bring to the field is an interest in new models of philanthropy. The Rockefeller Foundation employs "a new type of worldwide philanthropy that is collaborative and scientific in nature."[95] A number of the more recently established foundations also are seeking to play this new "social venture capital" role in global health. This novel approach to philanthropy focuses on strengthening nonprofits as opposed to simply targeting needs, implies active involvement of the foundation in the initiation or the early stages of a new nonprofit venture, and values capacity-building and a more goal-oriented giving process.

When it comes to incubating TB R&D projects, global health–minded venture philanthropy is well suited to the task of strengthening a socially responsible initiative while applying entrepreneurial principles to the nonprofit world. These trends clearly are critical to the sustainability of a public-private initiative to develop new drugs for TB.

5.3 Private Sector Involvement in TB Care

Democratic Republic of Congo

In DR Congo, private providers became involved in TB control in 1997 at the initiative of the NTP. The NTP offered training to teams consisting of a doctor, a laboratory technician, and a nurse—each from many of the Kinshasa city hospitals. The trained teams were expected to follow national guidelines in managing TB patients presenting to their health facilities. The NTP also provided drugs at subsidised costs. Periodic monitoring was undertaken by NTP supervisors. The team training proved useful as these teams established recommended procedures, managed patients according to guidelines, and maintained records and registers for scrutiny by the NTP. Unfortunately, when the NTP ran out of resources to continue training and monitoring, some of the private establishments discontinued the good practice they had put in place.

Egypt

The dynamic NTP manager invited leading private chest physicians to join hands with the NTP; one of these physicians also happened to be a university chancellor. With the help of university teachers, continuing TB education for in-practice chest physicians was initiated, and modifications to TB education in medical curricula was planned. Private laboratories were approached and asked to report results of sputum examinations of patients referred to them by private practitioners. As a consequence, university hospitals never involved in the NTP previously started their own DOTS clinics. Private laboratories in the pilot area also started reporting their sputum-positive cases to the local programme. A healthy relationship currently prevails between the public and the private health sectors.

India

- A private nonprofit city hospital initiated a DOTS project for patients referred by PPs in the catchment area. Treatment supervision is undertaken in neighbourhood centres located in private nursing homes, clinics, and dispensaries. The NTP provides drugs and supplies. This project is highly successful and achieves over 90% case detection and cure rates.
- A voluntary organisation acts as an interface between PPs and NTP to facilitate collaboration.
- Local treatment supervisors of an NTP unit in an urban area assign diagnosed TB patients to their preferred PP, who agrees to perform treatment supervision, maintain records, and report default.
- A local association of doctors is trying out graded involvement of PPs, ranging from referral to NTP to implementing a total DOTS programme in an area.

An important development in the nature of the anti-TB drug market is the increasing role of the private sector. While the national TB programmes (NTPs) are still the backbone of TB treatment and control strategies, a large proportion of TB patients are treated in the private sector. Also, it is believed that private providers (PPs) manage a large number of the unreported majority of TB cases.

As discussed in *Chapter 2* of this report, approximately two-thirds ($275 million to $318 million) of current anti-TB drug sales are made to the private sector. According to 1998 data from IMS Health, the three largest suppliers of anti-TB drugs to the private market are Aventis (17% market share), Novartis (14% market share), and American Home Products (11% market share). Nearly 60% of the private market sales of anti-TB drugs are to countries with developing or transitional economies. Thus, perceptions that sales of anti-TB drugs in countries with developing economies are made only in the public/tender market are misplaced.

WHO recently undertook a global assessment in 23 countries across six regions to understand the extent and nature of involvement of PPs in TB care. As provided in the study report by Uplekar and colleagues,[96] this section summarises the major findings of the WHO assessment and demonstrates that the role of the private sector is expected to expand further in the future. **The sidebars throughout the section provide salient features of several examples of private sector involvement**—often in collaboration with NTPs—in caring for TB patients: DR Congo, Egypt, India, Kenya, the Netherlands, and the Philippines. These examples clearly demonstrate that the private sector in countries with varying economies is an active, and possibly growing, market for anti-TB drugs.

In general, surveys on health care utilisation indicate that the private sector is an important source of care, even for the poor and even where public services are widely available.[97,98] Private providers are extensively used for diseases of public health importance such as TB, malaria, sexually transmitted infections, diarrhoeal disease, and acute respiratory infections.[99–101] In India, for instance, 80% of the households prefer the private

sector for minor illnesses and 75% for major ones.[102] In nine of the poorest countries, an average 47% of visits to health providers by the poorest 20% of the people were to the private sector as compared with 59% of visits to private providers among the richest 20%.[98] Studies in Ho Chi Minh City in Viet Nam found that the socioeconomic profile of individuals with TB symptoms and TB patients who approach PPs is similar to that of patients who approach the NTP.[99]

Despite increased worldwide attention and implementation of the WHO-recommended DOTS strategy by 119 countries, only 44% of the estimated TB cases are notified globally.[1] It is believed that PPs manage a large proportion of the unreported majority. Exhibit 47 shows that private expenditure on health accounts for a major portion of total expenditure in almost all of the 23 countries suffering a high TB burden. Furthermore, virtually all of this private expenditure is out-of-pocket, suggesting considerable utilisation of PPs and private pharmacies on a fee-for-service basis.

Studies investigating TB patients' health-seeking behaviour in many high-burden countries, such as India, Pakistan, Philippines, Viet Nam, and Uganda, indicate that a large proportion of patients with symptoms of TB first approach a private provider. A household survey in India found that about 60% individuals with a long-standing cough first went to a PP.[103] A subsequent study showed that 88% of the rural and 85% of the urban TB patients had started off with a PP.[104] A study in Karachi, Pakistan, found that 80% of the patients being treated by the NTP had first sought care from PPs.[105] In Manila, Philippines, a survey of TB patients in government health centres found that 53% had initially consulted a PP.[106] A study in Viet Nam showed that 84% of TB patients go to PPs and general hospitals before approaching the NTP.[99] A study in Uganda showed that 50% of the patients in the public sector had already started anti-TB medication prior to their first clinic visit.[107]

A substantial proportion of TB cases are treated by PPs as well. About 50% of TB cases in India are treated partly or fully in the private sector.[108] These alone account for one-sixth of world's burden of

Exhibit 47: Private Health Expenditure in High-Burden Countries[a]

Country	Private Health Expenditure (% of total)	Out-of-Pocket Expenditure (% of total)
Afghanistan	59.4%	59.4%
Bangladesh	54.0	54.0
Brazil	51.3	45.6
Cambodia	90.6	90.6
China	75.1	75.1
DR Congo	63.4	63.4
Ethiopia	63.8	63.8
India	87.0	84.6
Indonesia	63.2	47.4
Kenya	35.9	35.9
Myanmar	87.4	87.4
Nigeria	71.8	71.8
Pakistan	77.1	77.1
Peru	60.3	50.2
Philippines	51.5	49.5
Russia	23.2	23.2
South Africa	53.5	46.3
Tanzania	39.3	38.3
Thailand	67.0	65.4
Uganda	64.9	48.2
Viet Nam	80.0	80.0
Zimbabwe	56.6	38.2

[a] Data not available for Mozambique
Source: WHO[110]

Kenya

In Nairobi, a group of private hospitals and chest physicians, the NTP, and the national TB association have worked out a mutually acceptable scheme. The TB association manages the project, which provides subsidy on anti-TB drugs to private providers who, in turn, manage patients according to guidelines and maintain records. The goal is to make a self-sufficient public-private DOTS project. Documentation is in process.

The Netherlands

TB care in the Netherlands is decentralised and integrated within municipal health services: 45 of the 60 municipalities have TB clinics. Public-private partnership for TB control is deeply rooted in this country. Private physicians and laboratories report TB cases to the TB clinics. Once diagnosed, TB cases almost always are dually managed, with the physician handling clinical aspects and drug treatment and public health nurses handling motivation, education, defaulter retrieval, and management of social problems faced by patients. Spearheaded by the Royal Netherlands Chemical Society (KNCV), the effort is successful due to several key elements, including decentralisation, transparency, mutual respect, working through consensus, PP involvement at all levels (including policy making), continuing dialogue, and quality assurance.

The Philippines

A recent national prevalence survey in the Philippines showed that, of those TB-symptomatic individuals and patients who seek help at health care facilities, more than half are under care of private providers. Directly observed therapy for TB patients was first started in the country by a private infectious disease specialist in a private university hospital even before the NTP adopted DOTS as its official strategy. Inspired by the private initiative, more private DOTS projects have emerged, and all are welcomed and supported by the NTP through provision of drugs and supplies. An upper-class hospital in a rich area started a DOTS programme for both the rich inpatients and poor patients living in the neighbourhood. The project is running well and is achieving high cure rates, with plans to embark on a DOTS-plus programme for managing MDR-TB patients.

TB. In South Korea, 47% of cases are treated by PPs.[109] A similar situation prevails in many high-burden countries.

The report of the global assessment of private provider involvement in TB control[96] was presented and discussed in a consultation of experts held in Geneva in August 2000. The group endorsed the report and recommended further public-private collaboration within the DOTS framework, implementation and evaluation of intervention-research projects and scaling up of those found to be successful, availability of public sector support for provision of standardised TB care by private providers, and attention to the "public health" aspects of the control of TB and other communicable diseases in the medical curricula.[110] These recommendations suggest that the involvement of private providers in the treatment of TB will increase in the future.

5.4 Summary

Public-private partnerships are providing opportunities to share and balance the risks and investments associated with pharmaceutical research. To improve the treatment of TB, the Global Alliance for TB Drug Development is bringing together public and private sector resources and expertise to ensure the provision of new medicines with equitable access. Its R&D partners include pharmaceutical and biotechnology private industry firms, public research organisations involved in TB and/or anti-infectives R&D, and academic institutions conducting TB research.

A number of developments are occurring in public policy and philanthropy that might transform the context of TB control and R&D for anti-TB drugs. Pledges have been made by donors and high-burden countries alike to accelerate action against TB—one of three major infectious diseases threatening global health. Mechanisms are being designed to expand TB control programmes, procurement of anti-TB drugs, and TB research. Meanwhile, several foundations have placed global health as a central or key priority and are actively supporting innovative strategies to fight the disease.

The private sector is playing an increasing role in TB treatment. Studies investigating TB patients' health-seeking behaviour in many high-burden countries, such as India, Pakistan, Philippines, Viet Nam, and Uganda, indicate that a large proportion of patients with symptoms of TB first approach a private provider. Thus, perceptions that anti-TB drugs are sold only in the public/tender market in these countries are misplaced.

These essential trends and opportunities—combined with the analyses presented throughout this report—ought to reinvigorate interest in developing lead compounds into new, faster acting, more effective, and affordable TB treatment by the end of this decade. The report's findings point to a sizable TB market, relatively controlled costs, and attractive expectations in terms of return on investment and social benefits. A new drug that shortens the duration of treatment, improves the treatment of multidrug-resistant TB,

and provides a more effective treatment of latent TB infection will go a long way toward winning the battle against a disease that not only is a tremendous burden to the poorest countries but also is a threat to all nations.

References and Other Sources

References

[1] World Health Organization. 2001. *Global Tuberculosis Control: WHO Report 2001*. Geneva, Switzerland: WHO (WHO/CDS/TB2001.287).

[2] Mathieu MP, Foster TR (Eds.). 1999. *Parexel's Pharmaceutical R&D Statistical Sourcebook*. Waltham, Massachusetts: Parexel International Corporation.

[3] Murray CJL, Lopez, AD. 1997. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 349:1498–1504.

[4] Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. 1999. Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 282(7):677–686.

[5] O'Brien RJ, Nunn PP. 2001. The need for new drugs against tuberculosis: Obstacles, opportunities, and next steps. *Am J Respir Crit Care Med* 162:1055–1058.

[6] Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, Hoffner S, Rieder HL, Binkin N, Dye C, Williams R, Raviglione MC. 2001. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance. Surveillance. *N Engl J Med* 344(17):1294–1303.

[7] Joint United Nations Programme on HIV/AIDS. 2001. Press release: UNAIDS executive director calls for renewed action against tuberculosis and AIDS. Geneva, March 20.

[8] Styblo K. 1976. Impact of BCG vaccination programmes in children and young adults on the tuberculosis problem. *Tubercle* 57:17–43.

[9] Special Programme for Research and Training in Tropical Diseases. 2001. Tuberculosis Diagnostics Research Initiative (TBDI). http://www.who.int/tdr/diseases/tb/tbdi.htm (accessed Aug. 9, 2001).

[10] Ginsberg, AM. 2000. A proposed national strategy for tuberculosis vaccine development. *Clin Infect Dis* 30(Suppl 3):S233–242.

[11] Kochi A. 1991. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercule* 72(1):1–6.

[12] World Health Organization. 1994. *WHO Global Tuberculosis Programme. Framework for Effective Tuberculosis Control*. Geneva, Switzerland: WHO (WHOB/94.179).

[13] World Bank. 1993. World development report 1993: Investing in health. In: *World Bank 1993*. New York: Oxford University Press.

[14] Murray, CJL, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. 1991. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 338:1305–1308.

[15] China Tuberculosis Control Collaboration. 1996. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. *Lancet* 347:358–362.

[16] American Thoracic Society Medical Section of the American Lung Association. 1994. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 149.

[17] Joint Tuberculosis Committee of the British Thoracic Society. 1998. Chemotherapy and management of tuberculosis in the United Kingdom: Recommendations 1998. *Thorax* 53:536–548.

[18] Centers for Disease Control and Prevention, Division of Tuberculosis Elimination. 2000. Treatment of latent TB infection. In: *Core Curriculum on Tuberculosis*. 4th Edition.

[19] Godfrey-Faussett P. 1998. Policy statement on preventive therapy against tuberculosis in people living with HIV. Report of a Meeting held in Geneva 18–20 February 1998. World Health Organization Global Tuberculosis Programme and UNAIDS, 255.

[20] Datta M, Radhamani MP, Selvaraj R, Paramasivan CN, Gopalan BN, Sudeendra CR, Phabhakar R. 1993. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. *Tubercle and Lung Disease* 74:180–186.

[21] Centers for Disease Control and Prevention. 1999. Primary multidrug-resistant tuberculosis: Ivanovo Oblast, Russia, 1999. *Morb Mort Wkly Rpt* 48:661–663.

[22] Farmer P, Kim JY. 1998. Community based approaches to the control of multidrug resistant tuberculosis: Introducing "DOTS-plus." *BMJ* 317(7159):671–674.

[23] White VLC, Moore-Gillon J. 2000. Resource implications of patients and multidrug resistant tuberculosis. *Thorax* 55:962–963.

[24] Global Alliance for TB Drug Development. 2001. Scientific blueprint for TB drug development. *Tuberculosis* 81(Suppl.1):1–52.

[25] Fox W, Mitchison DA. 1975. Short-course chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 111:325–353.

[26] Christopher Dye, WHO, unpublished data, 2001.

[27] Bock NN, Metzger BS, Tapia JR, Blumberg HM. 1999. A tuberculin screening and isoniazid preventive therapy program in an inner-city population. *Am J Respir Crit Care Med* 159:1, 295–300.

[28] Corbett EL, Watt C, Walker N, Maher D, Lazzari S, Raviglione MC, Williams BG, Dye C. In prep. The global burden of tuberculosis associated with HIV.

[29] WHO, UNICEF, UNAIDS, World Bank, UNESCO, UNFPA. 2001. Health: A Key to Prosperity: Success Stories in Developing Countries. http://www.who.int/inf-new/tuber.htm (accessed Aug. 15, 2001).

[30] Centers for Disease Control and Prevention. 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection, *Morb Mort Wkly Rpt* 49(No. RR-6):1–51.

[31] Floyd K, Wilkinson D, Gilks CF. 1997. Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *BMJ* 315:1407–1411.

[32] Wilkinson D, Floyd K, Gilks CF. 1997. Costs and cost-effectiveness of alternative tuberculosis management strategies in South Africa: Implications for policy. *S Afr Med J* 87(4):451–455.

[33] Hanson K, Woelk G, Jackson H, et al. 1997. The cost of home based care for HIV/AIDS patients in Zimbabwe. University of Zimbabwe Medical School working paper, pp. 1-23.

[34] Brown RE, Miller B, Taylor WR, et al. 1995. Health-care expenditures for Tuberculosis in the United States. *Arch Intern Med* 155:1595–1600.

[35] Taylor Z, Marks SM, Rios Burrows NM, Weis SE, Stricof RL, Miller B. 2000. Causes and costs of hospitalization of tuberculosis patients in the United States. *Int J Tuberc Lung Dis* 4(10):931–939.

[36] Palmer CS, Miller B, Halpern MT, Geiter LJ. 1998. A model of the cost-effectiveness of directly observed therapy for treatment of tuberculosis. *J Public Health Management Practice* 4(3):1–13.

[37] Richard O'Brien, CDC, personal communication, August 2001.

[38] World Health Organization. 2001. Annex D: WHO survey on TB drug supply experiences in WHO member states: Interim summary results. In *Prospectus: Global TB Drug Facility*. Geneva, Switzerland: WHO (WHO/CDS/STB/2001.10a).

[39] Weil D, Mueen L. In prep. *Survey of External Commitments for TB control in Low and Middle-Income Countries, 1998-2001*. World Bank on behalf of the Stop TB Partnership.

[40] World Health Organization. 1998. *Tuberculosis*. Geneva, Switzerland: WHO (Fact Sheet No. 104).

[41] DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. 1995. Research and development costs for new drugs by therapeutic category: A study of the US pharmaceutical industry. *Pharmacoeconomics* 7(2):152–169.

[42] Pharmaceutical Research and Manufacturers of America. 2001. *Pharmaceutical Industry Profile 2001*. Washington, D.C.: PhRMA.

[43] Cole ST, Brosch R, Parkhill J, et al. 1998. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* 393:537–544.

[44] Wilson M, de Risi J, Kristensen HH, et al. 1999. Exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization. *Proc Natl Acad Sci* 96:12833–12838.

[45] Jungblut PR, Schaible UE, Mollenkopf HJ, et al. 1999. Comparative proteome analysis of *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG strains: Towards functional genomics of microbial pathogens. *Mol Microbiol* 33:1103–1117.

[46] Pelicic V, Jackson M, Reyrat JM, et al. 1997. Efficient allelic exchange and transposon mutagenesis in *Mycobacterium tuberculosis*. *Proc Natl Acad Sci* 94:10955–10960.

[47] Bardarov S, Kriakov J, Carriere C, et al. 1997. Conditionally replicating mycobacteriophages: A

system for transposon delivery to *Mycobacterium tuberculosis*. *Proc Natl Acad Sci* 94:10961–10966.

[48] Camacho LR, Ensergueix D, Perez E, et al. 1999. Identification of a virulence gene cluster of *Mycobacterium tuberculosis* by signature-tagged transposon mutagenesis. *Mol Microbiol* 34:257–267.

[49] Cox JS, Chen B, McNeil M, Jacobs WR. 1999. Complex lipid determines tissue-specific replication of *Mycobacterium tuberculosis* in mice. *Nature* 402:79–83.

[50] McKinney JD, Höner zu Bentrup K, Muñoz-Elias EJ, et al. 2000. Persistence of *Mycobacterium tuberculosis* in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. *Nature* 406:735–738.

[51] Goldberger MJ. 1997. Treatment of tuberculosis: Current status and future promise. *Sem Resp Crit Care Med* 18:439–448.

[52] Hopewell P, Cynamon M, Starke J, Iseman M, O'Brien R. 1992. Evaluation of new anti-infective drugs for the treatment and prevention of tuberculosis. *Clinical Infectious Diseases* 15(Suppl 1):S282–S295.

[53] http://www.fda.gov/cder/guidance/index.htm

[54] http://www.emea.eu.int/ index/indexh1.htm

[55] Ashtekar DR, Costa-Perira R, Nagrajan K, Vishvanathan N, Bhatt AD, Rittel W. 1993. *In vitro* and *in vivo* activities of the nitroimidazole CGI 17341 against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 37:183–186.

[56] Grosset J. 1978. The sterilizing value of rifampicin and pyrazinamide in experimental short course chemotherapy. *Tubercle* 59:287–297.

[57] Mackaness GB, Smith N. 1953. The bactericidal action of isoniazid, streptomycin and terramycin on extracellular and intracellular tubercle bacilli. *Amer Rev Tuberculosis* 67:322.

[58] Mitchison DA. 1970. Bacteriological mechanisms in recent controlled chemotherapy studies. *Bulletin of the International Union Against Tuberculosis* 43:322.

[59] Sbarbaro JA, Iseman MD, Crowle AJ. 1992. The combined effect of rifampin and pyrazinamide within the human macrophage. *Am Rev Respir Dis* 146:1448–1451.

[60] Orme IM, Collins FM. 1994. Mouse model of tuberculosis. In: Bloom BR (Ed.) *Tuberculosis: Pathogenesis, Protection, and Control*. Washington, DC: American Society for Microbiology, pp.113–134.

[61] McMurray DN. 1994. Guinea pig model of tuberculosis. Bloom BR (Ed.) *Tuberculosis: Pathogenesis, Protection, and Control*. Washington, DC: American Society for Microbiology, pp.135–147.

[62] Dannenberg AM. 1994. Rabbit model of tuberculosis. Bloom BR (Ed.) *Tuberculosis: Pathogenesis, Protection, and Control*. Washington, DC: American Society for Microbiology, pp.149–156.

[63] Kanyok T. 2000. Proposal for a single operating plan for the development and registration of a new compound for the treatment of TB. Presented at the WHO/IFPMA Meeting on Regulatory Harmonisation for Clinical Development of New Anti-TB Agents and Registration of WHO EDL Recommended Four Drug Fixed Dose Anti-TB Combinations. Geneva, Switzerland.

[64] Mole L, Ockrim K, Holodniy M. 1999. Decreased medical expenditures for care of HIV-seropositive patients: The impact of highly active antiretroviral therapy at a U.S. Veterans Affairs medical center. *Pharmacoeconomics*, 16(3):307–315.

[65] Andrew Vernon, CDC, personal communication, May and September 2000.

[66] Carol Hamilton, Duke University Medical Center, personal communication, March 2000.

[67] Center for Drug Evaluation and Research, Food and Drug Administration. 1998. Approval package for Priftin 150 mg tablets. http://www.fda.gov/cder/approval/index.htm (accessed Sept. 15, 2001)

[68] Tom Kanyok, WHO, personal communication, May 2000.

[69] John Johnson, Case Western Reserve University, personal communication, August 2000.

[70] Mark Goldberger, FDA, personal communication, March 2000.

[71] Bernard Fourie, South African Medical Research Council, personal communication, June 2000.

[72] Brealy RA, Myers SC. 2000. *Principles of Corporate Finance*. 6th Ed. Burr Ridge, Illinois: Irwin/McGraw Hill.

[73] Grabowski HG, Vernon JM. 1990. A new look at the returns and risks to pharmaceutical R&D. *Management Science* 36(7):804–821.

[74] Grabowski HG, Vernon JM. 1994. Returns to R&D on new drug introductions in the 1980s. *Journal of Health Economics* 13:384-406.

[75] U.S. Office of Technology Assessment. 1993. *Pharmaceutical R&D: Costs, Risks and Rewards*. Washington, D.C.: U.S. Government Printing Office.

[76] Myers SC, Shyam-Sunder L. 1995. Measuring pharmaceutical industry risk and the cost of capital. In: Helms RB (Ed.). *Competitive Strategies in the Pharmaceutical Industry*. Washington, DC: American Enterprise Institute for Public Policy.

[77] Myers SC, Howe CD. 1997. *A Life Cycle Financial Model of Pharmaceutical R&D.* Cambridge, Massachusetts: MIT Program on the Pharmaceutical Industry.

[78] Conroy R, Harris R, Massaro T. 1992. *Assessment of Risk and Capital Costs in the Pharmaceutical Industry*. Charlottesville, VA: University of Virginia.

[79] Reinhart U. 2001. The market for prescription drugs: Waking up the demand side. Presented to the Council on the Economic Impact of Health System Change, Washington, DC, March 28.

[80] Henry Grabowski, Duke University, personal communication, April 2001.

[81] DiMasi JA. 2001. Risks in new drug development: approval success rates for investigational drugs. *Clin Pharmacol Ther* 69(5):297–307.

[82] Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P. 1999. Socio-economic impact of tuberculosis on patients and family in India. *Int J Tuberc Lung Dis* 3(10):869–877.

[83] Needham DM, Godfrey-Faussett P, Foster SD. 1998. Barriers to tuberculosis control in urban Zambia: The economic impact and burden on patients prior to diagnosis. *Int J Tuberc Lung Dis* 2(10):811–817.

[84] Ahlburg DA. 2000. *The Economic Impacts of Tuberculosis*. Geneva, Switzerland: World Health Organization.

[85] Katherine Floyd, WHO, unpublished data, 2001.

[86] Saunderson P. 1995. An economic evaluation of alternative programme designs for tuberculosis control in rural Uganda. *Social Science and Medicine* 40(9):1203–1212.

[87] Carrin G, Gray E, Almeida J. 1999. Coping with ill health in a rickshaw puller's household in Chittagong, Bangladesh. *Southeast Asian J Trop Med Public Health* 30(1):136-148.

[88] Nair DN, George A, Chacko KT. 1997. Tuberculosis in Bombay: New insights from poor urban patients. *Health Policy and Planning* 12(1):77–85.

[89] Liefooghe R, Michiels RN, Habib S, Moran MB, De Muynck A. 1995. Perception and social consequences of tuberculosis: A focus group study of tuberculosis patients in Sialkot, Pakistan. *Soc Sci Med* 41(12):1685–1692.

[90] Widdus R. 2001. *Public-Private 'Partnership' Is Necessary to Improve the Health of the Poor*. Geneva, Switzerland: Initiative on Public-Private Partnerships for Health International Center Cointrin (ICC), p. 9.

[91] G8 Communiqué, Okinawa, July 23, 2000.

[92] European Council Resolution. 2001. *Programme for Action: Accelerated Action on HIV/AIDS, Malaria and Tuberculosis in the Context of Poverty Reduction*. Brussels: European Council.

[93] National Institute of Allergy and Infectious Diseases. 2001. *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. Washington D.C.: NIAID.

[94] UK Cabinet Office, Performance and Innovation Unit. 2001. *Tackling the Diseases of Poverty: A Package to Meet the Okinawa Millennium Targets for HIV/AIDS, Tuberculosis and Malaria*. London: UK Cabinet Office.

[95] Gordon Conway, Rockefeller Foundation, personal communication, 2001.

[96] Uplekar M, Pathania V, Raviglione M. 2001. *Involving Private Practitioners in Tuberculosis Control: Issues, Interventions and Emerging Policy Framework*. Geneva, Switzerland: World Health Organization (WHO/CDS/TB/2001.285).

[97] Bennett S, McPake B, Mills A (Eds.). 1997. *Private Health Providers in Developing Countries*. London: Zed Books.

[98] Gwatkin DR. 1999. Poverty and inequalities in health within developing countries. Reforming health sectors. In: *Ninth Annual Public Health Forum*. London: London School of Hygiene and Tropical Medicine.

[99] Lönroth K, Thoung LM, Linh PD, Diwan VK. 2001. Utilization of private and public health care providers among people with symptoms of

tuberculosis in Ho Chi Minh City, Vietnam. *Health Policy Plan* 16(1):47-54.

[100] Brugha R, Chandramohan D, Zwi A. 1999. Viewpoint: management of malaria: Working with the private sector. *Trop Med & Intl Health* 4(5):402–406.

[101] Brugha R, Zwi A. 1999. Sexually transmitted disease control in developing countries: The challenge of involving the private sector. *Sexually Transmitted Infections* 75(5):283–285.

[102] National Council of Applied Economic Research. 1995. *Household Survey of Health Care Utilisation and Expenditure*. New Delhi: NCAER (Working Paper No. 53).

[103] Uplekar M, Rangan S. 1996. *Tackling TB: The Search for Solutions*. Mumbai, India: The Foundation for Research in Community Health.

[104] Uplekar M, Juvekar S, Morankar S, Rangan S, Nunn P. 1998. Tuberculosis patients and practitioners in private clinics in India. *Int J Tuberc Lung Dis* 2(4):324–329.

[105] Marsh D, Hashim R, Hassany F, et al. 1996. Front-line management of pulmonary tuberculosis: An analysis of tuberculosis and treatment practices in urban Sindh, Pakistan. *Tuber Lung Dis* 77(1):86–92.

[106] Romulo RLC. 1997. TB control: Collaboration in the Philippines. In: *Proceedings of the Second Mid-Year Conference of IUATLD, North American Region*. Chicago: International Union Against Tuberculosis and Lung Disease.

[107] Nshuti L. 1998. The role of private providers in the care of tuberculosis patients in Uganda. MPH dissertation. Case Western Reserve University, Cleveland, Ohio and Makerere University, Kampala, Uganda.

[108] Pathania V, Almeida J, Kochi A. 1997. *TB Patients and For-Profit Health Care Providers in India*. Geneva: World Health Organization (WHO/TB/97.223).

[109] Hong Y, Kim SJ, Lee EG, Lew WJ, Bai JY. 1999. Treatment of bacillary pulmonary tuberculosis at the chest clinics in the private sector in Korea, 1993. *Int J Tuberc Lung Dis* 3(8):695-702.

[110] World Health Organization. 2000. *Informal Consultation on Private Practitioners' Involvement in Control of Communicable Diseases with a Focus on Tuberculosis*. Geneva, Switzerland: World Health Organization (WHO/CDS/TB/2000.282).

[111] Murray CJL, Lopez AD. 1996. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 274:740–743.

[112] Reith K, Keung A, Toren PC, Cheng L, Eller MG, Weir SJ. 1998. Disposition and metabolism of 14C-Rifapentine in healthy volunteers. *Drug Metabolism and Disposition* 26(8):732–738.

[113] Vital Durand D, Hampden C, Boobis AR, Park BK, Davies DS. 1986. Induction of mixed function oxidase activity in man by rifapentine (MDL 473), a long-acting rifamycin derivative. *British Journal of Clinical Pharmacy* 21:1–7.

[114] Birmingham AT, Coleman AJ, Orme ML'E, Pearson NJ, Short AH, Southgate PJ. 1978. Antibacterial activity in serum and urine following oral administration in man of DL473 (a cyclopentyl derivative of rifampicin). In: *Proceedings of the B.P.S.*, 455P– 456P.

[115] Keung A, Eller MG, McKenzie KA, Weir SJ. 1999. Single and multiple dose pharmacokinetics of rifapentine in man: Part II. *International Journal of Tuberculosis and Lung Disease* 3(5):437–444.

[116] Keung A, Reith K, Eller MG, McKenzie KA, Cheng L, Weir SJ. 1999. Enzyme induction observed in healthy volunteers after repeated administration of rifapentine and its lack of effect on steady-state rifapentine pharmacokinetics: Part I. *International Journal of Tuberculosis and Lung Disease* 3(5):426–436.

[117] Keung A, Eller MG, Weir SJ. 1998b. Single-dose pharmacokinetics of rifapentine in women. *Journal of Pharmacokinetics and Biopharmaceutics* 26(1):75–85.

[118] Marshall JD, Abdel-Rahman S, Johnson K, Kauffman RE, Kearns GL. 1999. Rifapentine pharmacokinetics in adolescents. *Pediatric Infectious Disease Journal* 18(10):882–888.

[119] Keung A, Eller MG, Weir SJ. 1998. Single-dose pharmacokinetics of rifapentine in elderly men. *Pharmaceutical Research* 15(8):1286–1291.

[120] Keung A, Eller MG, Weir SJ. 1999. Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. *Journal of Clinical Pharmacology* 38:517–524.

[121] Keung A, Owens RC, Eller MG, Weir SJ, Nicolau DP, Nightengale CH. 1999. Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus: A Phase I study.

Antimicrobial Agents and Chemotherapy 4(5):1230–1233.

[122] Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 1999. http://www.cdc.gov/nchstp/tb/surv/surv99/surv99.htm (accessed Feb. 23, 2001).

[123] Vernon A, Burman W, Bernator D, Khan A, Bozeman L. 1999. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 353:1843–1847.

[124] American Medical Association. 1999. *Current Procedural Terminology (CPT)*. Chicago, Illinois: American Medical Association.

[125] *St. Anthony's Complete Resources Based Relative Value Scale (RBRVS)*. 2000. Reston, VA: St. Anthony Publishing, Inc.

Other Sources

Bernstein D. 1995. GMP in R&D: Good science, good common sense. *BioPharm* 1995(January-February):20–25.

Bernstein DF, Hamrell MR. 2000. Integrating drug supply issues with strategic preclinical and clinical development. *Drug Information Journal* 34:909–917.

Bernstein DF. 1994. Investigational clinical trial material supply operations in new product development. *Pharmaceutical Technology* 1994(February):40–52.

Boston Consulting Group. 2000. Global Alliance for TB Drug Development Business Plan. Presented at the Global Alliance for TB Drug Development meeting, Geneva, Switzerland. September

Craig CR, Stizel RE (Eds.). 1990. *Modern Pharmacology*. Boston: Little, Brown and Company.

Division of Anti-Infective Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration. 1996. Points to Consider. Clinical Development and Labeling of Anti-Infective Drug Products. http://www.fda.gov/cder/guidance/infections.htm (accessed Sept. 17, 2001).

Dye C, Garnett GP, Sleeman K, Williams BG. 1998. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *Lancet* 352:1886–1891.

Facts and Comparisons. 1999. *Drug Facts and Comparisons*. St. Louis: Facts and Comparisons.

Herfindal ET, Gourley DR, and Hart LL. 1992. *Clinical Pharmacy and Therapeutics*. 5th Ed. Baltimore, Maryland: Williams & Wilkins.

Iseman MD. 1993. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 329:784–791.

Knoop SJ, Worden DE. 1988. The pharmaceutical drug development process. *Drug Information Journal* 22:259–268.

Murray CJL, Styblo K, Rouillon A. 1990. Original articles: Tuberculosis. *Bulletin of the International Union Against Tuberculosis and Lung Disease* 65(1).

Netto EM, Dye C, Raviglione MC. 1999. Progress in global tuberculosis control 1995-1196, with emphasis on 22 high-incidence countries. *Int J Tuberc Lung Dis* 3(4):310–320.

Nolan CM. 1999. Community-wide implementation of targeted testing for and treatment of latent tuberculosis infection. *Clin Infect Dis* 29:4, 880–887.

Roehr B. 1998. FDA Approves Rifapentine for the Treatment of Pulmonary Tuberculosis…The First New Drug in 25 Years to Combat the World's No. 1 Killer. http://www.iapac.org/coinfections/rifapentine_808.html (accessed Sept. 17, 2001).

Scanga CA, Mohan VP, Joseph H, Yu K, Chan J, Flynn JL. 1999. Reactivation of latent tuberculosis: Variations on the Cornell murine model. *Infect Immun* 67:9, 4531–4538.

Shawar RM, Humble DJ, Van Dalfsen JM, et al. 1997. Rapid screening of natural products for antimycobacterial activity by using luciferase-expressing strains of *Mycobacterium bovis* BCG and *Mycobacterium intracellulare*. *Antimicrob Agents Chemother* 41:570–574.

Singla N, Sharma PP, Singla R, Jain RC. 1998. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in

private clinics in India. *Int J Tuberc Lung Dis* 2:384–389.

Snewin VA, Gares MP, Gaora PO, et al. 1999. Assessment of immunity to mycobacterial infection with luciferase reporter constructs. *Infect Immun* 67:4586–4593.

Tuberculosis elimination revisited: Obstacles, opportunities, and a renewed commitment: Advisory Council for the Elimination of Tuberculosis (ACET). 1999. *Morb Mort Wkly Rpt* 48(RR09):1–13.

U.S. Food and Drug Administration, Guidance for Industry. 1997. *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Droducts—DRAFT*. Washington, D.C.: U.S. Department of Health and Human Services.

Uplekar MW, Shepard DS. 1991. Treatment of tuberculosis by private general practitioners in India. *Tubercule* 72(4):284–290.

Appendices

Appendix A: Methodology for Diagnosis and Treatment Costs

This appendix provides additional details about the diagnosis and treatment cost estimates presented in Chapter 1.

Multiplying country-specific health care use estimates by the country-specific unit cost estimates presented in Exhibit 8 and summing over the various health care services yields the estimated cost per treated smear-positive, smear-negative, and retreatment case in each country (Exhibit 9). Unit cost data and detailed health service use data were not available for the U.S. and U.K., but estimates of the total costs were available.

In general, data were available for each country regarding the standard treatment patterns for smear-positive, smear-negative, and retreatment cases who are treated using the WHO DOTS strategy. (Patients who were treated without DOTS probably would receive similar drugs and tests but a greater variety of regimens and would tend to visit clinics monthly to collect medicines instead of having the more frequent DOT visits.[111]) In Russia, however, DOTS currently is implemented in only a few pilot sites. For this country, recent and ongoing costing studies, combined with national documents concerning the existing TB control infrastructure, were used to estimate utilisation and costs associated with TB control as currently implemented in most of the country. Data on the treatment of MDR-TB were not collected for any country.

The diagnosis and treatment of TB in the United States involves an intensive use of medical resources. During the diagnostic evaluation, multiple specimens are collected for smear microscopy and culture, drug susceptibility testing of positive cultures is routinely performed, and diagnostic evaluation typically includes additional laboratory and radiographic tests. All patients are treated under the supervision of physicians, and approximately 50% of TB patients are hospitalised at some point during treatment.[35] DOTS is provided to 60% of patients by public health nurses or outreach workers, who often travel to the patient's home or worksite to provide treatment.[111] Drug costs in the United States are computed based on Redbook average wholesale prices minus 15% and U.S. guidelines for TB treatment.[16] For every person with a confirmed diagnosis of active TB, 3.22 persons with suspected TB are evaluated, begun on treatment, and ultimately determined not to have active disease;[34] the estimated total costs of $358 and drug costs of $169 for each of these suspected cases are not included in the U.S. cost estimates.

In the United Kingdom, TB is diagnosed using sputum smears as well as bronchoscopy, bronchial washings, and X-rays. Sputum smears and X-rays also are taken near the end of treatment. The patient is seen monthly, and tablet checks and urine tests for rifampicin are carried out at these visits.[17] U.K. costs were estimated using data on susceptible patients from the White and Moore-Gillon study.[23]

Appendix B: Methodology for Clinical Trials Development

The following methods were used to develop and cost the clinical trials:

- Multiple searches of medical literature databases, including Medline, HealthSTAR, International Pharmaceutical Abstracts, and Health Economic Evaluations Database (HEED)
- Meetings with experts on the design and implementation of clinical trials
- Internet searches on drug development, tuberculosis agents, and clinical trials including the homepages of the FDA, WHO, and the Center for Drug Evaluation and Research

To develop the clinical trial protocol outlines, medical literature databases were searched for studies regarding TB burden of illness, rifapentine drug development/clinical trials, and anti-infective clinical trial costs. Additional information was obtained from the approval package for rifapentine (Priftin®).[67]

The first step in clinical trial planning involved a determination of the studies necessary for national drug regulatory authority approval. Study objectives and methodology were reviewed to estimate the sample sizes, number and frequency of assessments, and the administrative and personnel needs required for each study. Clinical trial protocol outlines were based in part on studies submitted for rifapentine, a rifamycin derivative antibiotic that received accelerated approval for the treatment of pulmonary TB in June 1998 under orphan drug status. This appendix shows the various studies conducted and the number of subjects included for each phase of the rifapentine clinical trials.

The *Scientific Blueprint for TB Drug Development* was consulted to confirm that the number of clinical trials assumed in this chapter correspond to the number of studies required for national drug regulatory authority approval.[24] Finally, several individuals familiar with clinical trial design and implementation were contacted, including Mark Mathiew (Parexel), Peg Hewett (Tufts Center), Anca Serban (DataEdge), Dave Duch (independent consultant), and representatives at WHO. The information collected was used to develop a protocol outline for each trial phase in this report.

Rifapentine Clinical Trials in Pulmonary Tuberculosis

Trial[a]	Trial Design	Sample Size	Duration
Phase I			
Healthy Males			
Body Mass/Metabolism Study[112]	Open-label, prospective, single dose	4	72 hours
Hepatic Enzyme Induction Study[113]	Open-label, prospective, single-dose	6	24 days
Antibacterial Activity Study[114]	Open-label, prospective, repeated-dose	12	72 hours
Pharmacokinetic Study[115,116]	Two-period, incomplete block, cross-over design, with subjects randomized to two of four dosing regimens	24	33 days
Healthy Females[117]	Open-label, prospective, single dose	15	72 hours
Healthy Adolescents[118]	Open-label, prospective, single dose	12	72 hours
Elderly Males[119]	Open-label, prospective, single dose	14	72 hours
Hepatically Impaired Males and Females[120]	Open-label, prospective, single dose	15	96 hours
HIV-Positive Males and Females[121]	Open-label, prospective, randomized, two-way crossover under fasting or high-fat meal conditions	16	72 hours
Phase II			
Early Bactericidal Activity Study[122]	Data not available	44	14 days
Phase III			
Protocol 8[122]	Open label, randomized, multicenter study of subjects with previously untreated tuberculosis	722 subjects randomized, 570 evaluable for intent-to-treat analysis	12 months for FDA approval; total 32-month study
Phase III Post-Approval			
Protocol 22[123] (not submitted for FDA approval)	Randomized, open-label, multicenter comparison of rifapentine and rifampin in the continuation phase of therapy	1000 desired, 850 enrolled as of Jan. 1998	4 months of continuation therapy and 24-month follow-up

[a] Superscript numbers indicate the source of this information and correspond to the reference list for the report (p. 95).

Appendix C: U.S. Clinical Trial Cost Models and Inputs

This appendix includes the following information:

- The U.S. model for Phase I clinical trials:
  - Overhead cost calculations (Exhibit C-1)
  - Large studies (Exhibit C-2)
  - Small studies (Exhibit C-3)
  - Total trial costs (Exhibit C-4)
- The U.S. model for Phase II clinical trials:
  - Early bactericidal activity studies (Exhibit C-5)
  - Efficacy and safety study (Exhibit C-6)
  - Total trial costs (Exhibit C-7)
- The U.S. model for Phase III clinical trials:
  - Phase III trial (Exhibit C-8)
  - Total trial costs (Exhibit C-9)
- Summary of U.S. cost inputs for clinical trials, including administrative, treatment, data management, and assessment costs (Exhibit C-10)

Cost estimates were obtained from Andrew Vernon and Zachary Taylor of CDC, Carol Hamilton of the Duke University Medical Center, Bernard Fourie of SAMRC, Larry Geiter of the Sequella Foundation, Tom Kanyok and Toshiko Imamura of WHO, and the 1999 *Parexel's Pharmaceutical R&D Statistical Sourcebook*.[2]

Data for the cost of office visits, diagnostics, examinations, and laboratory procedures were obtained by assigning the correct current procedural terminology (CPT) code published by the American Medical Association.[124] The unit cost for each service was obtained using an extended version of Medicare's Resource Based Relative Value Scale reimbursement schedule.[125] A relative value unit for a service was obtained using the CPT code that corresponds to the service. The relative value unit was multiplied by a conversion factor that reflected the average cost per total relative value unit for the service. The cost models were validated against reported clinical trial costs provided by CDC.

Exhibit C-1: U.S. Model for Phase I Clinical Trials: Overhead Cost Calculations

Overhead/Admin Costs Incurred (independent of number of subjects)	Number	Unit Cost	Total Cost
Physician: Trial Tracking	1	$18,400	$18,400
Site Monitor (CRA)	1	$10,300	$10,300
CRA Travel	1	$1,080	$1,080
Clerical Staff	1	$7,000	$7,000
Epidemiologists	1	$20,000	$20,000
Data Entry Clerk	1	$5,600	$5,600
Programmer	1	$13,900	$13,900
Statistician	1	$23,100	$23,100
Physical Management	0.5	$8,400	$4,200
Space Rental	1	$12,500	$12,500
Communications	1	$560	$560
IRB Review	5	$500	$2,500
IRB Amendment	5	$50	$250
Total Overhead/Admin. Costs per Subject			**$1,147.98**
Total Overhead/Admin. Costs			**$119,390.00**

Exhibit C-2: U.S. Model for Phase I Clinical Trials: Large Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$2,500.00	$2,500.00
Inpatient Costs	1	$500.00	$500.00
Blood Samples	25	$14.00	$350.00
Drug Levels	25	$0.50	$12.50
Urine Samples	8	$22.58	$180.64
Physical Exam	1	$58.00	$58.00
Electrocardiography	1	$29.35	$29.35
General Health Panel: CPT 80050	1	$36.98	$36.98
Hepatitis B Screen	1	$27.79	$27.79
HIV Antibody Screen	1	$19.10	$19.10
Urine Toxicology Screen	1	$45.00	$45.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$20.64	$10.32
Total Cost Per Subject (without overhead/administrative costs)			**$3,770.00**
Total Individual Costs, All Subjects			**$90,472.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	2	$2,060.00	$4,120.00
PI Travel Costs	4	$1,080.00	$4,320.00
Research Coordinator (RC)	2	$10,300.00	$20,600.00
RC Travel Costs	4	$1,080.00	$4,320.00
Shipping Enrollment Packages	2	$10.00	$20.00
Population-Dependent Costs per Subject			**$1,390.83**
Total Population-Dependent Costs			**$33,380.00**

[a] 24 subjects in 2 sites
[b] Costs are weighted to account for only females being tested.

Exhibit C-3: U.S. Model for Phase I Clinical Trials: Small Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$2,500.00	$2,500.00
Inpatient Costs	1	$500.00	$500.00
Blood Samples	25	$14.00	$350.00
Drug Levels	25	$0.50	$12.50
Urine Samples	8	$22.58	$180.64
Physical Exam	1	$58.00	$58.00
Electrocardiography	1	$29.35	$29.35
General Health Panel: CPT 80050	1	$36.98	$36.98
Hepatitis B Screen	1	$27.79	$27.79
HIV Antibody Screen	1	$19.10	$19.10
Urine Toxicology Screen	1	$45.00	$45.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]		$20.64	$10.32
Total Cost Per Subject (without overhead/administrative costs)			**$3,770.00**
Total Individual Costs, All Subjects			**$60,315.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	1	$2,060.00	$2,060.00
PI Travel Costs	2	$1,080.00	$2,160.00
Research Coordinator (RC)	1	$10,300.00	$10,300.00
RC Travel Costs	2	$1,080.00	$2,160.00
Shipping Enrollment Packages	1	$10.00	$10.00
Population-Dependent Costs per Subject			**$1,043.13**
Total Population-Dependent Costs			**$16,690.00**

[a] 16 subjects in 1 site
[b] Costs are weighted to account for only females being tested.

Exhibit C-4: U.S. Model for Phase I Clinical Trials: Total Trial Costs

	Large Studies	Small Studies	Total Phase I Trial Cost
Cost/Subject[a]	$5,960.79	$6,308.49	
Number of Trials	3	2	
Subjects per Trial	24	16	**104**
Total Cost	**$454,211.58**	**$190,745.14**	**$644,956.72**

[a] Expected cost per subject is the sum of the overhead cost per subject and the individual treatment cost per subject and the population dependent costs per subject for either the large or small trials.

Exhibit C-5: U.S. Model for Phase II Clinical Trials: Phase II Early Bactericidal Activity Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$200.00	$200.00
Inpatient Costs	1	$500.00	$500.00
Shipping Samples	1.4	$10.00	$14.00
General Health Panel: CPT 80050	5	$36.98	$184.90
Physical Exam	5	$58.00	$290.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis. B screen	1	$27.79	$27.79
HIV Antibody Screen	1	$19.10	$19.10
Sputum Collection	12	$15.28	$183.36
Bacterial Cultures	12	$15.98	$191.76
Susceptibility Testing	2.2	$7.64	$16.81
RFLP Testing	0.2	$100.00	$20.00
Chest X-Ray	1	$34.73	$34.73
Urine Toxicology. Screen	1	$45.00	$45.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$20.64	$10.32
Total Cost Per Subject			**$1,798.00**
Total Individual Costs, All Subjects			**$115,063.00**
Overhead/Admin Costs Incurred (independent of number of subjects)	**Number**	**Unit Cost**	**Total Cost**
Physician: Trial Tracking	1	$18,400.00	$18,400.00
Site Monitor (CRA)	1	$10,300.00	$10,300.00
CRA Travel	2	$1,080.00	$2,160.00
Clerical Staff	1	$7,000.00	$7,000.00
Statistician	1	$23,100.00	$23,100.00
Independent Statistician	1	$1,080.00	$1,080.00
Independent Bacteriologist	1	$1,080.00	$1,080.00
Epidemiologist	1	$20,000.00	$20,000.00
Data Entry Clerk	1	$5,600.00	$5,600.00
Programmer	1	$13,900.00	$13,900.00
Physical Management	0.5	$8,400.00	$4,200.00
Space Rental	1	$12,500.00	$12,500.00
Communications	1	$560.00	$560.00
Sample Storage	1	$5,000.00	$5,000.00
IRB Review	1	$500.00	$500.00
IRB Amendments	3	$50.00	$150.00
Total Overhead/Administrative Costs			**$125,530.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators	1	$2,060.00	$2,060.00
PI Travel Costs	2	$1,080.00	$2,160.00
Research Coordinator	1	$10,300.00	$10,300.00
RC Travel Costs	2	$1,080.00	$2,160.00
Shipping Enrollment Packages	1	$10.00	$10.00
Total Population-Dependent Costs			**$16,690.00**
Expected Cost per Subject[c]			**$4,020.05**
Total Cost			**$257,282.91**

[a] 64 subjects in 1 site
[b] Costs are weighted to account for only females being tested.
[c] Sum of total costs divided by number of subjects.

Exhibit C-6: U.S. Model for Phase II Clinical Trials: Efficacy and Safety Study[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$200.00	$200.00
Inpatient Costs	1	$500.00	$500.00
Shipping Samples	1.4	$10.00	$14.00
General Health Panel: CPT 80050	7	$36.98	$258.86
Physical Exam	12	$58.00	$696.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis B Screen	1	$27.79	$27.79
HIV Antibody Screen	1	$19.10	$19.10
Sputum Collection	24	$15.28	$336.72
Bacterial Cultures	24	$15.98	$383.52
Susceptibility Testing	2.2	$7.64	$16.81
RFLP Testing	0.2	$100.00	$20.00
Chest X-ray	5	$34.73	$173.65
Urine Toxicology Screen	1	$45.00	$45.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$20.64	$10.32
Total Cost per Subject			**$2,792.00**
Total Individual Costs, All Subjects			**$558,372.00**
Overhead/Admin Costs Incurred (independent of number of subjects)	**Number**	**Unit Cost**	**Total Cost**
Physician: Trial Tracking	1	$220,000.00	$220,000.00
Site Monitor (CRA)	1	$123,400.00	$123,400.00
CRA Travel	4	$1,080.00	$4,320.00
Clerical Staff	1	$84,000.00	$84,000.00
Statistician	1	$276,500.00	$276,500.00
Independent Statistician	1	$1,080.00	$1,080.00
Independent Bacteriologist	1	$1,080.00	$1,080.00
Epidemiologist	1	$240,700.00	$240,700.00
Economist	1	$209,780.00	$209,780.00
Data Entry Clerk	1	$66,700.00	$66,700.00
Programmer	1	$166,600.00	$166,600.00
Physical Management	0.5	$100,000.00	$50,000.00
Space Rental	1	$150,000.00	$150,000.00
Communications	1	$6,000.00	$6,000.00
Storage	1	$5,000.00	$5,000.00
IRB Review	1	$500.00	$500.00
IRB Amendments	3	$50.00	$150.00
Total Overhead/Admin. Costs			**$1,605,810.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators	6	$24,680.00	$148,080.00
PI Travel Costs	36	$1,080.00	$38,880.00
Research Coordinator	6	$123,400.00	$740,400.00
RC Travel Costs	36	$1,080.00	$38,880.00
Shipping Enrollment Packages	6	$10.00	$60.00
Total Population-Dependent Costs			**$966,300.00**
Expected Cost per Subject[c]			**$15,652.41**
Total Cost			**$3,130,481.60**

[a] 200 subjects in 6 sites
[b] Costs are weighted to account for only females being tested.
[c] Sum of total costs divided by number of subjects.

Exhibit C-7: U.S. Model for Phase II Clinical Trials: Total Trial Costs

	EBA Studies	Efficacy and Safety Study	Total Phase II Trial Cost
Cost/Subject	$4,020.05	$15,652.41	
Number of Trials	1	1	
Subjects per Trial	64	200	**264**
Total Cost	**$257,282.91**	**$3,130,481.60**	**$3,387,764.51**

Exhibit C-8: U.S. Model for Phase III Clinical Trials: Phase III Trial[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$400.00	$400.00
Shipping Samples	1.4	$10.00	$14.00
General Health Panel: CPT 80050	7	$36.98	$258.86
Physical Exam	12	$58.00	$696.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis B screen	1	$27.79	$27.79
HIV Antibody Screen	1	$19.10	$19.10
Sputum Collection	14	$15.28	$213.92
Bacterial Cultures	14	$15.98	$223.72
Susceptibility Testing	2.2	$7.64	$16.81
RFLP Testing	0.2	$100.00	$20.00
Chest X-ray	5	$34.73	$173.65
Urine Toxicology Screen	1	$45.00	$45.00
Urine Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$8.68	$4.34
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$20.64	$10.32
Total Screening Cost per Subject			**$345.25**
Total Cost Per Subject			**$2,184.00**
Total Individual Costs, All Subjects			**$2,183,598.00**
Overhead/Admin Costs Incurred (independent of number of subjects)	**Number**	**Unit Cost**	**Total Cost**
Physician: Trial Tracking	1	$550,000.00	$550,000.00
Site Monitor (CRA)	2	$308,500.00	$617,000.00
CRA Travel	40	$1,080.00	$43,200.00
Clerical Staff	1.5	$209,800.00	$314,700.00
Epidemiologists	2	$601,600.00	$1,203,200.00
Data Entry Clerk	1	$166,600.00	$166,600.00
Programmer	1	$416,500.00	$416,500.00
Statistician	1	$691,100.00	$691,100.00
Physical Management	0.5	$250,000.00	$125,000.00
Economist	1	$524,450.00	$524,450.00
Space Rental	1	$375,000.00	$375,000.00
Communications	1	$67,000.00	$67,000.00
Sample Storage	1	$5,000.00	$5,000.00
IRB Review	1	$500.00	$500.00
IRB Amendments	5	$50.00	$250.00
Independent Review Committee: Domestic	60	$1,080.00	$64,800.00
Independent Review Committee: International	45	$2,080.00	$93,600.00
Total Overhead/Admin. Costs			**$5,257,900.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	30	$61,700.00	$1,851,000.00
PI Travel Costs	360	$1,080.00	$388,800.00
Research Coordinator (RC)	40	$308,500.00	$12,340,000.00
RC Travel Costs	480	$1,080.00	$518,400.00
Shipping Enrollment Packages	30	$10.00	$300.00
Total Population Dependent Costs			**$15,098,500.00**

[a] 1,000 subjects in 30 sites
[b] Costs are weighted to account for only females being tested.

Exhibit C-9: U.S. Model for Phase III Clinical Trials: Total Trial Costs

Subjects per Trial	1,000
Cost/Subject Phase III Trial	$22,540.16
Additional Subjects Screened Due to Dropout	176
Screening Costs/Subject	$345.25
Phase III Trial Total	**$22,600,924.47**
Maximum Total Cost/Phase III Trial per Subject[a]	$22,600.92
Maximum Total Cost/Phase III Trial (n = 1,000, assumes 15% dropout at screening)	$22,600,924.47
Minimum Total Cost/Phase III Trial per Subject[a]	$26,264.91
Minimum Total Cost/Phase III Trial (n = 850, assumes 15% dropout at screening and 15% dropout during trial)	$22,325,172.27
Maximum Potential Cost Savings Due to 15% Dropout During Trial	$275,752.20

[a] Sum of total costs divided by number of subjects.

Exhibit C-10: Summary of U.S. Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment

Costs	Phase I	Phase II	Phase III	Source/Notes
Physician: Tracking Trial	$18,400: 2-month trial = 1/6 annual salary.	$18,400 for EBA: 2-month EBA trial = 1/6 annual salary. $220,000 for Phase II: 2-year Phase II = double annual salary.	$550,000; 5-year Phase III trial = five times annual salary.	Based on $110,000 annual salary for a pulmonary MD. One per trial. Source A.
Site Monitor (CRA)	$10,300: 2-month trial = 1/6 annual salary. One RN coordinator per trial.	$10,300 for EBA: 2-month EBA trial = 1/6 annual salary. One RN coordinator per trial. $123,400 for Phase II; 2-year Phase II = double annual salary. One RN coordinator per trial.	$308,500; 5-year Phase III trial = five times annual salary. Two RN coordinators per trial.	Annual salary of $50,000/yr. + 23.4% fringe benefits. Source A.
CRA Travel	$1,080 per trip. One trip per Phase I study.	$1,080 per trip. Two trips per EBA study and two trips per year for 2 years per Phase II study.	$1,080 per trip. Four trips per year for 5 years for the Phase III study.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Source A.
Principal Investigator (PI) Costs	$2,060: 2-month trial = 1/6 of 10% of annual salary + 23.4% fringe benefits.	$2,060 for EBA; 2-month EBA trial = 1/6 of 10% of annual salary + 23.4% fringe benefits. $24,680 for Phase II; 2-year Phase II = double 10% of annual salary + 23.4% fringe benefits.	$61,700; 5-year Phase III = five times 10% of annual salary + 23.4% fringe benefits.	Based on 10-20% of annual salary, with Infectious Disease physician at $80,000-$130,000 per year and Pulmonary physician at $110,000-$160,000 per year. One per trial site. Costs may be higher if salaries are in the upper range of the 10-20% described by experts. Source A.
Research Coordinator (RC) Costs	$10,300: 2-month trial = 1/6 annual salary. One RN coordinator per trial site.	$10,300 for EBA: 2-month EBA trial = 1/6 annual salary. One RN coordinator per trial site. $123,400 for Phase II; 2-year Phase II = double annual salary. One RN coordinator per trial site.	$308,500; 5-year Phase III trial = five times annual salary. One to two RN coordinators per trial site.	Assumed similar to CRA costs. Source A.
Costs of Training Project Personnel/Trial Investigator Meeting: PIs and RCs	$1,080 per trip. Two trips per Phase I study.	$1,080 per trip. Two trips per EBA study and two trips per year for 2 years per Phase II study.	$1,080 per trip. Two trips per year for 5 years plus one training and one closing trip.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Source A.
Epidemiologists	$20,000; 2-month trial = 1/6 of annual salary. One per trial.	$20,000 for EBA; 2-month EBA trial = 1/6 of annual salary. One per trial. $240,700 for Phase II; 2-year Phase II = double annual salary. One per trial.	$601,600; 5-year Phase III trial = five times annual salary. Two per trial.	Annual salary of $97,500/year + 23.4% fringe benefits, based on RTI pay scale. Source A.
Independent Data and Safety Monitoring Board: Domestic Members			$1,080 per trip. Four members, three trips per year for 5 years. No salary expected.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Independent Data and Safety Monitoring Board: International Members			$2,080 per trip. Three members, three trips per year for 5 years. No salary expected	Estimated $1,500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.

(continued)

Exhibit C-10: Summary of U.S. Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Phase I	Phase II	Phase III	Source/Notes
Independent Bacteriologist		$1,080 per trip. One trip per trial. No salary expected.		Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Economist		$209,780 for Phase II; 2-year Phase II = double annual salary. One per trial.	$524,450; 5-year Phase III trial = five times annual salary. One per trial.	Annual salary of $85,000/year + 23.4% fringe benefits.
Independent Statistician		$1,080 per trip. One trip per trial. No salary expected.		Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Programmer	$13,900; 2-month trial = 1/6 of annual salary.	$13,900 for EBA; 2-month EBA trial = 1/6 of annual salary. $166,600 for Phase II; 2-year Phase II = double annual salary.	$416,500; 5-year Phase III trial = five times annual salary.	Annual salary of $67,500/year + 23.4% fringe benefits. One per trial. Based on RTI pay scale. Source A.
Statistician	$23,100; 2-month trial = 1/6 of annual salary.	$23,100 for EBA; 2-month EBA trial = 1/6 of annual salary. $276,500 for Phase II; 2-year Phase II = double annual salary.	$691,100; 5-year Phase III trial = five times annual salary.	Annual salary of $112,000/year + 23.4% fringe benefits. One per trial. Based on RTI pay scale. Source A.
Physical Management	$8,400; 2-month trial = 1/6 of annual salary.	$8,400 for EBA; 2-month EBA trial = 1/6 of annual salary. $100,000 for Phase II; 2-year Phase II = double annual salary.	$250,000; 5-year Phase III = five times annual salary.	Annual salary of $50,000/year. Half-time employee per trial. Estimate. Source A
Data Entry clerk	$5,600; 2-month trial = 1/6 of annual salary.	$5,600 for EBA; 2-month EBA trial = 1/6 of annual salary. $66,700 for Phase II; 2-year Phase II = double annual salary.	$166,600; 5-year Phase III = five times annual salary.	Annual salary of $27,000/year + 23.4% fringe benefits. One per trial. Based on RTI pay scale. Source A.
Clerical Staff	$7,000; 2-month trial = 1/6 of annual salary. One per trial.	$7,000 for EBA; 2-month EBA trial = 1/6 of annual salary. One per trial. $84,000 for Phase II; 2-year Phase II = double annual salary. One per trial.	$209,800; 5-year Phase III = five times annual salary. One and one-half per trial.	Annual salary of $34,000/year + 23.4% fringe benefits. Based on RTI pay scale. Source A
Subject Incentives/ Reimbursement	$2,500/pt.	$200/pt.	$400 for completing trial. ~$25/visit; ~$150/6 mo.; $250-$400/total trial. Typically given as food coupons instead of cash.	Phase I and II estimates from PPD Development trials based on similar subject requirements at the RTP clinical site. Phase III estimates – Source A.

(continued)

Exhibit C-10: Summary of U.S. Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Phase I	Phase II	Phase III	Source/Notes
Inpatient Costs per day	$500	$500		Source A. However, there may be no cost—NIH approved protocols can use general clinical research centers at no charge. $500 is a conservative estimate.
Space Rental	$12,500	$12,500 for EBA $150,000 for Phase II	$375,000	Source A. Space rental is for 2,500 sq.ft., at a cost of $30/sq.ft./yr. rented.
Shipping Enrollment Package	$10.00 per shipment	$10.00 per shipment	$10.00 per shipment	Cost to ship up to one pound, cross-country, 2-day priority, by FedEx. FedEx rate scale. One per trial site.
IRB Review	$500 for initial IRB review per protocol, thus $4500 for 9 Phase I trials	$500 for initial IRB review per protocol, thus $1500 for 2 EBAs and 1 pilot Phase III trial	$500 for initial IRB review	Source A.
IRB Review: Amendments	$50 per amendment. Anticipate 1 amendments per Phase I protocol.	$50 per amendment. Anticipate 3 amendments per Phase II protocol.	$50 per amendment. Anticipate 5 amendments per Phase III protocol.	Discussions with Bernard Fourie.
Communications	$560. Calculated as one hour/person/week for 11 people, at $0.06/min. over 2 months plus one-time $20 hook-up fee per person.	$560 for EBA; EBA study calculated as one hour/person/ week for 11 people, at $0.06/min. over 2 months plus one-time $20 hook-up fee per person. $6,000 for Phase II. Phase II calculated as one hour/person/week for 15 people, at $0.06/min. over 2 years, plus one-time $20 hook-up fee per person.	$67,000. Calculated as one hour/person/week for 70 people, at $0.06/min. over 5 years, plus one-time $20 hook-up fee per person.	Based on RTI phone charges. Source A.
Sample Storage		$5,000	$5,000	Industrial, lab quality refrigerator. Discussions with Andrew Vernon and Zachary Taylor.
Sample shipment		$10.00 per shipment	$10.00 per shipment	Cost to ship up to one pound, cross-country, 2-day priority, by FedEx. FedEx rate scale. For susceptibility testing, a randomly selected 10% of samples will also be shipped to the CDC at each of two rounds of testing. In addition, the second susceptibility test will be performed by CDC, thus shipping for susceptibility testing will be 1.2 per patient. For RFLP testing, 20% of samples will be tested by CDC, thus, total shipping will be 1.4 per patient.
Blood Samples into Heparinized Tubes	$14.00			

(continued)

Exhibit C-10: Summary of U.S. Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Phase I	Phase II	Phase III	Source/Notes
Drug Levels	$0.50/drug			Discussions with Andrew Vernon and Zachary Taylor
Urine Sample to Evaluate Cortisol and Beta-Hydroxycortisol	$22.58			CPT 82533
Physical Exam	$58.00	$58.00	$58.00	
Sputum Collection		$15.28	$15.28	CPT 89350
Bacterial Cultures		$15.98	$15.98	CPT 87117
Susceptibility Testing		$7.64	$7.64	CPT 87190; Performed twice. Once by site, once by CDC. An additional 10% will be randomly selected for additional testing by CDC each time, so the total per patient is 2.2.
Chest X-ray		$34.73	$34.73	CPT 71020
RFLP Testing		$100.00	$100.00	Discussions with Carol Hamilton, Andrew Vernon, and Zachary Taylor. 20% of samples will be randomly selected for testing.
Neurological Exam		$44.11	$44.11	CPT 95834
Visual Acuity/Red-Green Color Perception		$15.98	$15.98	CPT 92283
Electrocardiography	$29.35			
General Health Panel	$36.98	$36.98	$36.98	CPT 80050
Hepatitis B Screening	$27.79	$27.79	$27.79	CPT 87515
HIV Antibody Screening	$19.10	$19.10	$19.10	CPT 86703
Urine Toxicology Screen for Alcohol and Illicit Drugs	$45.00	$45.00	$45.00	
Serum and Urine Testing for Beta-Human Chorionic Gonadtropin test (females)	$20.64 serum; $8.68 urine	$20.64 serum; $8.68 urine	$20.64 serum; $8.68 urine	

Source A: Communication with Andrew Vernon (CDC), Zachary Taylor (CDC), Carol Hamilton (Duke University), and Bernard Fourie (South African Medical Research Council)

Appendix D: Uganda Clinical Trial Cost Models and Inputs

This appendix includes the following information:

- The Uganda model for Phase I clinical trials:
  - Overhead cost calculations (Exhibit D-1)
  - Large studies (Exhibit D-2)
  - Small studies (Exhibit D-3)
  - Total trial costs (Exhibit D-4)
- The Uganda model for Phase II clinical trials:
  - Early bactericidal activity studies (Exhibit D-5)
  - Efficacy and safety study (Exhibit D-6)
  - Total trial costs (Exhibit D-7)
- The Uganda model for Phase III clinical trials:
  - Phase III trial (Exhibit D-8)
  - Total trial costs (Exhibit D-9)
- Summary of Uganda cost inputs for clinical trials, including administrative, treatment, data management, and assessment costs (Exhibit D-10)

Cost estimates were obtained from Andrew Vernon and Zachary Taylor of CDC, Carol Hamilton of the Duke University Medical Center, Bernard Fourie of SAMRC, Larry Geiter of the Sequella Foundation, Tom Kanyok and Toshiko Imamura of WHO, John L. Johnson and Marla Manning of Case Western Reserve University, and the 1999 *Parexel's Pharmaceutical R&D Statistical Sourcebook*.[2]

Data for the cost of office visits, diagnostics, examinations, and laboratory procedures were obtained by assigning the correct current procedural terminology (CPT) code published by the American Medical Association.[124] The unit cost for each service was obtained using an extended version of Medicare's Resource Based Relative Value Scale reimbursement schedule.[125] A relative value unit for a service was obtained using the CPT code that corresponds to the service. The relative value unit was multiplied by a conversion factor that reflected the average cost per total relative value unit for the service. The cost models were validated against reported clinical trial costs provided by CDC.

Exhibit D-1: Uganda Model for Phase I Clinical Trials: Overhead Cost Calculations

Overhead/Admin Costs Incurred (independent of number of subjects)	Number	Unit Cost	Total Cost
Physician: Trial Tracking	1	$2,300	$2,300
Site Monitor (CRA)	1	$9,586	$9,586
CRA Travel	1	$1,080	$1,080
Clerical Staff	1	$767	$767
Epidemiologists	1	$2,013	$2,013
Data Entry Clerk	1	$863	$863
Programmer	1	$1,342	$1,342
Statistician	1	$21,467	$21,467
Physical Management	0.5	$4,792	$2,396
Space Rental	1	$12,500	$12,500
Communications	1	$1,000	$1,000
IRB Review	5	$150	$750
IRB Amendment	5	$150	$750
Home Visitor	1	$863	$863
Laboratory Technician	1	$767	$767
Pharmacist	1	$672	$672
Counselor	1	$920	$920
Driver	1	$767	$767
Vehicle	1	$2,000	$2,000
Administrative Supplies	1	$834	$834
Total Overhead/Admin. Costs per Subject			**$611.89**
Total Overhead/Admin. Costs			**$63,637.00**

Exhibit D-2: Uganda Model for Phase I Clinical Trials: Large Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$48.00	$48.00
Inpatient Costs	1	$15.00	$15.00
Blood Samples	25	$5.75	$143.75
Drug Levels	25	$0.50	$12.50
Urine Samples	8	$3.25	$26.00
Physical Exam	1	$0.00	$0.00
Electrocardiography	1	$20.00	$20.00
General Health Panel: CPT 80050	1	$34.19	$34.19
Hepatitis B Screen	1	$5.75	$5.75
HIV Antibody Screen	1	$4.75	$4.75
Urine Toxicology Screen	1	$5.00	$5.00
Standard TB Drug Therapy	1	$45.00	$45.00
Other Non-TB Drug Therapy	1	$15.00	$15.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Total Cost Per Subject (without overhead/administrative costs)			**$378.44**
Total Individual Costs, All Subjects			**$9,082.56**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	2	$1,342.00	$2,684.00
PI Travel Costs	4	$1,080.00	$4,320.00
Research Coordinator (RC)	2	$1,840.00	$3,680.00
RC Travel Costs	4	$1,080.00	$4,320.00
Shipping Enrollment Packages	2	$75.00	$150.00
Population-Dependent Costs per Subject			**$631.42**
Total Population-Dependent Costs			**$15,154.00**

[a] 24 subjects in 2 sites
[b] Costs are weighted to account for only females being tested.

Exhibit D-3: Uganda Model for Phase I Clinical Trials: Small Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$18.00	$18.00
Inpatient Costs	1	$15.00	$15.00
Blood Samples	25	$5.75	$143.75
Drug Levels	25	$0.50	$12.50
Urine Samples	8	$3.25	$26.00
Physical Exam	1	$0.00	$0.00
Electrocardiography	1	$20.00	$20.00
General Health Panel: CPT 80050	1	$34.19	$34.19
Hepatitis B Screen	1	$5.75	$5.75
HIV Antibody Screen	1	$4.75	$4.75
Urine Toxicology Screen	1	$5.00	$5.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Standard TB Drug Therapy	1	$45.00	$45.00
Other Non-TB Drug Therapy	1	$15.00	$15.00
Total Cost Per Subject (without overhead/administrative costs)			**$348.44**
Total Individual Costs, All Subjects			**$5,575.04**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	1	$1,342.00	$1,342.00
PI Travel Costs	2	$1,080.00	$2,160.00
Research Coordinator (RC)	1	$1,840.00	$1,840.00
RC Travel Costs	2	$1,080.00	$2,160.00
Shipping Enrollment Packages	1	$75.00	$75.00
Population-Dependent Costs per Subject			**$473.56**
Total Population-Dependent Costs			**$7,577.00**

[a] 16 subjects in 1 site
[b] Costs are weighted to account for only females being tested.

Exhibit D-4: Uganda Model for Phase I Clinical Trials: Total Trial Costs

	Large Studies	Small Studies	Total Phase I Trial Cost
Cost/Subject[a]	$1,621.75	$1,433.90	
Number of Trials	3	2	
Subjects per Trial	24	16	**104**
Total Cost	**$116,766.00**	**$45,884.80**	**$162,650.80**

*Expected cost per subject is the sum of the overhead cost per subject and the individual treatment cost per subject and the population dependent costs per subject for either the large or small trials.

Exhibit D-5: Uganda Model for Phase II Clinical Trials: Early Bactericidal Activity Studies[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$42.00	$42.00
Inpatient Costs	1	$15.00	$15.00
Shipping Samples	0.05	$160.00	$8.00
General Health Panel: CPT 80050	5	$34.19	$170.95
Physical Exam	5	$0.00	$0.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis B Screen	1	$5.75	$5.75
HIV Antibody Screen	1	$4.75	$4.75
Sputum Collection	12	$5.66	$67.92
Bacterial Cultures	12	$15.98	$191.76
Sample Storage	12	$3.25	$39.00
Susceptibility Testing	1.05	$43.00	$45.15
RFLP Testing	0.05	$100.00	$5.00
Chest X-ray	1	$7.50	$7.50
Urine Toxicology Screen	1	$5.00	$5.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Standard TB Drug Therapy	1	$45.00	$45.00
Other Non-TB Drug Therapy	1	$15.00	$15.00
Total Cost Per Subject			**$731.37**
Total Individual Costs, All Subjects			**$46,807.67**
Overhead/Admin Costs Incurred (independent of number of subjects)	**Number**	**Unit Cost**	**Total Cost**
Physician: Trial Tracking	1	$2,300.00	$2,300.00
Site Monitor (CRA)	1	$9,586.00	$9,586.00
CRA Travel	2	$1,080.00	$2,160.00
Clerical Staff	1	$767.00	$767.00
Statistician	1	$21,467.00	$21,467.00
Independent Statistician	1	$1,080.00	$1,080.00
Independent Bacteriologist	1	$1,080.00	$1,080.00
Epidemiologist	1	$2,013.00	$2,013.00
Data Entry Clerk	1	$863.00	$863.00
Programmer	1	$1,342.00	$1,342.00
Physical Management	0.5	$4,792.00	$2,396.00
Space Rental	1	$12,500.00	$12,500.00
Communications	1	$1,000.00	$1,000.00
IRB Review	1	$150.00	$150.00
IRB Amendments	3	$150.00	$450.00
Home Visitor	1	$863.00	$863.00
Laboratory Technician	1	$767.00	$767.00
Pharmacist	1	$672.00	$672.00
Counselor	1	$920.00	$920.00
Driver	1	$767.00	$767.00
Vehicle	1	$2,000.00	$2,000.00
Administrative Supplies	1	$834.00	$834.00
Total Overhead/Administrative Costs			**$65,977.00**

(continued)

Exhibit D-5: Uganda Model for Phase II Clinical Trials: Early Bactericidal Activity Studies[a] (continued)

Population-Dependent Costs Incurred (based on enrollment)	Number	Unit Cost	Total Cost
Principal Investigators	1	$1,342.00	$1,342.00
PI Travel Costs	2	$1,080.00	$2,160.00
Research Coordinator	1	$1,840.00	$1,840.00
RC Travel Costs	2	$1,080.00	$2,160.00
Shipping Enrollment Packages	1	$75.00	$75.00
Total Population-Dependent Costs			**$7,577.00**
Expected Cost per Subject[c]			**$1,880.65**
Total Cost			**$120,361.68**

[a] 64 subjects in 1 site
[b] Costs are weighted to account for only females being tested.
[c] Sum of total costs divided by number of subjects.

Exhibit D-6: Uganda Model for Phase II Clinical Trials: Efficacy and Safety Study[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$78.00	$78.00
Inpatient Costs	1	$15.00	$15.00
Shipping Samples	0.05	$160.00	$8.00
General Health Panel: CPT 80050	7	$34.19	$239.33
Physical Exam	12	$0.00	$0.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis B Screen	1	$5.75	$5.75
HIV Antibody Screen	1	$4.75	$4.75
Sputum Collection	24	$5.66	$135.84
Bacterial Cultures	24	$15.98	$383.52
Sample Storage	24	$3.25	$78.00
Susceptibility Testing	1.05	$43.00	$45.15
RFLP Testing	0.05	$100.00	$5.00
Chest X-ray	5	$7.50	$37.50
Urine Toxicology Screen	1	$5.00	$5.00
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Standard TB Drug Therapy	1	$45.00	$45.00
Other Non-TB Drug Therapy	1	$15.00	$15.00
Total Cost per Subject			**$1,164.43**
Total Individual Costs, All Subjects			**$232,886.00**

(continued)

Exhibit D-6: Uganda Model for Phase II Clinical Trials: Efficacy and Safety Study[a] (continued)

Overhead/Admin Costs Incurred (independent of number of subjects)	Number	Unit Cost	Total Cost
Physician: Trial Tracking	1	$27,600.00	$27,600.00
Site Monitor (CRA)	1	$115,000.00	$115,000.00
CRA Travel	4	$1,080.00	$4,320.00
Clerical Staff	1	$9,200.00	$9,200.00
Statistician	1	$257,600.00	$257,600.00
Independent Statistician	1	$1,080.00	$1,080.00
Independent Bacteriologist	1	$1,080.00	$1,080.00
Epidemiologist	1	$24,150.00	$24,150.00
Data Entry Clerk	1	$10,350.00	$10,350.00
Programmer	1	$16,100.00	$16,100.00
Economist	1	$195,500.00	$195,500.00
Physical Management	0.5	$57,500.00	$28,750.00
Space Rental	1	$150,000.00	$150,000.00
Communications	1	$12,000.00	$12,000.00
IRB Review	1	$150.00	$150.00
IRB Amendments	3	$150.00	$450.00
Home Visitor	1	$10,350.00	$10,350.00
Laboratory Technician	1	$9,200.00	$9,200.00
Pharmacist	1	$8,050.00	$8,050.00
Counselor	1	$11,040.00	$11,040.00
Driver	1	$9,200.00	$9,200.00
Vehicle	1	$24,000.00	$24,000.00
Administrative Supplies	1	$10,000.00	$10,000.00
Total Overhead/Admin. Costs			**$935,170.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators	6	$16,100.00	$96,600.00
PI Travel Costs	36	$1,080.00	$38,880.00
Research Coordinator	6	$22,080.00	$132,480.00
RC Travel Costs	36	$1,080.00	$38,880.00
Shipping Enrollment Packages	6	$75.00	$450.00
Total Population-Dependent Costs			**$307,290.00**
Expected Cost per Subject[c]			**$7,376.73**
Total Cost			**$1,475,346.00**

[a] 200 subjects in 6 sites
[b] Costs are weighted to account for only females being tested.
[c] Sum of total costs divided by number of subjects.

Exhibit D-7: Uganda Model for Phase II Clinical Trials: Total Trial Costs

	EBA Studies	Efficacy and Safety Study	Total Phase II Trial Cost
Cost/Subject	$1,880.65	$7,376.73	
Number of Trials	1	1	
Subjects per Trial	64	200	**264**
Total Cost	**$120,361.68**	**$1,475,346.00**	**$1,595,707.68**

Exhibit D-8: Uganda Model for Phase III Clinical Trials: Phase III Trial[a]

Costs Incurred Per Subject	Number	Unit Cost	Total Cost
Subject Incentives	1	$84.00	$84.00
Shipping Samples	0.05	$160.00	$8.00
General Health Panel: CPT 80050	7	$34.19	$239.33
Physical Exam	12	$0.00	$0.00
Neurological Exam	1	$44.11	$44.11
Visual Acuity: Red/Green Perception	1	$15.98	$15.98
Hepatitis B Screen	1	$5.75	$5.75
HIV Antibody Screen	1	$4.75	$4.75
Sputum Collection	14	$5.66	$79.24
Bacterial Cultures	14	$15.98	$223.72
Susceptibility Testing	1.05	$43.00	$45.15
RFLP Testing	0.05	$100.00	$5.00
Chest X-ray	5	$7.50	$37.50
Urine Toxicology Screen	1	$5.00	$5.00
Urine Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Serum Test: Beta-Human Chorionic Gonadotropin[b]	0.5	$7.00	$3.50
Standard TB Drug Therapy	1	$45.00	$45.00
Other Non-TB Drug Therapy	1	$15.00	$15.00
Total Screening Cost per Subject			**$352.17**
Total Cost Per Subject			**$910.03**
Total Individual Costs, All Subjects			**$910,030.00**

(continued)

Exhibit D-8: Uganda Model for Phase III Clinical Trials: Phase III Trial[a] (continued)

Overhead/Admin Costs Incurred (independent of number of subjects)	Number	Unit Cost	Total Cost
Physician: Trial Tracking	1	$69,000.00	$69,000.00
Site Monitor (CRA)	2	$287,500.00	$575,000.00
CRA Travel	40	$1,080.00	$43,200.00
Clerical Staff	1.5	$23,000.00	$34,500.00
Epidemiologists	2	$60,375.00	$120,750.00
Data Entry Clerk	1	$25,875.00	$25,875.00
Programmer	1	$40,250.00	$40,250.00
Statistician	1	$644,000.00	$644,000.00
Physical Management	0.5	$143,750.00	$71,875.00
Economist	1	$488,750.00	$488,750.00
Space Rental	1	$375,000.00	$375,000.00
Communications	1	$30,000.00	$30,000.00
IRB Review	1	$150.00	$150.00
IRB Amendments	5	$150.00	$750.00
Independent Review Committee: Domestic	60	$1,080.00	$64,800.00
Independent Review Committee: International	45	$2,080.00	$93,600.00
Home Visitor	1	$25,875.00	$25,875.00
Laboratory Technician	1	$23,000.00	$23,000.00
Pharmacist	1	$20,125.00	$20,125.00
Counselor	1	$27,600.00	$27,600.00
Driver	1	$23,000.00	$23,000.00
Vehicle	1	$60,000.00	$60,000.00
Administrative Supplies	1	$25,000.00	$25,000.00
Total Overhead/Admin. Costs			**$2,882,100.00**
Population-Dependent Costs Incurred (based on enrollment)	**Number**	**Unit Cost**	**Total Cost**
Principal Investigators (PI)	30	$40,250.00	$1,207,500.00
PI Travel Costs	360	$1,080.00	$388,800.00
Research Coordinator (RC)	40	$55,200.00	$2,208,000.00
RC Travel Costs	480	$1,080.00	$518,400.00
Shipping Enrollment Packages	30	$75.00	$2,250.00
Total Population Dependent Costs			**$4,324,950.00**

[a] 1,000 subjects in 30 sites
[b] Costs are weighted to account for only females being tested.

Exhibit D-9: Uganda Model for Phase III Clinical Trials: Total Trial Costs

Subjects per Trial	1,000
Cost/Subject Phase III Trial	$8,179.23
Additional Subjects Screened Due to Dropout	176
Screening Costs/Subject	$352.17
Phase III Trial Total	**$8,179,227.65**
Maximum Total Cost/Phase III Trial per Subject[a]	$8,179.23
Maximum Total Cost/Phase III Trial (n = 1,000, assumes 15% dropout at screening)	$8,179,227.65
Minimum Total Cost/Phase III Trial per Subject[a]	$9,524.17
Minimum Total Cost/Phase III Trial (n = 850, assumes 15 % dropout at screening and 15% dropout during trial)	$8,095,548.65
Maximum Potential Cost Savings Due to 15% Dropout During Trial	$83,679.00

[a] Sum of total costs divided by number of subjects.

Exhibit D-10: Summary of Uganda Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment

Costs	Phase I	Phase II	Phase III	Source/Notes
Physician: Tracking Trial	$2,300; 1/6 of $12,000 annual salary +15% benefits	$2,300 for EBA; 1/6 of $12,000 annual salary +15% fringe benefits. $27,600 for Phase II: 2-year Phase II = double annual salary.	$69,000 for Phase III; $12,000/yr. for five years +15% fringe benefits	Based on data provided by John Johnson and Marla Manning of CWRU
Site Monitor (CRA)	$9,586; 1/6 of $50,000/yr. +15% benefits; Assumes RN as coordinator	$9,586 for EBA; 1/6 of $50,000/yr. +15% fringe benefits $115,000 for Phase II; $50,000/yr. for two years +15% fringe benefits. Assumes RN as coordinator	$287,500 for Phase III; $50,000/yr. for five years+15% fringe benefits.	Annual salary of $50,000/yr. + 23.4% fringe benefits. Source A.
CRA Travel	$1,080 per trip. One trip per Phase I study.	$1,080 per trip. Two trips per EBA study and two trips per year for 2 years per Phase II study.	$1,080 per trip. Four trips per year for 5 years for the Phase III study.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Source A.
Principal Investigator (PI) Costs	$1,342; 1/6 of 10% of $70,000 +15% benefits. Based on 10-20% of annual salary	$1,342 for EBA; 1/6 of 10% of $70,000 annual salary +15% fringe benefits.. $16,100 for Phase II; 10% of $70,000 for two years +15% fringe benefits.	$40,250 for Phase III; 10% of $70,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Research Coordinator (RC) Costs	$1,840; 1/6 of $9,600 +15% benefits; Assumes RN as coordinatorOne RN coordinator per trial site.	$1,840 for EBA; 1/6 of $9,600/yr. +15% fringe benefits $22,080 for Phase II; $9,600/yr. for two years +15% fringe benefits. One RN coordinator per trial site.	$55,200 for Phase III; $9,600/yr. for five years.	Based on data provided by John Johnson and Marla Manning of CWRU
Costs of Training Project Personnel/Trial Investigator Meeting: PIs and RCs	$1,080 per trip. Two trips per Phase I study.	$1,080 per trip. Two trips per EBA study and two trips per year for 2 years per Phase II study.	$1,080 per trip. Two trips per year for 5 years plus one training and one closing trip.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Source A.
Epidemiologists	$2,013; 1/6 of $10,500/yr. + 15% benefits	$2,013 for EBA; 1/6 of $10,500/yr. +15% fringe benefits $24,150 for Phase II; $10,500/yr. for two years +15% fringe benefits. One per trial.	$60,375 for Phase III; $10,500/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Independent Data and Safety Monitoring Board: Domestic Members			$1,080 per trip. Four members, three trips per year for 5 years. No salary expected.	Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Independent Data and Safety Monitoring Board: International Members			$2,080 per trip. Three members, three trips per year for 5 years. No salary expected	Estimated $1,500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.

(continued)

Exhibit D-10: Summary of Uganda Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Phase I	Phase II	Phase III	Source/Notes
Independent Bacteriologist		$1,080 per trip. One trip per trial. No salary expected.		Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Economist		$195,500 for Phase II; 2-year Phase II = double annual salary. One per trial.	$488,750; 5-year Phase III trial = five times annual salary. One per trial.	Annual salary of $85,000/year + 15% fringe benefits. U.S. costs assumed.
Independent Statistician		$1,080 per trip. One trip per trial. No salary expected.		Estimated $500 Travel; $300 lodging; $180 meals and expenses; $100 meeting materials. Based on discussions with Bernard Fourie.
Programmer	$1,342; 1/6 of $7,000/yr. +15% benefits	$1,342 for EBA; 1/6 of $7,000/yr. +15% fringe benefits. $16,100 for Phase II; $7,000/yr. for two years +15% fringe benefits.	$40,250 for Phase III; $7,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Statistician	$21,467; 1/6 of $112,000/yr. +15% benefits	$21,467 for EBA; 1/6 of $112,000/yr. +15% fringe benefits. $257,600 for Phase II; $112,000/yr. for two years +15% fringe benefits..	$644,000 for Phase III; $112,000/yr. for five years+15% fringe benefits.	Annual salary of $112,000/year + 23.4% fringe benefits. One per trial. Based on RTI pay scale. Source A.
Physical Management	$4,792; 1/6 of $25,000/yr. +15% benefits.	$4,792 for EBA; 1/6 of $25,000/yr. +15% fringe benefits. $57,500 for Phase II; $25,000/yr. for two years+15% fringe benefits..	$143,750 for Phase III; $25,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Data Entry clerk	$863; 1/6 of $4,500/yr. +15% benefits.	$863 for EBA; 1/6 of $4,500/yr. +15% fringe benefits. $10,350 for Phase II; $4,500/yr. for two years +15% fringe benefits..	$25,875 for Phase III; $4,500/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Clerical Staff	$767; 1/6 of $4,000/yr. +15% benefits. One per trial.	$767 for EBA; 1/6 of $4,000/yr. +15% fringe benefits. $9,200 for Phase II; $4,000/yr. for two years +15% fringe benefits. One per trial.	$23,000 for Phase III; $4,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Subject Incentives/ Reimbursement	$48/pt./Large trial, $18/pt./Small trial; $6 per evaluation day	$42/pt. for EBA; $78/pt. for Phase II. $6/pt. per evaluation day.	$84 for completing trial; $6/pt. per evaluation day.	Based on data provided by John Johnson and Marla Manning of CWRU
Home Visitor	$863; 1/6 of $4,500/yr. +15% benefits	$863 for EBA; 1/6 of $4,500/yr. +15% fringe benefits. $10,350 for Phase II; $4,500/yr. for two years+15% fringe benefits.	$25,875 for Phase III; $4,500/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU

(continued)

Exhibit D-10: Summary of Uganda Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Phase I	Phase II	Phase III	Source/Notes
Laboratory Technician	$767; 1/6 of $4,000/yr. +15% benefits	$767 for EBA; 1/6 of $4,000/yr. +15% fringe benefits. $9,200 for Phase II; $4,000/yr. for two years+15% fringe benefits.	$23,000 for Phase III; $4,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Pharmacist	$672; 1/6 of $3,500/yr. +15% benefits	$672 for EBA; 1/6 of $3,500/yr.+15% fringe benefits. $8,050 for Phase II; $3,500/yr. for two years+15% fringe benefits.	$20,125 for Phase III; $3,500/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Counselor	$920; 1/6 of $4,800/yr. +15% benefits	$920 for EBA; 1/6 of $4,800/yr.+15% fringe benefits. $11,040 for Phase II; $4,800/yr. for two years+15% fringe benefits.	$27,600 for Phase III; $4,800/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Driver	$767; 1/6 of $4,000/yr. +15% benefits	$767 for EBA; 1/6 of $4,000/yr. +15% fringe benefits. $9,200 for Phase II; $4,000/yr. for two years+15% fringe benefits.	$23,000 for Phase III; $4,000/yr. for five years+15% fringe benefits.	Based on data provided by John Johnson and Marla Manning of CWRU
Vehicle	$2,000; 1/6 of $12,000 annual cost.	$2,000 for EBA; 1/6 of $12,000 annual cost. $24,000 for Phase II; $12,000/yr. for two years.	$60,000 for Phase III; $12,000/yr. for five years.	Based on data provided by John Johnson and Marla Manning of CWRU
Administrative Supplies	$834; 1/6 of $5,000 annual cost.	$834 for EBA; 1/6 of $5,000 annual cost. $10,000 for Phase II; $5,000/yr. for two years.	$25,000 for Phase III; $5,000/yr. for five years.	Based on data provided by John Johnson and Marla Manning of CWRU
Inpatient costs per day	$15.00/pt.	$15.00/pt.	$15.00/pt.	Based on data provided by John Johnson and Marla Manning of CWRU
Standard TB drug therapy	$45.00/pt.	$45.00/pt.	$45.00/pt.	Based on data provided by John Johnson and Marla Manning of CWRU
Other Non-TB drugs	$15.00/pt.	$15.00/pt.	$15.00/pt.	Based on data provided by John Johnson and Marla Manning of CWRU
Space Rental	$12,500	$12,500 for EBA $150,000 for Phase II	$375,000	Source A. Space rental is for 2,500 sq.ft., at a cost of $30/sq.ft./yr. rented.
Shipping Enrollment Package	$75.00 per trial	$75.00 per trial	$75.00 per shipment	Based on data provided by John Johnson and Marla Manning of CWRU
IRB Review	$150/review	$150/review	$150/review	Based on data provided by John Johnson and Marla Manning of CWRU
IRB Review: Amendments	$150/amendment. Anticipate 1 amendments per Phase I protocol.	$150/amendment. Anticipate 1 amendments per Phase I protocol.	$150/amendment. Anticipate 5 amendments per Phase I protocol.	Based on data provided by John Johnson and Marla Manning of CWRU. Discussions with Bernard Fourie.

(continued)

Exhibit D-10: Summary of Uganda Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Cost for Phase I Trials	Cost for Phase II Trials	Cost for Phase III Trials	Source/Notes
Communications	$1,000; $500 per month.	$1,000 for EBA; $12,000 for Phase II	$30,000 for Phase III; $6,000/yr. for five years.	Based on data provided by John Johnson and Marla Manning of CWRU
Sample Storage		$3.25/sample	$3.25/sample	Based on data provided by John Johnson and Marla Manning of CWRU
Sample Shipment		$160.00 per shipment	$160.00 per shipment	Cost to ship up to one pound, cross-country, 2-day priority, by FedEx. FedEx rate scale. Discussions with John Johnson and Marla Manning of CWRU. Only need to ship the 5% of isolates that need fingerprinting by Univ of Arkansas.
Blood Samples into Heparinized Tubes	$5.75			Based on data provided by John Johnson and Marla Manning of CWRU
Drug Levels	$0.50/drug			Discussions with Andrew Vernon and Zachary Taylor
Urine Sample to Evaluate Cortisol and Beta-Hydroxycortisol	$3.25			Based on data provided by John Johnson and Marla Manning of CWRU
Physical Exam	$0.00	$0.00	$0.00	Based on data provided by John Johnson and Marla Manning of CWRU
Sputum Collection		$5.66	$5.66	Based on data provided by John Johnson and Marla Manning of CWRU
Bacterial Cultures		$15.98	$15.98	CPT 87117
Susceptibility Testing		$43.00	$43.00	Discussions with John Johnson and Marla Manning of CWRU. Do drug susceptibility tests for all patients. A repeat test is done on treatment failures and relapses (5-10%) of the total number enrolled. 5% was used as conservative estimate. All tests done in Uganda.
Chest X-ray		$7.50	$7.50	Based on data provided by John Johnson and Marla Manning of CWRU
RFLP Testing		$100.00	$100.00	Discussions with John Johnson and Marla Manning of CWRU. RFLP is only done on those who relapse (about 5% of the total enrolled). RFLP tests are sent to the U.S. for testing, thus need to include 0.05 for shipping.
Neurological Exam		$44.11	$44.11	CPT 95834
Visual Acuity/Red-Green Color Perception		$15.98	$15.98	CPT 92283

(continued)

Exhibit D-10: Summary of Uganda Cost Inputs for Clinical Trials: Administrative, Treatment, Data Management, and Assessment (continued)

Costs	Cost for Phase I Trials	Cost for Phase II Trials	Cost for Phase III Trials	Source
Electrocardiography	$20.00			Based on data provided by John Johnson and Marla Manning of CWRU
General Health Panel	$34.19	$34.19	$34.19	Based on data provided by John Johnson and Marla Manning of CWRU
Hepatitis B screening	$5.75	$5.75	**$5.75**	Based on data provided by John Johnson and Marla Manning of CWRU
HIV Antibody Screening	$4.75	$4.75	$4.75	Based on data provided by John Johnson and Marla Manning of CWRU
Urine Toxicology Screen for Alcohol and Illicit Drugs	$5.00	$5.00	$5.00	Based on data provided by John Johnson and Marla Manning of CWRU
Serum and Urine Testing for Beta-Human Chorionic Gonadtropin Test (females)	$7.00	$7.00	$7.00	Based on data provided by John Johnson and Marla Manning of CWRU

CWRU = Case Western Reserve University

Source A: Communication with Andrew Vernon (CDC), Zachary Taylor (CDC), Carol Hamilton (Duke University), and Bernard Fourie (South African Medical Research Council)

Appendix E: Summary of Clinical Trial Costs in Developing Countries

This appendix outlines the costs of various Phase I, II and III clinical trials in India and South Africa.

Summary of Phase I, II and III Clinical Trial Costs in Developing Countries (U.S. Dollars)

Country	Trial Description	Costs Included (per subject)	No. of Subjects	Total Cost	Cost per Subject
India[a]	Phase I bioequivalence study comparing two formulations of a new anti-TB agent. Cross-over, single IM dose with 7-day washout period between doses	Subjects were hospitalized for 2 days. Assessments included 22 blood samples per subject, CBC with differential, serum electrolytes, LFTs, audiometery, HIV screen, pregnancy test, urinalysis, physical exam. Included costs for HPLC assay development and validation.	16	$29,000[a]	$1,812
India[a]	Multi-center, Phase III study of a new anti-visceral leishmaniasis compound versus a control	30-day inpatient treatment with a 6-month outpatient follow-up period. Investigator fees were $700 per subject and included all laboratory assessments such as CDC with differential, blood chemistry, LFTs, urinalysis, HIV screen, audiometry, and ECG. Other costs included CRF development, shipping, investigator meetings, data management, reports, and monitor fees.	500	$727,000	$1,454
Africa[a]	Multi-center, Phase III study of new antimalarial compound versus control	3-day treatment with a 14-day follow-up. Investigator fees were $320 per subject and included all laboratory assessments such as CDC with diff, blood chemistry, metheglobin, and PCR analysis. Other costs included CRF development, shipping, investigator meetings, data management, reports, and monitor fees	2000	$1,289,200	$644.60
South Africa (1996)[a]	Phase II EBA Study of new anti-TB agent	3-day study drug administration, hospitalization – 5 days, CBC with differential x 2, blood chemistry x 2, Audiometry, EBA mycobacteriology, Physical Exam, chest X-ray, HIV screen, and urinalysis. Personnel costs included one medical doctor and two nursing staff. Overhead was responsible for 30 percent of the total costs.	120	$140,000	$1,167
South Africa[b]	Phase II EBA Study of a new anti-TB agent	Includes hospitalization for 7 days, sputum level monitoring for 3-6 days. Other costs include laboratory assessments such as ,physical exam, x-ray, hematology, blood, data collection and storage, subject reimbursement of $150 per subject, bacteriological studies, and department overhead. Does not include monitoring or data validation.	13	$33,638	$2,678
South Africa[b]	Phase III single-center trial of a new anti-TB agent	A 3-year trial with a 6-month assessment period. Costs include consumables, administrative services, travel, computer costs, maintenance, capital equipment, laboratory costs, and ½ of all staff costs. Costs for monitoring, hospitalization, and ½ of the clinical trial staff are not included.	400	$600,000	$3,525

[a] Average cost to WHO TDR. Does not include overhead costs, or costs for IRB review (personal communication with Tom Kanyok of WHO).

[b] Figures reported by Bernard Fourie of the South African Medical Research Council. Costs include $15 per patient per day for indirect government or other TB subsidies. Costs do not include cost of data monitoring, etc., which would be contracted out and may double the cost of the clinical trial.

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