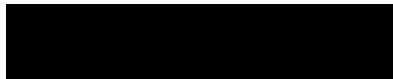


executive summary for the
economics of
TB Drug Development



THE GLOBAL ALLIANCE FOR
TB Drug Development



The Global Alliance for TB Drug Development is a not-for-profit organisation created to accelerate the discovery and development of new drugs to fight TB. It is one of a new breed of public-private partnership that pursues a social mission by employing the best practices of the private sector and by drawing upon resources from the public and private realms. To achieve its vision of the provision of new medicines with equitable access for the improved treatment of TB, the Global Alliance functions as a lean, virtual research and development organisation that outsources R&D projects to public or private partners.

More information about the Global Alliance for TB Drug Development is available online: www.tballiance.org

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Introduction



The Economics of TB Drug Development provides data required for industry, philanthropic foundations, and global financial and health organisations to make informed decisions about investing in TB drug development. The result of 12 months of expert research, analysis, and consultations, the report explores the economic obstacles and opportunities in TB drug development and provides novel data, analyses of recent trends, and calculates the financial and social benefits of developing new drugs.

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

Tuberculosis is a leading threat to global health, infecting one-third of the world's population. Every year, an additional 30 million people are infected with the bacterium, and 8 million people develop the active disease. TB takes the lives of nearly 6,000 people a day. It kills young and middle-aged adults faster than any other disease apart from AIDS. It also is the leading cause of death of HIV-positive people worldwide. The incidence of the disease is rising yearly. In 2001, TB will kill more people than any previous year in history.

Although TB is treatable, current drugs have limitations that are contributing to the spread of the disease:

- ▶ A treatment duration of at least 6 months is required.
- ▶ The most effective strategy for treating TB—DOTS (directly observed treatment, short-course)—is cumbersome, labour intensive, and expensive, particularly for such a long treatment regimen.
- ▶ Strains of TB that are resistant to more than one of the first line of anti-TB drugs—that is, multidrug-resistant TB (MDR-TB)—have become more prevalent in recent years, and second-line drugs are not as effective as the standard therapy and are more toxic and expensive.
- ▶ It is important to treat latent TB infection (LTBI)—that is, infection with *Mycobacterium tuberculosis* but not active disease—in certain high-risk patients, such as those coinfecting with HIV; however, the standard LTBI treatment regimen lasts from 2 months to 12 months, depending on the medicines used.

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.

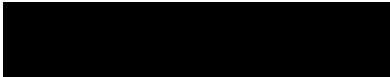
Dr. Harvey E. Bale, Jr., Director-General
International Federation of Pharmaceutical Manufacturers
Associations (IFPMA)

The current anti-TB drugs, although effective when properly administered, ultimately cannot win the fight against the tuberculosis epidemic.

To control the TB epidemic more effectively, new drugs are urgently needed: new compounds that (1) shorten the duration of treatment to 2 months or less and/or significantly reduce the number of doses needed to be taken under DOTS supervision, (2) improve treatment of multidrug-resistant strains, and (3) provide a more effective treatment of LTBI to prevent the progression from infection to disease.

Despite this need, no new class of anti-TB drug has been introduced in over 30 years, and TB has been a neglected disease. The Global Alliance for TB Drug Development believes that TB research and development (R&D) remains low, at least in part, because the real size of the market and costs for drug development are not fully understood.

In order to stimulate interest in R&D for new anti-TB drugs in the pharmaceutical industry, the Global Alliance for TB Drug Development commissioned a study into the economics of TB drug development. It sought to examine the epidemiology of TB, the market for TB drugs, the costs to develop TB drugs, the potential return on investment, and essential trends that are affecting the TB drug development environment.



We believe that this research into the economics of anti-TB drugs will reinvigorate the interest of the pharmaceutical industry and public research organisations in the battle against a disease that is not only a tremendous burden to the poorest countries but also a threat to all nations.

Dr. Giorgio Roscigno
Global Alliance for TB Drug Development

The Economics of TB Drug Development is a groundbreaking analysis that ultimately may alter the status quo with regards to TB drug development and enable the introduction of new compounds for a new, faster acting, more effective, and affordable TB treatment by the end of the decade. This Executive Summary provides a synopsis of the full *Economics* report.

The Burden of Tuberculosis

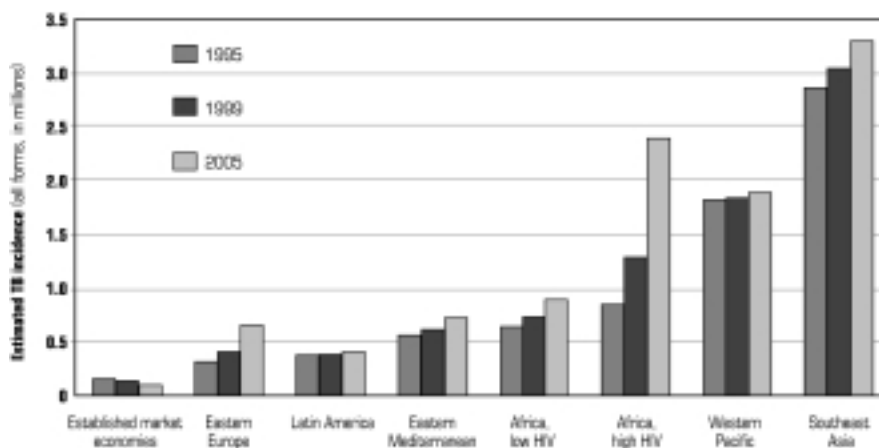
1



According to the World Health Organization (WHO), the estimated number of new TB cases worldwide in 1999 was 8.4 million.¹ However, TB incidence varies dramatically around the world. Twenty-three countries accounted for 80% of the world's new cases in 1999: Afghanistan, Bangladesh, Brazil, Cambodia, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Peru, Philippines, Russian Federation, South Africa, Thailand, Uganda, United Republic of Tanzania, Viet Nam, and Zimbabwe. By far the largest number of estimated cases were in India (1.8 million) and China (1.3 million), representing more than one-third of the world's TB cases.

WHO projections indicate that the number of TB cases will increase worldwide except for countries with established market economies (Exhibit 1). 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 global number of new cases will increase to 10.2 million in 2005 and to 11.6 million in 2010.**

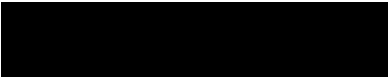
Exhibit 1: Estimated Number of New TB Cases by Region: 1995, 1999, and 2005



Source: WHO¹

1.1 Estimated MDR-TB Trends

The number of new TB cases worldwide in 2000 that are resistant to two or more drugs in the standard regimen (i.e., MDR-TB) is estimated to be roughly 273,000.² Many more cases are resistant to at least one drug, as suggested by a survey conducted by WHO and the International Union Against Tuberculosis and Lung Disease.³ This survey found that, among new TB cases, the median proportion that were resistant to at least one drug was 10.7%. This would mean that **1 in 10 cases of TB harbours resistance to at least one of the currently available anti-TB drugs.** Countries that showed a significant increase in the proportion of new cases with resistance to at least one TB drug included Estonia, Denmark, Peru, New Zealand, and Germany. The problem of drug resistance also persists in several Eastern European countries. 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, only half have relevant data available regarding drug resistance, so the magnitude of the problem is unclear.



1.2 Estimated LTBI Trends

Treating latent TB infection 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 them will never progress to active TB (unless they also are HIV-positive), it has not been thought practical or efficient to establish programs to treat them.

Individuals who are HIV-positive are highly susceptible to tuberculosis and, in turn, active TB disease boosts HIV levels in the blood. Current estimates are that about 12 million adults are living with HIV-TB coinfection, but probably fewer than 5% (30,000) are currently given treatment for LTBI. However, some initiatives suggest that this figure might increase in the coming years. For example, a new WHO initiative in sub-Saharan Africa—ProTest—promotes voluntary counselling and testing for HIV as an entry point for a range of HIV and TB prevention and care interventions.⁴ With the concern over HIV-TB coinfection, **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 around 1 million to 2 million per year over the next decade.**

In countries with a low HIV prevalence, around 110,000 cases of TB are currently detected each year,¹ and perhaps 50,000 of these arise in immigrant and other high-risk populations. 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. An upper boundary for this estimate might be 1.25 million people treated per year, assuming a goal of 50% reduction in TB burden and depending on the efficacy of the treatment.

1.3 Average Public Sector Health System Costs

Health care expenditures associated with TB can be estimated by using data on (1) the unit costs of services required to diagnose and treat TB and (2) the numbers of these services provided to treat an infectious case of TB. Exhibit 2 presents the estimated public sector health system costs per treated case for selected countries. **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—ranging from \$7 in India to nearly \$800 in the United States—make up only a small fraction of the per-patient total costs for TB treatment.

Upon considering the per-patient treatment costs presented in Exhibit 2 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

Exhibit 2: Estimated Public Sector Health System Costs per Treated Case of Infectious TB (in \$US)^a

	Total	Drugs
Bangladesh	\$64–\$319	\$33
China	\$61–\$75	\$18
Egypt	\$164–\$981	\$75
Ethiopia	\$71–\$94	\$33
India	\$57–\$201	\$7
Indonesia	\$51–\$111	\$33
Kenya	\$345–\$579	\$43
Myanmar	\$68–\$82	\$43
Peru	\$189	\$30
Russia	\$1,115–\$1,395	\$83
South Africa	\$1,350–\$1,486	\$55
Syria	\$183–\$353	\$73
Thailand	\$219–\$280	\$43
U.K.	\$9,029	\$200
U.S.	\$10,376–\$25,117	\$797
Uganda	\$430–\$541	\$32
Zimbabwe	\$148–\$164	\$43

^a Drug costs are conservatively estimated using public/tender prices (see Section 2).

Sources: Totals were calculated based on estimates of health care usage and the unit cost data presented in published costing studies;^{5–13} 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 review of national plans and guidelines.

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 of TB treatment 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.**

These health system and drug costs should be considered lower bound estimates, as many additional costs are associated with TB control. Furthermore, drug costs included in Exhibit 2 are the costs for drugs bought in the public/tender market for use in the public health system. Private sector drug prices (i.e., prices in pharmacies and hospitals) are higher. Section 2 discusses the differences between the private and public/tender markets further.

Market for TB Drugs

2



photo credit: WHO/TDR/Grump

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.

The potential market for a new anti-TB drug is estimated to range from \$316 million to \$432 million (\$US). This range is based on several assumptions as summarised in this section and thoroughly discussed in the full report.

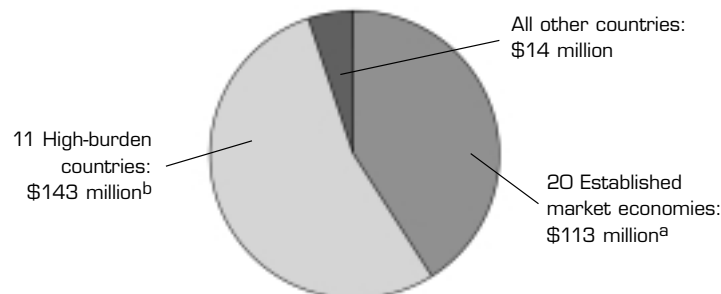
2.1 Estimated 2000 Market for Anti-TB Drugs

To estimate the current market for anti-TB drugs, one must consider sales of these drugs in the private market and in the public/tender market. As discussed in this section, **the current total global market for anti-TB drugs is estimated to be between \$412.5 million and \$470.5 million.**

2.1.1 Private Market

According to data on anti-TB drug sales provided by IMS Health,* the global private market for anti-TB drugs has been relatively stable between 1997 and 2000. **Annual dollar volume of anti-TB drug sales worldwide in 2000 was nearly \$275 million.** As presented in Exhibit 3, this private market was split almost evenly between countries with established market economies and countries with a high TB burden. However, it should be noted that recent private market sales data were available for only 11 of the 23 countries with a high TB burden. Calculations based on the percentage of all new TB cases represented in these 11 countries suggest that **the total private market for anti-TB drugs could total as much as \$318 million.**

Exhibit 3: Proportion of \$275 Million (\$US) in Private-Sector TB Drug Sales in Various Countries (2000)



^a Australia, Austria, Belgium, Canada, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Republic of Korea, New Zealand, Norway, Portugal, Spain, Switzerland, United Kingdom, and United States

^b Bangladesh, Brazil, China, India, Indonesia, Pakistan, Peru, Philippines, Russian Federation, South Africa, and Thailand

Source: IMS Health

*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>).

According to 1998 data from IMS Health, the majority of the private anti-TB drug market (59%) is shared by Aventis, Novartis, American Home Products, Lupin Industries, and Pharmacia. Indian producers of generic formulations make up about 12% of the private market, while the remaining 29% of the private market is shared by a number of smaller, independent producers worldwide.

2.1.2 Public/Tender Market

Conservative estimates suggest that the public/tender market for anti-TB drugs is at least \$125 million to \$140 million.* It is believed that approximately \$40 million to \$60 million of this total is being provided by international donors. 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, which 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 sold 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.

2.1.3 Market for Drugs to Treat MDR-TB

The number of new MDR-TB cases worldwide in 2000 is estimated to be roughly 273,000.² **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. This total was calculated according to the drug prices for treating MDR-TB organisms that are resistant to only two drugs. Therefore, it is assumed that the market would be substantially higher if these patients were treated with the more expensive regimens needed to treat four- and six-drug resistance.

2.1.4 Market for Drugs to Treat LTBI

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

* 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).

being treated for LTBI due to their HIV status, being immigrants, or being in other high-risk populations (e.g., health care workers).

The 2000 market for drugs to treat LTBI is estimated to be approximately \$17 million. This total is included in the total anti-TB drug sales in the private market.

2.2 Estimated 2010 Market for Anti-TB Drugs

As shown in Exhibit 4, **the anti-TB drug market in 2010 is projected to be between \$612 million and \$670 million.** This projection is based on several assumptions:

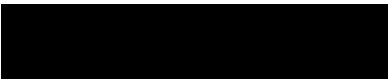
- ▶ The private market in 2000 will remain the same to 2010, except for the treatment of LTBI (see fourth assumption).
- ▶ The public/tender market will increase as DOTS coverage continues to expand, enabled in part by the Global TB Drug Facility's expected annual contribution of approximately \$50 million.
- ▶ While the total number of MDR-TB patients is assumed not to increase, the relative market will increase due to DOTS expansion, which would result in an increase in the percentage of MDR-TB patients diagnosed and treated.
- ▶ The market for drugs to treat LTBI will increase due to increases in the percentage of patients treated.

Exhibit 4: Estimated Market for TB Drugs in 2000 and 2010 (\$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 Global TB Drug Facility's expected annual contribution of approximately \$50 million.
- The market for MDR-TB drugs will increase due to increases in the percentage of patients treated.
- The market for drugs to treat LTBI will increase due to increases in the percentage of patients treated.



2.3 Potential Market for a New Anti-TB Drug

The potential market for a new anti-TB drug can be considered making several assumptions of how the new drug might affect annual expenditures for anti-TB drugs in 2010:

- ▶ 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.

With the above assumptions, **the potential market for a new anti-TB drug is estimated to be at least between \$316 million and \$345 million**, as detailed in Exhibit 5.

Exhibit 5: Estimated Potential Market for a New Anti-TB Drug Introduced in 2010 (\$US)^a

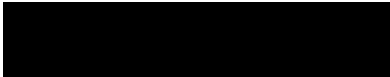
Market	Market Available for Current Drugs If No New Drug Is Introduced	Market Available for New Drug ^b	Market Available for New Drug If Some Markets Pay Premium ^c
Private (excluding LTBI)	\$258M–\$301M	\$129M–\$150.5M	\$174.2–\$203.2M
Public/Tender	\$175M–\$190M	\$87.5M–\$95M	\$87.5M–\$95M
MDR-TB drugs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

^a Market estimates are only a projection based on specific assumptions. Different assumptions would yield a different potential market.

^b **Assumptions**

- 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.

^c A 35% premium (at a minimum) is assumed in the private, MDR-TB, and LTBI markets (see p.14). No premium would be charged in the public/tender market for active TB.



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. **If a minimum premium of 35% is charged in all but the public/tender market, the estimated potential market for a new anti-TB drug increases to between \$396 million and \$432 million.** 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 could be substantial.

Estimating Drug Development Costs

3

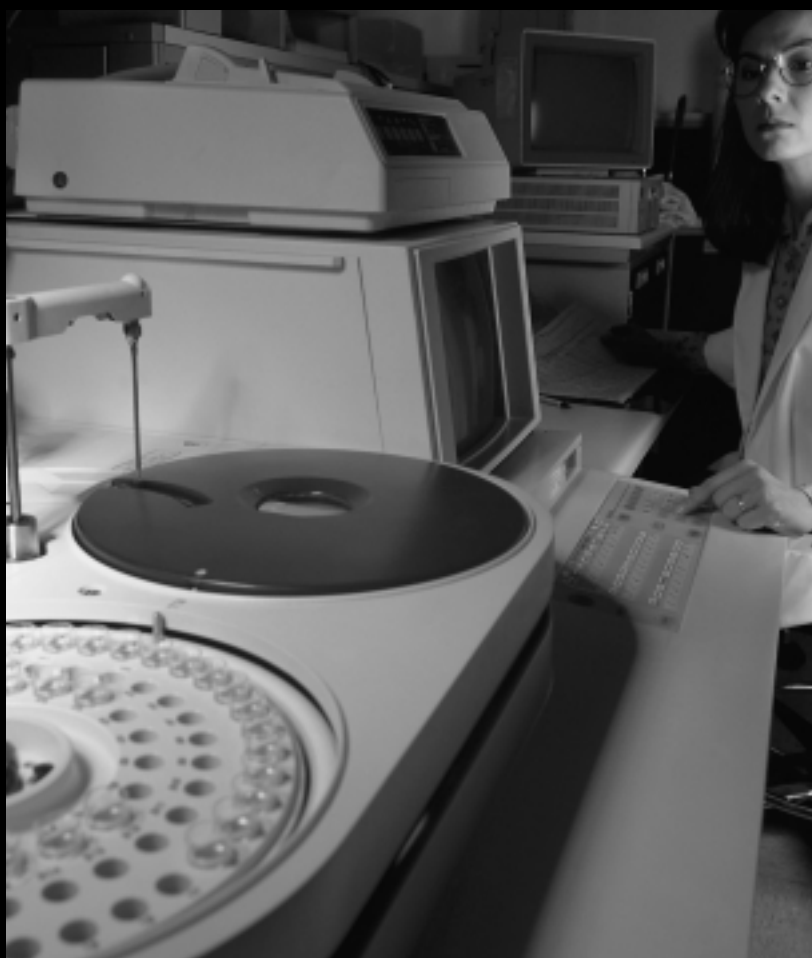


photo credit: WHO/TDR/Grump

The costs of developing a new chemical entity (NCE) to treat TB include the value of the purchased resources plus the value of company-owned resources employed in the effort from discovery through preclinical studies, 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 *Economics* report developed all cost estimates based on the assumption that all components of the drug discovery process are contracted out.

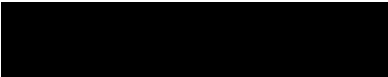
Furthermore, all cost estimates are TB-specific and based on the development process outlined in the *Scientific Blueprint for TB Drug Development*, published by the Global Alliance for TB Drug Development.¹⁴

As discussed in this section, **the costs of successfully developing an NCE to treat TB have been estimated to total approximately \$36.8 million to \$39.9 million (U.S. costs, excluding costs of failure)**. This estimated range covers preclinical development (\$4.9 million to \$5.3 million), pharmaceutical development (at least \$5.3 million), and Phases I through III of clinical development (\$26.6 million). All of these efforts are designed to reach regulatory approval.

An alternative approach to arrive at estimates of total development period costs is to include the costs of unsuccessful projects.¹⁵ Under this method, **estimates of the costs of developing an NCE are approximately \$76 million to \$115 million, including the costs of failure** and depending on development time and discount rate, 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 the costs for total discovery and development. **The estimated costs of discovering and developing a new anti-TB drug (including the costs of failure) are between \$115 million and \$240 million.** 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 (see Section 5.1).

3.1 Estimating Discovery Costs

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.¹⁶ 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,¹⁶ 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.



3.2 Estimating Preclinical Costs

The preclinical studies used to calculate costs are those likely to be needed for an NCE that has not been previously evaluated in preclinical or clinical studies. Proposed studies include adequate toxicology studies to allow at least 6 months of clinical administration as well as to satisfy all of the requirements for regulatory approval. Also proposed are pharmacokinetic and absorption, distribution, metabolism, and elimination (ADME) studies. The proposed studies have been based on recommendations presented in manuscripts^{17,18} as well as in guidance documents provided by the Food and Drug Administration¹⁹ and the European Agency for the Evaluation of Medicinal Products.²⁰ Cost estimates were obtained from a survey of contract research organisations specialising in microbiology, toxicology, and drug metabolism. Due to these organisations' lower recharge costs, these costs might appear lower than average costs at larger, research-based pharmaceutical companies.

The total costs of 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. A breakdown of the costs for various stages of preclinical development is as follows:

- Microbiological studies required to evaluate the activity of a drug candidate would cost at least \$406,350.
- Preclinical safety studies to characterise toxic effects and determine the feasibility of continuing studies would cost at least \$3.88 million.
- Pharmacokinetic and ADME studies would cost between \$575,000 and \$840,000.

It should be noted that not all of the proposed preclinical studies need be initiated prior to entry of the drug candidate into the clinical setting. In addition, actual costs and development time are dependent on the drug candidate as well as on the number of major metabolites.

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

In general, the overall costs for the CMC development program are estimated to be at least \$5.3 million, although Paraxel's 1999 *Pharmaceutical R&D Statistical Sourcebook* suggests that these costs could be as high as \$8 million.²¹ The estimate includes the following elements:

- Manufacture of bulk drug substance to produce the supply of the active pharmaceutical ingredient 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 estimated costs should be considered an approximation based on previous development costs for marketed drugs. Factors such as development timelines, the complexity of the synthetic route, cost of chemical intermediates, amounts of drug product needed for clinical testing, or other factors could significantly alter the development costs.

3.4 Estimating Clinical Costs

For this report, researchers estimated the costs for a full program of clinical trials for a new anti-TB agent, including Phase I to Phase III trials conducted in an established economy and in a country with a developing economy. The studies include testing a new TB agent in 1,368 patients over all phases of clinical trials. **In an established economy, the clinical trials were estimated to cost \$26.6 million and to take 7 to 10 years to complete. Comparable studies in a developing economy were estimated to cost \$9.9 million.** The costs related to the probability of failure are not included in these cost estimates.

From the initial Phase I trial of a new TB agent in humans, it is estimated that it will take approximately 10 years to gain regulatory approval. Time savings of up to 3 years might be possible if some Phase I trials are conducted concurrently, or if provisional regulatory approval is sought following completion of the 6-month drug therapy or after completion of 6 months of the total 24-month follow-up period.

Financial and Social Returns on Investment in TB Drug Development

4



The information summarised in the preceding sections—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. For other investors, especially those in the public sector, a new 2-month anti-TB drug is expected to provide substantial benefits to health care systems and public health as well as to patients, their families, and their communities.

4.1 Internal Rate of Return

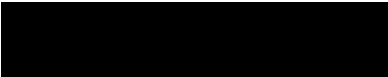
IRR is defined as the rate of return that equates the discounted stream of income to the discounted stream of costs generated by an investment.²² In their analysis of the internal rate of return for new drug introductions in the first half of the 1980s, Grabowski and Vernon found that the mean IRR was 11.1%.^{23,24} 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 1983.²⁵

Depending on where the clinical trials are conducted, the pace of development, and the size of the revenues, the IRR for a new anti-TB drug is estimated to range from 15% to 32%. Exhibit 6 presents the IRR for various scenarios. 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.

Exhibit 6: Internal Rate of Return for a New Anti-TB Drug

Scenario			Internal Rate of Return
Economy in Country Conducting Drug Development	Pace	Revenue	
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%

Note: The IRR shown here is based on many assumptions (see the full report *The Economics of TB Drug Development*). Changes in any of these assumptions will affect the IRR.



4.2 Social Returns

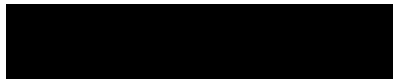
New TB drug development will bring significant public health and socio-economic benefits worldwide. Improvement would be tied mostly to the improved compliance likely to occur with a new drug that shortens the regimen to 2 months and/or requires less intensive supervision.²⁶

The potentially profound reduction in disease burden will result in improved treatment success rates, reduced overall treatment costs, possible reduction in the number of MDR-TB cases, decreased morbidity and TB transmission in the long term, and decreased medical and nonmedical costs for long-term TB treatment.

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—include the following:

- ▶ 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 is expected to reduce total per-patient treatment costs, even if total drug costs 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 program 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 new, shorter TB treatment also 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.



Essential Trends and Opportunities for TB Drug Development

5



After three decades of limited investment by the private sector in researching new classes of anti-TB compounds, new opportunities are being offered by the promises of new science. Furthermore, a number of trends in public-private partnerships, public policy, philanthropy, and private sector involvement in TB care are affecting the market for anti-TB drugs. These trends and developments are summarised in this section.

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

The public sector is increasingly investing in TB basic sciences and operational research but lacks the infrastructure and know-how for R&D that private industry has mastered in the past century. The need for collaboration is self-evident, and public-private partnerships are changing the economics of drug development. Public-private partnerships can combine their resources and strengths to help improve the health of the poor, particularly in R&D for neglected diseases.²⁷ Public agencies can complement their own capabilities by working with the private sector, whose capabilities fall in other areas (e.g., preclinical development, production process development, manufacturing, marketing/distribution).

The Global Alliance for TB Drug Development is a public-private partnership established by a wide range of stakeholders to bring together public and private sector TB drug R&D resources and expertise. Its vision is the provision of new medicines with equitable access for the improved treatment of TB. Its mission is to accelerate discovery and/or development of cost-effective new anti-TB drugs that will shorten or simplify TB treatment, provide for more effective treatment of MDR-TB, and/or improve the treatment of LTBI.

The Global Alliance stimulates and enrolls research capacity and resources on all continents. Functioning as a lean R&D organisation, it develops a portfolio of new drugs, outsourcing its R&D to private labs and public research outlets, providing funds, some infrastructure, and scientific and management expertise.

Exploring innovative intellectual property strategies to balance access and incentives, the Global Alliance pursues two complementary goals: (1) retaining the ability to deliver new anti-TB drugs equitably to those areas most in need and (2) encouraging private industry to help develop new TB indications.

The R&D partners of the Global Alliance for TB Drug Development include private industry firms, academic institutions, public research organisations, researchers in TB-endemic countries, nongovernmental organisations (NGOs), and regulatory agencies. The Global Alliance will capitalise on the initiatives of its partners and develop further partnerships with academic, private, and public sector researchers and investigators worldwide.

5.2 On the Public Policy Agenda

A number of developments are occurring on the public policy agenda that ultimately might transform the context of TB control and R&D for anti-TB drugs:

- ▶ **Commitment of High-Burden Countries:** At a March 2000 Ministerial Conference on Tuberculosis and Sustainable Development in Amsterdam, representatives from 20 high-burden countries comprising 80% of the global TB burden committed themselves to accelerate action against TB.
- ▶ **G8 Commitment:** In its July 2000 communiqué in Okinawa, the Group of Eight nations committed 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 2010.²⁸
- ▶ **Mobilisation:** Even in lower burden countries, various institutions have highlighted the threat of TB and called for mobilisation. For example, in the United States, the Council on Foreign Relations highlighted global health as an emerging new dimension to the foreign policy interests, and the Institute of Medicine recommended an “aggressive, multi-step strategy to short-circuit the cycle of TB resurgence in the United States.”
- ▶ **Research and Investment Plans:** The European Council has committed to strengthening and increasing financial support for TB R&D and has recognised the need to strengthen capacity in countries with developing economies and to provide incentives for the development of specific global public goods.²⁹ The U.S. National Institutes of Health is expanding its focus on basic and applied research to prevent, diagnose, and treat TB,³⁰ and increased funding from the U.S. Congress has been proposed.
- ▶ **Public Policy Debates:** The necessary role of the public sector in enabling the environment for drug R&D aimed at infectious and neglected diseases is now widely acknowledged, and public policy debates centre around the “push” and “pull” mechanisms to be put in place. One such example is the UK Cabinet Office report published in May 2001, discussing models for balancing issues of intellectual property and access/equity.³¹ The 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 intellectual property rights and access. It also calls for incentives for R&D into TB to be strengthened and for additional policies to establish the purchasing power of the market.

Most recently in public policy, the Global Fund for AIDS and Health was announced in July 2001 with total initial funding of about \$1.2 billion. The fund is aimed at tackling infectious diseases such as AIDS, malaria, and TB in developing countries. In addition, the Stop TB Partnership, a global movement to accelerate social and political action to stop the spread of TB, will unveil its Global Plan to Stop Tuberculosis in October 2001.

5.3 On the Philanthropic Agenda

Developments in the philanthropic sector should be of interest to industry and other TB stakeholders, as well. Several major philanthropic institutions have embraced the global health agenda and seek to accelerate the development of innovative approaches while engaging in the public policy debate. Additionally, new philanthropic initiatives adopting a “social venture capital” model are well suited to the task of coaching and supporting the development of public-private R&D partnership since they seek to strengthen socially responsible initiatives while applying entrepreneurial principles to the nonprofit world.

5.4 Private Sector Involvement in TB Care

Finally, the increasing role of the private sector in treating tuberculosis is an important development in the nature of the TB drug market. This increased role is discussed in a 2001 report published by WHO.³²

The private sector is an important source of care, even for the poor and even where public services are widely available.^{33,34} 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 private providers manage a large proportion of the unreported majority.

Studies investigating TB patients’ help-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.^{35–39} Furthermore, a substantial proportion of TB cases are treated by private providers. About 50% of TB cases in India are treated—partly or fully—in the private sector.³⁶ These alone account for one-sixth of world’s burden of TB. In South Korea, 47% of cases are treated by private providers.⁴⁰ A similar situation prevails in many high-burden countries.

The WHO report was presented and discussed with a consultation of experts in Geneva in August 2000.³² The group endorsed the report and made several recommendations for further public-private collaboration. These recommendations suggest that the involvement of private providers in the treatment of TB will increase in the future.

New Data Challenge Common Myths

The wealth of data presented in *The Economics of TB Drug Development* serves to dispel many myths long associated with TB, the need for new drugs to improve its treatment, and several issues tied to new drug development.

Myth: TB is an epidemic of the past.

Fact: In 1999, an estimated 8.4 million people around the world developed active TB, more than any year in history.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.

Fact: The TB and HIV epidemics are dangerously fuelling each other. People with HIV-TB coinfection are 30 times more likely to develop active TB than people who are HIV-negative. The number of people coinfecting with TB and HIV was approximately 10.7 million in 1997 and is expected to increase dramatically in the coming years. TB cases in Africa are likely to double over the next decade because of the spread of HIV/AIDS.

Myth: There is no unmet medical need because TB is curable with currently available drugs.

Fact: Current drugs impose long treatment durations that are hindering the progress of TB control. After a decade-old global effort, only a fraction of the TB patient population receives full and effective treatment under DOTS. The effective but labour-intensive directly observed process is a challenge to maintain with long treatment durations.

Fact: TB threatens to spin out of control, both in terms of deaths and costs, if multidrug resistance increases. High rates of patient nonadherence in suboptimal conditions—partly because of the length of treatment—have led to increased mortality and the creation of chronic, infectious drug-resistant cases for which most drugs are ineffective and/or toxic.

Fact: New sterilising drugs (i.e., medicines that destroy the *M. tuberculosis* bacterium while it is still in its latent stage) with shorter regimens are needed for those most at risk of having latent TB infection develop into active TB. Preventive treatments with current drugs are long, cumbersome, and poorly followed.

Myth: The market for a new anti-TB drug is small in size.

Fact: The current global market for anti-TB drugs is estimated to be between approximately \$412.5 million and \$470.5 million. This global market is expected to increase to an estimated \$612 million to \$670 million by 2010.

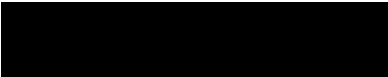
Fact: At a minimum, a new anti-TB drug that enables a 2-month treatment regimen might be able to capture a market of between approximately \$316 million and \$345 million. This estimate is based on several assumptions.

Fact: Some markets might be willing to pay a premium for the new anti-TB drug if it enables a shorter treatment than is allowed by current pharmaceuticals. Depending on which markets pay a premium and how high the premium is, the market for a new anti-TB drug might expand to at least an estimated \$396 million to \$432 million.

Myth: The TB market is complex to access, run through fragmented public tenders only.

Fact: The current global market for anti-TB drugs includes a sizable \$275 million to \$318 million worldwide private market. Furthermore, the private sector is playing an increasing role in TB treatment.

Fact: Renewed interest from donors and high-burden countries as well as initiatives such as the Global TB Drug Facility are expected to help secure the public/tender market.



Myth: The costs to develop a new anti-TB drug are too high.

Fact: The actual costs—without factoring the costs of failure—to bring a lead compound from preclinical development to regulatory approval are estimated to total between approximately \$36.8 million and \$39.9 million. An alternative approach that includes the costs of failure estimates that the total cost is approximately \$76 million to \$115 million (depending on total development time and discount rate).

Fact: Discovery costs 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).

Fact: Public-private partnerships, such as the Global Alliance for TB Drug Development, are providing opportunities to share the costs and risks of investing in TB drug development.

Myth: Investments into a new anti-TB drug could not be recouped.

Fact: The internal rate of return for developing 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 revenue generated. This range is calculated on the basis of total development costs from preclinical research through regulatory approval and indicates that investing in development of a lead compound is an attractive commercial venture.

Fact: With the support of public-private partnerships, development costs can be significantly reduced within negotiated agreements to provide access to drugs in high-burden countries while retaining industry incentives. The Global Alliance for TB Drug Development—and the opportunities for partnering that the new organisation and its associated institutions offer—constitute a new incentive for industry to revisit its TB market strategy.

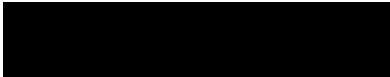
These facts ultimately may alter the status quo with regards to TB drug development.

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