

# **INCENTIVES AND DISINCENTIVES FOR NEW ANTI-TUBERCULOSIS DRUG DEVELOPMENT**

## **SITUATIONAL ANALYSIS**

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## EXECUTIVE SUMMARY

Despite the fact that tuberculosis affects between seven to eight million people per year and causes up to three million deaths, there has been virtually no anti-tuberculosis drug development in over twenty-five years. The current method of treatment endorsed by WHO, DOTS (Directly Observed Treatment, Short-Course) has been demonstrated to have up to a 95% cure rate, but DOTS is labor-intensive and difficult to deliver in developing countries. A new drug that could shorten chemotherapy from its minimum six-months or decrease dosage frequency from daily or thrice weekly would ease treatment and improve disease control efforts.

To analyse the dearth of drug development, the Global Tuberculosis Programme/Tuberculosis Research Unit (GTB/TRS), World Health Organization (WHO), initiated a pharmaceutical industry survey. Thirty-six individuals in 19 companies were interviewed, of which five companies had active or pending tuberculosis research programmes. The exercise revealed the underlying deterrents to tuberculosis research, thereby providing WHO with insight into corporate priorities. Equipped with this information, WHO can better create incentives to motivate and facilitate private-sector involvement in anti-tuberculosis drug development.

### PRIMARY DISINCENTIVE

Most pharmaceutical companies reported that they do not pursue tuberculosis research because of the high investment and lack of perceived commercial return. Other significant disincentives exist and include: the biologic difficulty of working with *M. tuberculosis*, the lengthy development process, the risk of patent violations, the reservation of drug agents solely for tuberculosis treatment, and the aversion to working with governments. Yet the primary disincentive is the perceived absence of financial opportunity; if reasonable profit could be made, the additional disincentives could be overcome. This suggests that to engage the interest of industry in new drug development, the public sector itself must initiate the dialogue and brain-storming sessions needed to address these development obstacles. Industry will not be persuaded to commit resources on a long-term basis unless the convictions they hold, outlined below, are recognised as barriers and are effectively lowered:

- ✓ **DRUG DEVELOPMENT IS COSTLY:** The average cost of developing a drug, from laboratory to market, is \$300 to \$500 million, with the largest expense for clinical trials. The environment is competitive, with companies trying to recoup investment and profit quickly. Big-hitters are aiming for US \$1 billion at peak sales. Due to high development costs, companies measure the price of investment *and* the associated opportunity costs. Relative to other therapeutic areas, tuberculosis research requires long-term scientific commitment and offers uncertain and limited financial reward.

- ✓ **MARKET IS INSUFFICIENT:** The industry estimates that the tuberculosis market is less than \$150 million, although defining 'market size' is a moving target. Targets vary for companies, but many want to generate a minimum US \$200 million per annum. Tuberculosis is considered to be declining in the industrialised world, so companies see no commercial potential. Because 95% of new tuberculosis cases fall in the developing world, industry perceives few patients who could pay high prices.
- ✓ **NOT AN UNMET MEDICAL NEED:** If delivered properly and adhered to, DOTS can cure tuberculosis. Since a cure exists, pharmaceutical companies are not interested in developing another treatment. The occurrence of multi-drug resistant tuberculosis is not compelling enough reason to develop new drugs, particularly as drug-resistance could be avoided if treatment is properly administered and followed.
- ✓ **PRICING PRESSURES ARE STRONG:** The total drug cost of using a DOTS regimen can be as little as \$11, which, when combined with caseload, is too low to generate interest. Companies assume that WHO will pressure them to sell new drugs at the same price or below. To justify higher prices, companies have to develop a product superior to the current regimen, which is scientifically difficult. With anti-tuberculosis drugs, a multi-tiered pricing scheme is considered inevitable, which opens up the risk of parallel importing.

## **ACTIONS TO TAKE**

Most of private industry will not undertake new anti-tuberculosis drug development voluntarily. The public sector needs to mobilise and coordinate efforts, and WHO is uniquely positioned to carry out that task. WHO can pool resources to finance research and development, and establish cross-sectoral links among stakeholders. WHO can also work with public finance institutions to influence governments to improve health infrastructure and build sustainable financing mechanisms, thereby increasing the number of global purchasers. Using 'push' and 'pull' dynamics, WHO can guide drug development outcomes. To reach that end goal, WHO should direct energies to:

### ➤ **BUILD RELATIONSHIP AND NURTURE PREVIOUS/NEW CONTACTS IN INDUSTRY**

WHO cannot tackle this problem alone and industry must be a willing partner. Dr. Gro Harlem Brundtland, Director-General, has initiated reaching out to industry, as is evidenced by the October 21, 1998 meeting with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Bridge-building at high executive levels needs to continue at regular intervals. When formed, the Industry Council should be used as a vehicle to clearly enunciate to pharmaceutical companies where new anti-tuberculosis drugs fall on WHO's priority list, and how these drugs can enhance the DOTS programme. At another level, the Research and Development department of the Communicable Diseases Cluster should maintain dialogue with those companies currently engaged in new anti-tuberculosis drug research to prevent 'drop out'. As these companies move forward, WHO may be instrumental in helping them jump development hurdles. The team can also identify ways that efforts to increase drug development might be modelled after the successes of the *Medicines for Malaria Venture*.

➤ **PROVOKE DISCUSSION, GENERATE IDEAS, DISSEMINATE KNOWLEDGE**

WHO has the political clout to host round-table discussions among academia, government, the donor community and industry. WHO should create a neutral forum to generate novel ideas, brainstorm solutions for incentive-building, and perhaps broker the appropriate partnerships. Working groups can define gaps in the anti-tuberculosis drug development process, identify pressure points and critical junctures for intervention, and prioritise needed actions. Information that is gathered at these meetings should then be shared more broadly so that relevant parties are kept involved and informed, and the problem kept visible.

➤ **HELP BUILD, DEFINE & PROTECT MARKETS**

To address industry's perception of market opportunity, WHO needs to provide better quantification of what the tuberculosis market is, today and in the future. For industry, estimates of global disease burden are insufficient without delineation of where potential customers are, and how these individuals will access and pay for new drugs. Longer term, WHO needs to keep strengthening DOTS programmes and work with government Ministries to build up health infrastructure so that drugs have an avenue for distribution. In addition, WHO should be pressuring governments to place value on financing tuberculosis drugs, where possible, and strongly encouraging them to protect and enforce international patent laws.

➤ **FACILITATE JUMPING DEVELOPMENT HURDLES**

Companies involved in anti-tuberculosis drug development are uncertain where to conduct reliable trials in the developing world. The Research and Development department of the Communicable Diseases Cluster can offer its expertise in identifying clinical trial sites and offer other technical assistance which may help companies contain the cost of implementing trials. This may also give WHO more leverage in negotiating drug prices that are satisfactory to countries and industry. WHO can also work with regulatory agencies and the scientific community to define acceptable alternative, less costly endpoints for clinical trial design.

The recent genome sequencing of *M. tuberculosis* opens up new possibilities for rational drug design, virtual drug screening and drug target identification. Yet the technical progress has not been matched by commercial interest; the tools for drug development exist, but the will does not. The positive energy generated by Director-General Brundtland to work collaboratively with industry should therefore be seized by WHO as offering new possibility. With WHO holding a better understanding of private industry values, the barriers facing new anti-tuberculosis drug development can be cast in new light, with increased hope for creating innovative solutions.



## INTRODUCTION

### DEFINING THE PROBLEM

Tuberculosis is the leading infectious disease killer among adults and youth, with one-third of the world's population infected with *M. tuberculosis*. The World Health Organization (WHO) estimates that active cases of tuberculosis afflict seven to eight million people annually, and lead up to three million deaths per year. Furthermore, a person infected with human immuno-deficiency virus (HIV) is ten times more likely to develop tuberculosis than an HIV-negative individual; consequently, the spread of HIV is accelerating the rise in tuberculosis case rates.

Yet despite these global health conditions, there has been virtually no novel anti-tuberculosis drug development in over twenty-five years.<sup>1</sup> By current drug industry projections, it takes a minimum of ten years, and as many as fifteen, for a new medicine to travel through research and development, pass regulatory approval, and achieve distribution.<sup>2</sup> New therapeutics often first penetrate industrialised markets, as buyers are more willing and able to pay at price levels that match a supplier's desire to sell. Middle and low-income countries will not have access to new therapies until several years later, when prices have declined, although these levels may remain unaffordable. Given that 95% of tuberculosis cases are found in the developing world, this timeline holds grave implications for those countries most seriously afflicted. Assuming research remains sluggish, then countries such as Indonesia or Bangladesh may not access better treatment methods until almost 2020.<sup>3</sup>

Currently, WHO promotes the five-component DOTS strategy as the best approach toward treatment and global tuberculosis control.<sup>4</sup> A study in China has shown that cure rates as high as 95% can be achieved through DOTS implementation, but treatment is labour-intensive and complicated, making it difficult to deliver in developing countries.<sup>5</sup> If DOTS is not adhered to properly, the risk of multi-drug resistance increases. As more multi-drug resistant strains of *M. tuberculosis* are transmitted across populations, drugs

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<sup>1</sup> In June 1998, the United States Food and Drug Administration (FDA) approved rifapentine, the first anti-tuberculosis drug advancement since 1972. Rifapentine is indicated for the treatment of pulmonary tuberculosis and may simplify chemotherapy by decreasing the frequency of drug dosages required.

<sup>2</sup> See Appendix A for estimated drug development timeline in the United States.

<sup>3</sup> As of 1997, Indonesia reported 436,500 new tuberculosis cases and Bangladesh reported 265,000 new cases per year.

<sup>4</sup> DOTS is an acronym for Directly Observed Treatment, Short-course chemotherapy. The DOTS strategy is the encapsulation of results from research and practice from recent years, and is generally recognised as the current best international practice in tuberculosis control.

<sup>5</sup> Murray, C.J.L., "Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis," *The Lancet*. 10 February 1996, pp. 358-362.

currently in our possession become impotent for effective treatment and control. Ultimately, without the advent of improved tools, the longer-term outlook for global tuberculosis control appears grim.

## **PURPOSE OF REPORT**

This report was commissioned by the Global Tuberculosis Programme/Tuberculosis Research Unit (GTB/TRS) of WHO. Prior to the project, GTB/TRS hypothesised that few pharmaceutical companies were actively involved in new anti-tuberculosis drug research, which was confirmed by the data compiled. Additionally, this report strives to answer the following three questions:

- What is the current level of activity in the pharmaceutical industry with respect to new anti-tuberculosis drug development?
- What are the factors influencing a pharmaceutical company's decision to pursue or avoid anti-tuberculosis drug research and development?
- What strategies should be used to stimulate more industry activity in new anti-tuberculosis drug research and development?

GTB/TRS hopes that with a more explicit understanding of the primary incentives and disincentives faced by pharmaceutical companies, WHO will be better equipped to stimulate anti-tuberculosis drug development. The contents of the report are intended to enable WHO to better concentrate on those factors which industry most values.

The report begins with a brief description of current anti-tuberculosis research and development. This section is followed by a summary of major findings, compiled from interviews with pharmaceutical representatives. The report then concludes with an analysis of the themes revealed during the survey process and offers broad recommendations.

## **BACKGROUND ON ANTI-TUBERCULOSIS DRUG DEVELOPMENT**

According to the International Federation of Pharmaceutical Manufacturers Association, the global industry spent US \$25 billion dollars on pharmaceutical research and development in 1995. This matches an assessment made by the Ad Hoc Committee on Health Research (1996 WHO study), which estimated that the global drug industry invested US \$24.7 billion in health research and development in 1992. Of this, US \$400 million was directed to address the health problems of low-income and middle-income countries.<sup>6</sup>

The pharmaceutical biotechnology industry continues to advance rapidly, with a 1998 survey conducted by the Pharmaceutical Research and Manufacturers of America

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<sup>6</sup> On a global level, the Committee estimated that US\$19-33 million was spent in 1992 for private/ public sector research and development in tuberculosis.

(PhRMA) recording 350 biotechnology medicines in development. The report categorises 36 medicines as targeting infectious diseases and 20 as targeting respiratory diseases, with no drug or vaccine specifically indicated for use against tuberculosis.

A report completed for the August 1998 Technical Research Advisory Committee also revealed little activity in the field of new anti-tuberculosis drug development (see Appendix B).

Why the apparent lack of interest in anti-tuberculosis drug research and development? According to several industry studies, including a January 1996 study conducted by the Boston Consulting Group, it is estimated that a pharmaceutical company invests between US \$360 million and \$500 million to develop, license and distribute a new medicine. Assuming that in the best case scenario a new anti-tuberculosis drug could reach all 8 million patients with active tuberculosis, it is probably perceived as unlikely that these patients could pay enough for a company to recoup investment and make a reasonably attractive profit.

But if profitability is the sole factor in a company's decision to develop new therapeutic agents, then the factors in the equation must be altered to change the balance. To effectively combat tuberculosis globally, improved drugs are and will be needed. Because GTB/TRS and WHO do not have the singular capacity to develop new drugs, they must engage pharmaceutical companies in the process. It is for this reason and in this spirit that this project was launched.

## **DOTS AND ITS SHORTCOMINGS**

The DOTS (Directly Observed Treatment, Short-course) strategy is the framework for tuberculosis control that WHO currently recommends. As of 1996, 96 countries had adopted the DOTS strategy. In 63 of these countries, national programmes were estimated to reach 90 percent of the population.<sup>7</sup>

The DOTS regimen lasts a minimum of six months. The initial intensive phase of two months requires four drugs – rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin. All four drugs must be administered either daily or intermittently (WHO recommends three times weekly). The continuation phase can last four to six months, during which rifampicin or ethambutol is combined with isoniazid. If a patient is being re-treated or suffers a relapse, the regimen is seven months and more drugs are given in the intensive and continuation phases.

A World Bank sponsored project executed in China in the early 1990's demonstrated that when DOTS is administered properly, the cure rate can be as high as 95%.<sup>8</sup> Adherence to the full treatment schedule is necessary to achieve high cure rates among the population. However, for some, adherence to full treatment is difficult and many patients stop

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<sup>7</sup> Global Tuberculosis Programme, Global Tuberculosis Control (Geneva: World Health Organization, May 1998), p 1.

<sup>8</sup> Murray, C.J.L., "Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis," *The Lancet*. 10 February 1996, pp. 358-362.

treatment before completing the regimen. Non-compliance is often attributable to programme limitations or failures, such as the lack of steady medicine supply within a country. One important component of DOTS, the “directly observed treatment” requires a health worker to supervise patients swallowing every tablet. As many patients do not adhere to self-administered treatment, this method is the most full-proof way of ensuring that all drug doses are taken in the proper quantity and at the proper intervals. If a patient misses a treatment dose, the health care worker follows up with the patient to prevent drop-out. The DOTS strategy is effective, but it is very labor-intensive and requires a strong health infrastructure.

Current DOTS regimens are challenging to deliver in developing countries. Patients may have to travel long distances to reach the health clinic and may not have access to transportation. Daily or thrice weekly travel to a health centre results in lost time on the job or with family. In areas where payment is required, some patients may be unable to afford the cost of six-month treatment. The country itself may have difficulty transporting the drugs to the hospital or clinic. Barriers such as these lead to treatment interruption, which holds serious consequences. Treatment failures will increase the number of tuberculosis cases and in particular, drug resistant strains. The spread of multi-drug resistant tuberculosis is dangerous, as it dramatically threatens control efforts; existing treatment is expensive and the outlook for recovery less optimistic. Increased cases of multi-drug resistant tuberculosis translate into a loss of global control over the epidemic, as there are so few effective and safe drugs available.

New tools that simplify treatment would make a significant difference to global tuberculosis control efforts. For example, a new regimen that could shorten chemotherapy from its minimum six-month duration or decrease dosage frequency from daily or three times weekly would substantially ease the burden of treatment. Patients would be cured faster, treatment delivery would be less resource-intensive, failure rates would decline and the spread of multi-drug resistance would be contained.

## METHODOLOGY

In addition to conducting ten interviews with WHO staff members within GTB and the Special Programme for Research and Training in Tropical Diseases (TDR), four interviews were conducted with health institutions engaged in the area of tuberculosis drug development.<sup>9</sup> Within industry, 44 individuals from 23 research-based pharmaceutical companies were contacted, of which 36 individuals in 19 companies were successfully interviewed.<sup>10</sup>

Pharmaceutical companies selected for interviews can be divided into three categories:

- Companies known to have active research or development programmes for anti-tuberculosis drugs (based upon best available public information);
- Companies historically active in anti-tuberculosis drug discovery;
- Companies for which anti-tuberculosis drug discovery would be in line with other research efforts (i.e., infectious diseases, respiratory diseases).

Of the 19 companies successfully interviewed, 16 are among the top-twenty ranked pharmaceutical companies for research and development spending.<sup>11</sup> It should be emphasised that a company may fall in more than one category, and that the sample of companies under each category is not exhaustive. Where possible, professional or personal referrals were used to approach individuals.

Contact was initiated through an introductory letter and questionnaire (see Appedix D). Most interviews were conducted by phone and lasted approximately one hour.<sup>12</sup> To allow for candor, interviews were not tape-recorded. All survey questions were posed, but additional questions varied with each interviewee, depending on the content and flavor of the interview.

Though the sampling of companies was not comprehensive, responses and statements did not vary dramatically, offering assurance that viewpoints held across industry are fairly consistent. Of the 19 companies interviewed, three-quarters were not conducting active tuberculosis research programmes. It is therefore assumed that reaching out to more companies would have provided marginally more relevant information about anti-tuberculosis drug discovery.

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<sup>9</sup> This includes the Centers for Disease Control, Food and Drug Administration, National Institute of Health and University of London, Department of Microbiology.

<sup>10</sup> Every targeted interviewee was initially faxed a letter of explanation and an interview request. The letter was then followed-up with a minimum of two phone calls to request interviews. 'Failed' interview scheduling was due to either phone calls being unreturned, or people on travel who did not respond before the project deadline.

<sup>11</sup> Refer to Appendix C for a 1997 ranking of the top twenty pharmaceutical companies.

<sup>12</sup> Personal visits were made with Chugai Pharmaceutical, Eli Lilly, Glaxo Wellcome, Hoechst Marion Roussel, Novartis, Rhône-Poulenc Rorer, Roche, SmithKline Beecham and Stanford Rook.

Because of the qualitative nature of this analysis, the report is a collection and synthesis of the major themes that arose from interviews and draws a general picture of the constraints and wishes of industry as a whole. The report is a summary of what private drug industry overall is *thinking*, although any given company may not have raised each point as an issue.

## INTERVIEW FINDINGS

Tuberculosis is life threatening, but it has no commercial lure.

Interviewee

It's a major problem today, the disease tuberculosis. (The lack of new drug development) is not a problem of interest, it's a problem of strategy.

Interviewee

We live in a world where economics determine research investments.

Interviewee

### PRIMARY DISINCENTIVE

There is little industrial research activity directed towards anti-tuberculosis drugs. Of 19 companies interviewed, three companies were conducting active research on novel agents and two companies had initiated significant projects but have put additional research on hold pending clinical trial results. The remaining 14 were not funding active tuberculosis research programmes, although some companies continue to screen compounds secondarily for anti-mycobacterial activity.

Why is new anti-tuberculosis drug development not considered a priority research area? From interviews conducted with pharmaceutical representatives, it is apparent that companies hold common principles in corporate decision-making. The field of tuberculosis research is seen to require significant investment with no guarantee of success. New anti-tuberculosis drug development necessitates clearing high scientific and regulatory hurdles, and the financial return is anticipated to be both uncertain and minimal. In a world of limited resources, where companies must measure opportunity costs, tuberculosis research fares poorly in comparison to work on other anti-infectives. In deciding where to allocate resources, a company will invest funds where shareholders maximise return while minimising risk.. As captured one interviewee, "Fundamentally, from a business point of view, return on investment is a major, major problem." This

primary disincentive can be best understood when disaggregated into four core positions taken by industry, as follows.<sup>13</sup>

## **DRUG DEVELOPMENT IS COSTLY**

Estimates of the cost of drug development – from discovering a lead molecule through manufacturing a product for distribution – fall within the range of \$300 million to \$500 million dollars. The bulk of these costs is incurred during the clinical trial phase, rather than in the earlier discovery phase. For every lead compound that is successfully developed into a new medicine, thousands of molecules -- if not tens of thousands – fail to reach production; hence, the cost of development is a rough average of total research and development expenditure relative to the number of new products launched.

The industry environment is highly competitive, with companies as large as Roche and Glaxo Wellcome aiming to introduce only two or three new products each year. If fortunate enough, at least one of these products will completely ‘new’ – derived from pure research as opposed to an extension of an existing product.. Because of the extreme challenge, pharmaceutical companies aspire to ‘hit it big’ with a blockbuster product. According to one interviewee, “There is an increasing pressure to pick winners.”

Drug patent life is usually 20 years, so assuming ten years in the research and development phase, a company can have ten years of market exclusivity for its product to recoup investment costs and generate a satisfactory return. Companies are trying to maximise their sales revenue as fast as possible, with the very largest companies aspiring to capture one billion dollars in sales by Year Five, when product sales usually hit peak levels. As a standard, companies are seeking to generate \$300 million to \$500 million per annum at maximum sales. Although financial goals may vary across companies, the principle is generally uniform:

- ✓ The goal is to reach \$300 to \$500 million per year, after 3 to 5 years. The company will settle for \$200 million to \$300 million, at a minimum.
- ✓ If the company invests in research, it needs drug sales and benefits. Drug sales of \$100 million is not acceptable.
- ✓ After 5 to 7 years in the market, the company wants to achieve \$350 million in peak sales.
- ✓ A company nowadays won’t get involved in anything where at the peak of sales it’s less than \$100 million per year.
- ✓ In 1994, the goal was \$200 million, 3 years after introduction. Now in 1998, \$350 million in sales is a precondition. If it doesn’t have that potential, a compound doesn’t survive.

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<sup>13</sup> It should be emphasised that all statements made represent the personal and professional opinions of individuals interviewed. The comments do not reflect the ‘official’ corporate positions of the companies specified, but rather the private opinions of individuals who currently consult, work or previously worked within those companies named. The comments are therefore not to be widely distributed or published.

- ✓ A good product gives \$200 to \$500 million in sales per year, looking at a 5 year rate of return.
- ✓ Tuberculosis is not a target area because there is not a significant commercial opportunity...you want to see at least, a minimum, of 100£ million (\$170 million) per year.
- ✓ Unless you could be assured peak sales at about 100£ to 200£ million (\$170 to \$340 million per year), it's liable not to be worthwhile.

With respect to the development of new anti-tuberculosis drugs, a number of interviewees assert that cost estimates are less extreme. The estimate of \$300 to \$500 million in drug development is an average that encompasses the whole of industry -- including investments in project areas as varied as cancer or rheumatoid arthritis -- and therefore overestimates the development cost of a drug specifically targeted against *M. tuberculosis*. Several interviewees believed that a programme focused directly on anti-tuberculosis drug discovery and development could be potentially successful with a budget of \$150 to \$200 million.

From the corporate perspective, costs are measured not only in terms of funds that are expended, but also in terms of how the money *could have been invested* in other programs within the company (i.e., opportunity costs). There is therefore a cost, as one representative states, to "having a scientist in research and development working on a drug that doesn't make money." The ultimate responsibility a company holds is to its shareholders, and if the company cannot show that investors' funds are being used responsibly to maximise returns, the company jeopardises future investments. Bearing that principle in mind, it can be inferred that most companies have determined that anti-tuberculosis drug research is not a worthy pursuit because of relatively unsatisfactory returns:

- ✓ All companies have limited resources. If you have to decide which drug to discover, you will try to choose those areas that provide a quick return because of less competition, high volume and price...where you can get your return back fast. You will be looking in cancer, hypertension, Alzheimer's, central nervous system. Tuberculosis...maybe somebody else will think about tuberculosis.
- ✓ We have thought about it from time to time, doing tuberculosis research again. But allocating the resources is difficult, especially when you are looking among a wider range of therapeutic areas...We have to compete against other divisions too, like cancer products, for instance.

## **MARKET SIZE IS INSUFFICIENT**

To attain blockbuster sales, pharmaceutical companies target their products at the major markets: United States, Europe and Japan. Despite the fact that seven to eight million cases of tuberculosis occur annually, only five percent, or approximately 400,000 of these cases occur in the industrialised world. According to a Scrip report published in 1995, the total annual sales of all anti-tuberculosis drugs in the Western world were less than \$150 million. Most pharmaceutical companies observe disease trends within these major markets to assess whether tuberculosis research is a fruitful investment. One interviewee

stated that the incidence of disease in these countries forms the perception of “a small target market.” This is affirmed by another individual, “It’s not strategic for the company. The tuberculosis market is small from the corporation’s point of view.”

In fact, many interviewees noted that pharmaceutical companies shut down active research in the late 1970s and early 1980s because tuberculosis was declining in the industrialised world and multi-drug resistance was not readily apparent. For instance, one company had an active tuberculosis research program about twenty-five years ago, with both in-vitro and in-vivo facilities, but the program was stopped because, according to a company representative, “There were plenty of therapies available and multi-drug resistance was not known or seen at the time.” Along the same lines, a former employee of another company explains the company’s rationale for curtailing its anti-microbial research in the early to mid ‘80s:

It was no longer a public health problem, from a business perspective, and therefore there was nothing worth doing. There was no need for new products in the area of anti-infectives. The thinking was that the super potent antibiotics being delivered in the ‘80’s were as good as you could get. The company decided to continue marketing products, but not conducting research. It wanted to go strategic at the time...and that area was in AIDS research.

Because tuberculosis is perceived as well-controlled in the industrialised world – with evidence that new case rates are declining -- there remains little incentive for pharmaceutical companies to re-ignite activity or launch new programmes. According to one source, “The company would be influenced dramatically if tuberculosis became a real concern in the United States or Western Europe.”

Additionally, because tuberculosis is a disease affecting mostly developing countries, it is assumed that the bulk of drug purchasers are not wealthy enough to afford the cost of treatment. Companies deterred from investing in anti-tuberculosis drug research postulate that if most individuals cannot afford the expense of existing treatment today, they could ill afford the cost of superior and more expensive treatment tomorrow. Across interviews, there were multiple references to this concern about patients’ inability to pay:

- ✓ There is a medical need, but there is no market...if tuberculosis were a Western country problem, then you’d have investment.
- ✓ The market size is quite limited. The highest number of cases is in Africa, Asia, where low prices are of importance. With highly priced medicines, they can’t afford it.
- ✓ Developing countries cannot afford expensive treatment, they are looking for cheaper alternatives....Developing countries are viewed as high volume/low return.
- ✓ There is a gigantic market of patients, but the market size is relatively small in terms of paying patients. The third world holds the population that has the least ability to pay.
- ✓ The need for tuberculosis research is mainly coming from emerging markets, the third world. But multinational companies are located in first world countries, and they are looking at the needs of the first world. Indigent patients cannot afford the prices (of goods) that will come out of these companies.

- ✓ Drug development is based on profit. You're trying to discover antibiotics where infections are frequent, but tuberculosis afflicts countries without the social means to pay.
- ✓ The nature of tuberculosis makes it an enormous global burden, but the bulk of people cannot afford the drug.

For those companies attempting to develop new anti-tuberculosis agents, there is a serious hurdle in being able to define the 'market size' for tuberculosis, which increases risk and confounds efforts to defend the research as a solid business investment. The perception is that market size is a 'moving target.' Several companies echo this uncertainty:

- ✓ What is the market for tuberculosis? Whether there is a market, we don't have the answers. It's still pretty small in the industrialised world, the burden on Western society is not very high. We're looking at the developing world...we'll need to look toward the World Bank (for aid)...
- ✓ We do not have an estimate of market size. We are not sure we know what it means. It is not clear what front line agent could be replaced, making that estimation depend on whether (the new drug) is like isoniazid or rifampicin. That is one of the big imponderables. We're in a major phase of economic change in the third world, in the Pacific Rim. It's hard to know how that will all shake out.
- ✓ We don't have a really good picture on market size. No one has a good sense of what the need is until you get a good product out there...The market needs to be reassessed, looking at the tuberculosis market in Western cities, at those that will pay. The marketplace changes and evolves, and we're cognisant of that. It's not like the pneumonia market that will always be there, the tuberculosis market is always in flux.

### **CURRENT THERAPY EXISTS: NOT AN 'UNMET' MEDICAL NEED**

To maximise profits in a competitive environment, pharmaceutical companies try to identify niche markets, defining areas of 'unmet' medical need. Because of the existence of Directly Observed Treatment, Short-Course (DOTS strategy), most companies perceive no compelling reason for market entry. Many believe that a sufficient array of treatment drugs already exists, and that DOTS is highly effective in curing tuberculosis. According to one interviewee, "If there are a few number of drugs, then a company can get into the market substantially. Penetration can be high. If there's already saturation, then the (new) therapy can only capture 10-20% of the market." If, as in the case of tuberculosis, the market is seen as both too small AND flooded with drugs, then little incentive exists to invest resources.

The rise of multi-drug resistant tuberculosis was discussed in interviews, but the number of global cases was not considered sufficient to stimulate market entry. Despite the fact that more effective, simpler drugs could decrease the risk of multi-drug resistant tuberculosis, creating new drugs to fill this void was infrequently viewed as a strategic opportunity. For many, multi-drug resistance to tuberculosis drug agents was not a problem to be addressed by the production of new and better first-line antibiotics. Instead, as recognised publicly by WHO, it is viewed as a problem of compliance and public health systems:

- ✓ With the successful maintenance of current regimens, if the protocol is followed, it can be successful. To develop a drug that is effective (in shorter periods) is a big challenge.
- ✓ Tuberculosis is not considered as an unmet need. All the drugs exist...The main problem is compliance.
- ✓ The fear that multi-drug resistance will spread and that resistant strains will spread, it hasn't materialised. Multi-drug resistant tuberculosis is not widespread.
- ✓ The anti-infective tuberculosis market is small and well-served by the existing multi-drug combinations. The incidence of resistant tuberculosis in the United States is stable or decreasing in certain areas, making the market opportunities small in comparison with the anti-bacterial market as a whole.
- ✓ If you appropriately administer the drugs, then multi-drug resistance goes away in developed countries, through observed therapy. Multi-drug resistance tuberculosis is a public health problem. If people take the drugs the way they are supposed to, then they do not develop strains or spread it.
- ✓ There is no need for new medications. There are medicines that exist now that are ample and very active. The problem is how to implement observed therapy.
- ✓ There are a lot of tuberculosis drugs around. It's a relatively large population, but as an unmet need, the need is relatively low. It's low necessity/big market. Drug resistance is not a huge problem.

In contrast, companies that are currently active in tuberculosis research do view the arising presence of multi-drug resistance tuberculosis as a market opportunity:

- ✓ It's still a tricky thing, there's difficulty proving we have a drug that's better than what exists. It's not easy because the existing drugs work well. We're focused on people who are multi-drug resistant.
- ✓ We reinitiated activity in the early 90s because of the rise in multi-drug resistance against first line drugs, enabling agents like isoniazid and rifampicin. Also, we were observing the tremendous impacts in HIV...
- ✓ There remains a lot of concern about multi-drug resistance and tuberculosis, particularly in Eastern Europe. There's lot of indication that the disease isn't declining. That's good for us.
- ✓ Our TOBI (tobramycin solution for inhalation) product, that's a speciality treatment. It's an antibiotic aerosol, aimed for in-patient use. It's not a big market, but it would be used for multi-drug resistant tuberculosis or severe cases.

Despite the synergies between HIV and *M. tuberculosis*, only one company saw the potential opportunity for a growing market. This is most likely due to this company's unique approach of using its compound, a heat-killed *M. vaccae*, to attempt to boost immune response. Other companies, however, considered tuberculosis an opportunistic infection among those who are HIV positive and did not see sustainable avenues for market growth, particularly in the developed world:

- ✓ The perception is that HIV is partially treatable, and tuberculosis is a secondary infection. HIV patients are experienced at treating themselves and going through long treatment programs. The potential for increased caseload is not persuasive.
- ✓ We're not sure how much of a problem TB-AIDS is. The perception is that once you deal with AIDS, tuberculosis will not be a problem. It's a linked perception, what is an opportunistic infection for AIDS? This issue may disappear.
- ✓ The HIV and tuberculosis combination is not compelling because the thinking is that if you control the viral burden of HIV, it does dramatic things for tuberculosis.

## **PRICING PRESSURES ARE STRONG**

In order to recoup investment costs and generate a profit, companies must give serious consideration to product pricing. According to one representative, a company needs a commercial margin of at least 30% above the cost of the drug to maintain business operations. The company may charge up to 50% above cost, although target numbers differ across companies. One of the more significant disincentives to new anti-tuberculosis drug research is not simply that current medications exist, but that current medications exist *at relatively low prices*. The World Health Organization (WHO) estimates that the total cost of all drugs for full-course treatment can be as low as \$11 in some regions, and is often no higher than \$40. According to a June 1998 publication by Decision Resources, the total cost of all drugs for full-course treatment in the United States is just below \$1100.<sup>14</sup> In either setting – the developing or industrialised world – these current prices, when combined with the volume and demographics of new caseload, are not perceived as sufficiently appealing. In order to command premium prices that would make tuberculosis research more financially attractive, pharmaceutical companies would need to develop a drug superior to what already exists. Given that current medications have been shown to attain a 95% cure rate, the hurdle and its associated risks are viewed as too high for most companies.

- ✓ If drugs are priced as low as isoniazid or rifampicin, the company doesn't make money.
- ✓ The risks are high. There is inexpensive therapy and it works effectively (DOTS). That's the biggest disincentive, more than anything. The current therapy is 95% to 98% effective, can you show improvement?
- ✓ Six years ago, I asked the question at a two or three-day conference, do we need to start an anti-tuberculosis program again? The main conclusion was that we would never enter this field. The major concern was turnover, payback. The standard regimen, isoniazid, pyrazinamide, it costs nothing, it's peanuts.
- ✓ The cost of current therapy is so low, there is no way for equality, there is no other way to price drugs except to risk that there is no market -- we can't compete if the current therapy costs \$13.

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<sup>14</sup> Decision Resources produces research publications and offers consulting services to the pharmaceutical and biotechnology industries, assisting them in analysing and forecasting market trends.

- ✓ The pricing structure will be in excess of current therapy, it will be what the market can bear. It's a major issue.
- ✓ We are only looking at the tuberculosis market in North America, not the whole world. We might like to enter other markets beside the United States, but the pricing pressures are so high, we don't know.

In conjunction with pricing pressures sourced from the existing drug market, companies also perceive that any company developing a new anti-tuberculosis agent would be subjected to pricing pressure from WHO. Several interviewees expressed frustration that WHO often pushes for drugs to be given for free or at dollars a dose, which companies believe is unrealistic and serves as a deterrent to development:

- ✓ It would help if WHO felt more comfortable with the profit motive...If we can't keep support of the shareholders, we can't help anybody.
- ✓ It is normal for a pharmaceutical company to make money. We cannot lose money. WHO asks, 'Can you give it free of charge?' It doesn't work. WHO must recognise the need to make money, and help accept to pay for it -- maybe not at a 50% margin, but with a margin.
- ✓ WHO always wants (the product) to fit into a programme at a very low price, but there is a real cost of the good. It's a real problem.
- ✓ There is concern over pricing issues. WHO wants to get the drug to everybody. There is a fear in the company that WHO rhetoric would affect pricing issues. But somebody has to pay for it, maybe the World Bank. The company needs to recover its costs and make a profit.
- ✓ WHO should support normal pharmaceutical markets. Using Merck's ivermectin donation as an example...it has stopped other companies from world-wide drug development. There's no economic incentive. Merck earns \$1 billion in sales from it as a dog heartworm product, which allows the company to give the drug away for river blindness. But now there is an expectation from WHO that companies have to give drugs for free...it's shutting down other companies from world-wide drug development.
- ✓ WHO always wants cheap drugs, but wants to have the pharmaceutical industry pay for development costs. WHO does not want to appear publicly aligned with companies, yet at the same time still wants companies to stick their necks out for WHO.

Because the greatest burden of tuberculosis affects developing nations -- where companies believe they cannot secure a sufficient profit -- pricing strategy is focused upon industrialised nations, where costs can be recouped. In essence, pharmaceutical companies charge one price for a drug in a developing country, while charging a higher price for the same product in an industrialised country. This policy of dual or multi-tiered pricing holds political implications which companies prefer to avoid, and also makes the company vulnerable to parallel importing. A number of companies expressed the concern that through parallel importing, its own product, sold in a developing country for a very low price, would re-enter an industrialised country at a higher price (although lower than

the existing industrialised country price), thereby undercutting the company's profits. The issue was identified in several interviews as a barrier:

- ✓ Through parallel importing, channels – legal and illegal – are used. We need mechanisms where that is not possible. The company is losing lots of money, but the patient does not see a lot of savings, maybe three or four percent.
- ✓ Multi-tiered pricing is an economic concern. A company can generate some bad press.
- ✓ Multi-tiered pricing is always going to be an issue. It's a difficult proposition, the acceptability of selling a product at a different price, from country to country, region to region, and then not expect movement between areas. With the risk of parallel importing, we wouldn't touch it, because as a company you need to have a profit margin.
- ✓ Assume that we bear the cost and sell the drug to developed countries while giving it away to India, Africa and Asia. The history of giving away drugs to developing countries is corrupt. The free drug is diverted to the developed world for other indications. The drug is diverted and sold, while it costs one-cent a pill in these other places.
- ✓ It's a concern facing any company, given the pricing structure. We need to be reassured that because of dual pricing, profits made from the developing world (from parallel importing) are not undermining commercialisation in the industrialised world. Is the supply to the developing world watertight?

One representative raised a unique perspective regarding the flaw behind tiered pricing for tuberculosis drugs. Typically, a company can successfully dual price because losses in the developing world can be recouped through higher prices in the industrialised world. But this strategy was ineffective for tuberculosis drugs because the bulk of Western patients could not pay high prices for drugs; the impression being that these patients were disenfranchised individuals, such as immigrants or HIV positive drug-users.

## **ADDITIONAL DISINCENTIVES**

Lack of commercial opportunity was the reason most immediately cited by interviewees as an explanation of pharmaceutical industry's reluctance to engage in anti-tuberculosis drug discovery. However, there are other significant reasons why tuberculosis research is considered an unattractive business endeavour. These additional disincentives compound the cost, pricing and market barriers that already exist, and in entirety make tuberculosis research riskier and unappealing. Responses suggest, however, that these disincentives alone would not likely deter research and development attempts if the opportunity for large profits existed.

## **SCIENCE IS CHALLENGING**

*M. tuberculosis* is an unusual and formidable organism with which to work. It is a slow-replicating bacteria and resistant to most conventional anti-microbial agents, partly due to its relatively impermeable cell wall. Furthermore, *M. tuberculosis* may persist in a dormant or latent form, unsusceptible to agents targeting growing bacteria. An interviewee confirms, “It’s difficult and particular research, compared to other pathogens.” As aptly summarised by another individual:

*M. tuberculosis* is difficult to treat. It’s a very, very, difficult biologic target. It grows so slowly and it is difficult to get drugs into the target. If it was a piece of cake, more companies would do it.

Because of laboratory infection risk, tuberculosis research cannot be an add-on activity to a company’s work plan. Laboratory safety regulations require specialised programs with dedicated Pathogen 3 laboratory facilities, which in turn demand specially constructed rooms with independent ventilation. In-vivo research requires additional investment in animal facilities and in programmes for maintenance, care and disposal of experimental animals. Companies are unlikely to commit the additional resources necessary for such a project when success is viewed as uncertain and the financial return unsatisfactory. In the words of one company representative, “It’s expensive, difficult and dangerous.”

It is very difficult to prove the superiority of new anti-tuberculosis agents when, under controlled conditions, current therapy has proven to be up to 95% effective. Very large trials may be required to demonstrate marginal improvements. Ethical considerations prohibit the use of prolonged mono-therapy, so new agents must be tested in conjunction with existing drugs. Demonstrating discrete and additive benefits of a new agent when used in combination with other active drugs is a fundamental problem in the clinical evaluation of new drugs.

Nevertheless, it should be noted that a number of interviewees believed these obstacles could be overcome if sound financial arguments or corporate will existed. This point is illustrated by the fact that the recent genome sequencing of *M. tuberculosis*, which facilitates the ability to find susceptible drug targets, was not voluntarily raised in interviews to have great import on corporate decision-making. As emphasised by one individual, “The main driver is the market. The difficulties of the science are not as much of an impediment. If anyone wants to do it, they can get into it, although it would be more of a challenge for a smaller company.”

## **DEVELOPMENT IS LENGTHY & POSES OBSTACLES**

Launching a commercial tuberculosis drug research programme requires a long-term commitment. The initial investment in facilities and scientific equipment is costly. Clinical trials, which comprise the most expensive part of drug development, are lengthy, running at least six months to conventionally two years of follow-up. The prolonged treatment and required follow-up increases the difficulty of successfully completing trials with all patients. As well, the more extended the timeline for clinical trials, the more time is ‘eaten away’ from the compound’s patent life and the less time a company has to maximise profits before generics enter the market. Given that companies calculate

opportunity costs, tension exists over whether company resources would be better appropriated elsewhere. For example, rather than working on an anti-microbial that would require clinical trials running for six months of treatment, companies could be working on a more profitable antibiotic that cures a urinary tract infection in five days. According to one representative, “The company would definitely need a specifically directed tuberculosis programme. And that would be hard to justify, to push for that type of programme balanced against other projects.”

Many interviewees expressed the difficulty with finding appropriate clinical test sites, particularly in the developing world. This is partly due to the lack of knowledge of *where* to proceed, as reflected by one statement, “We don’t know where to go in developing countries, so we would need practical help to do clinical trials.” But it is also because many developing countries lack the health infrastructure or adequately trained personnel to provide consistent and uniform data critical to clinical testing. According to one source, “We can’t tell you it’s no problem to do the trials...we need reliable trials and results.” Statements by other representatives reveal unique challenges to working outside developed economies:

- ✓ Many patients are illiterate or semi-literate, they don’t understand that you have to come back within a certain window of time for the data to be consistent. So there is a need for educating patients. The people employed locally also need to understand the reasons behind clinical research. You need clinical data, but you also need to follow protocol. And in many African countries, the infrastructure is developing, but not entirely established. This also pushes up the cost of research conducted in emerging markets.
- ✓ I don’t know that conducting trials in developing countries necessarily brings down the costs. It may not be as expensive to do clinical trials in developing countries, but you still have to collect data in a manner that is acceptable to regulatory authorities...It’s the record-keeping and the production of books that makes its so expensive...

The complication and costs of clinical trials, however, would not sufficiently deter companies if there was genuine incentive in that area of research. As captured by one interviewee, “It’s not about clinical trials...they’re not super difficult. You may have to go into places that people don’t want to go, but people will do it. At the end of the day, it’s about return on effort.”

## **PATENT PROTECTION IS NOT ADEQUATELY ENFORCED**

A frustration voiced by several interviewees concerned the pricing pressures and profit losses derived from competing with generic products. Industry expects that new anti-tuberculosis drugs will enter countries where patent law does not exist or is blatantly disrespected. If the molecule is easy to copy, the drug will be re-produced by local manufacturers. The copied drug will be priced significantly cheaper, since the local manufacturer does not have to recoup research and development costs. Pharmaceutical companies cannot compete with this very low pricing structure, and are ultimately undercut and pushed out of the region’s market.

The competitive pressure from generic drugs is a disincentive to the pharmaceutical industry, but the situation is exacerbated if generics are produced during a period when the drug developer is supposed to hold market exclusivity. As one company representative explains:

India copies Western medicines and then gets a higher profit margin. WHO must press governments to invest in controlling their disease burdens and tell governments that copying doesn't help because it stymies further research...It's not about screwing patients for profits, it's about covering costs. When you enter these countries, it's not about making huge amounts of money.

A representative from another company describes the consequence more forebodingly:

What happens these days will affect research conducted for tuberculosis in the future. Certain companies – as an example, Novartis, SmithKline Beecham, Glaxo Wellcome, Hoescht Marion Roussel -- consider that tuberculosis isn't worth it. They won't come back into research and that will be dangerous. WHO will have products, but they will be copies from Italy, India, Korea. If these pirate companies and generic companies are allowed to thrive, there will never be research in tuberculosis.

## **DRUG WILL BE RESERVED FOR TUBERCULOSIS TREATMENT**

Drug discovery costs are diminished if a compound is found to have multiple uses. In the case of tuberculosis, however, pharmaceutical companies are concerned that if an anti-infective with market potential in another area is found useful for tuberculosis treatment, public health interests will demand that the drug be reserved solely for tuberculosis, hindering the company's ability to penetrate the more profitable market.

The result of this situation is that companies are ambivalent about discovering if their anti-infectives have activity against *M. tuberculosis*, and are in fact relieved when they find that their compounds are not sufficiently active. As captured by one individual and echoed by others, "You don't want a broad-spectrum antibiotic reserved for tuberculosis. It's the last thing a company wants." Along the same lines, someone else states, "If you're going to develop a broad spectrum antibiotic, you want it to work against chest infections, urinary infections, meningitis. For tuberculosis, it would be an anti-infective for a single indication. From a development point of view, it's costly."

Some interviewees found this concern thought-provoking, but were not persuaded that this was a significant business threat. Specifically, they were doubtful that public health agencies would have the ability to dictate drug use.

Despite the undesirability of discovering a new anti-bacterial agent with superior mycobacterial activity, one interviewee was able to hypothesise a strategy to circumvent the restriction:

We would likely develop it for the major indication first. Then as a post-registration exercise, we would look to develop it for tuberculosis.

It would remove the ability of regulators to restrict it for tuberculosis use once it's already on the market and launched. Once the cat's out of the bag, it's difficult to restrict its use for the primary indication.

## **WORKING WITH GOVERNMENTS IS DIFFICULT**

Pharmaceutical companies are generally not eager to work closely with governments, which are viewed to be more cumbersome and bureaucratic than private industry. In the case of tuberculosis, there was hesitation expressed about the inevitability of interacting with government officials on aspects of tuberculosis treatment. Since tuberculosis therapy is often government regulated, there is concern that industry would be subject to regulatory, delivery and pricing controls that are politically motivated, and not based on free-market principles.

## **INTERACTIONS WITH ACTIVISTS HAVE BEEN NEGATIVE**

Some interviewees referred to an aversion of industry to facing strong lobbying groups, primarily because companies suffer bad press and verbal attacks. Historically, industry has not had positive experiences when confronted with the agenda of political activists. Although the cause of tuberculosis does not have strong advocacy groups behind it, the link to HIV indirectly allies it with the mission of AIDS activists, which in turn causes industry to be wary.

## **WHERE IS THE OPPORTUNITY?**

Given the multiple barriers that pharmaceutical companies face when considering anti-tuberculosis drug development, why do some companies perceive opportunity? The dynamic can be partially explained by the fact that companies now active in research recognise or have the means to control costs, such as by working collaboratively with research institutes and academic centres, launching production where costs are cheaper, or through various grants.

Beyond the ability to curb costs, these companies assume the risks associated with anti-tuberculosis drug discovery because they foresee potential gains. The basic strategy behind capitalising on these benefits can be grouped into three general areas, as identified below.

## **IDENTIFYING A MARKET NICHE**

If a company can discover a novel therapeutic that ensures a cure rate at least as good as a current DOTS regimen and which reduces either the total length of therapy or the frequency of dosing, it has created a market niche for itself. Companies investing in tuberculosis research assume that there are patients or national tuberculosis programmes that could and would be willing to pay significantly more for this superior treatment method. A company can recoup costs by meeting this demand and charging the highest prices the market will absorb.

- ✓ The big goal, although it's probably unrealistic, is to replace all four pills with one pill. It's a very tall order, scientifically. Very tall order. But it would bring in BIG money.
- ✓ If you can create it, then you can command premium prices for it. It will never be in the realm of acute infection, but we believe we can get or make a return on investment, or at least not make a big loss.
- ✓ We pursue it because we think there's a market for us to capture. The goal as a company is to shorten the course of chemotherapy or make the drug regimen easier to use. If we can significantly impact either of those, we can access the US market and people would be willing to pay a premium price...the drug will be perceived as a worthwhile price.

The fundamental premise of this strategy is that a pool of patients willing to pay high prices actually exists. To this end, companies target markets with the economic means to pay. Looking beyond industrialised nations, companies do not have a very clear or detailed plan on how to generate revenue in the developing world, although they remain fully aware that the issue must be confronted. Save for one company, which possesses the license to market products in one region, all other companies assumed that any new product would have to be marketed for global use. Expressing a unique perspective, another company contended that it must enter the developing world so that volume sales can sufficiently recoup investment.

Two companies outlined similar ideas about how a novel anti-tuberculosis therapy could acceptably command a higher price. The true value of DOTS represents the price of drugs and a continuum of service including the cost of labour for doctors and health care providers, the cost of X-rays, the use of treatment facilities, etc. If a novel drug reduces the length of chemotherapy, or decreases the number of times a health care provider has to observe a patient ingest a pill, then cost savings are realised. As service provision during full-therapy reflects a large proportion of the total cost, there is significant room to push up the price of a new drug by absorbing a margin of the costs savings from improving DOTS. Overall, the cost of treatment has decreased, while the market value of the drug has skyrocketed.<sup>15</sup>

This marketing strategy has its risks, as an interviewee from one company muses: "Drug therapy is a very small part of DOTS -- (a new drug) will enable governments to save billions of dollars. *But maybe the company won't get to share in these savings.*"

## **BUILDING A LEGACY**

Beyond financial reward, companies value building or preserving a good reputation. Companies struggle to balance their mandate of maximising profit with the call to address global health needs. When resources are 'sacrificed', companies welcome positive publicity and visibility. The accolades will enable the company to sell more products

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<sup>15</sup> An illustration was given that in the United States, the comprehensive cost of therapy ranges from \$30,000 to \$50,000, of which the drug comprises \$300 or less. With a truly superior therapy that halves the length of chemotherapy, the total cost could be reduced to \$15,000 to \$25,000; the drug could then command several thousand dollars in price and treatment would still be more cost-effective than before.

outside of tuberculosis and generate more profit. Conducting research in tuberculosis, where few other companies are drawn, allows the company to set itself apart and vigorously self-promote:

- ✓ It might not bring in profit in terms of money, but in other terms, it will. It could be a good PR exercise. We could win goodwill, win a name.
- ✓ Corporate brand begins to matter more now. We are more concerned with explaining who we are and what we stand for. There are kudos to be gained. It reflects well on the company that we're in tuberculosis.
- ✓ As an international company, you need international presence. You can get mileage out of a tuberculosis drug, as a global disease. You want to go to places where you get much less return, but you have global visibility.
- ✓ What is at the end of the line is prestige, money and political clout.
- ✓ The company is quite proud of what we do.
- ✓ It's not always a profit motivation...public image and legacy has value to the company.

## **ESTABLISHING MARKET ENTRY**

A company may benefit by marketing tuberculosis drugs to developing countries because after establishing a good name regionally, the company increases the potential to access other drug markets. Under the assumption that an emerging economy eventually has to 'emerge', companies that enter developing markets position themselves at an advantage. Because of the ground it has covered through marketing a tuberculosis drug, a company may receive regulatory approval of new drugs faster or have its products be considered worthier of purchase. The company essentially entices brand name loyalty and creates a way 'in'.

- ✓ The registration of (products) to a company is beginning to matter more. We do want governments to realise we have products that they like.
- ✓ Maybe through registration (of a tuberculosis drug) a company can avoid red tape. If they do register a tuberculosis drug, can they register other drugs faster? Maybe they can get rewarded in another field.
- ✓ If you can impact the health of a given country, it opens up market potential for other parts of the portfolio...the country may be more receptive for the acceptance of your other products.
- ✓ There is an opportunity to establish a presence, generate income, branch out and grow.

## A SEEMING ANOMALY

Of fourteen companies with no intent to develop anti-tuberculosis drugs, at least eight are testing compounds for mycobacterium activity. Why do companies test compounds if there is no active commitment to develop a drug? The reasons are varied.

Firstly, the motivation for testing is research driven, rather than business driven. Despite the fact that the management or marketing arm of a company may have no interest in developing a novel anti-tuberculosis agent, the research branch is still committed to the science and often pursues the analysis independently. If significant activity is discovered in these early stages, then decisions on how to proceed are made post-facto, after consultation with management. Most researchers were fully cognisant that the company would never seriously commit resources for development, but still continued screening in the hopes that compelling scientific results would open possibilities out-of-house. Several individuals expressed personal interest in knowing more about their compounds and activity levels, but had no idea what would happen if positive results were discovered. According to one source, “Chemists like to see activity against anything. Maybe there would be interest in it.”

Other companies test for anti-tuberculosis activity on the possibility that there could be benefits gained from the process. Perhaps if high activity were discovered, licensing the molecule to another institution could bring compensation or merit to the discovering company. Or, according to one individual, perhaps the company could gain faster registration for the drug’s primary indication:

The strategy would involve attached prestige to your product. You might get an accelerated evaluation of your product, but you’re not depending on tuberculosis to give you a return.

Or perhaps, quite simply, companies engage in the research because it is easy and quick to do, and prevents the risk of missing a small opportunity. According to one source, mycobacterial activity is a standard test conducted, one of fifty or more other tests that are routinely performed. Ultimately, if the company does not engage in this comprehensive screening, “someone else would do it.”

## RECOMMENDATIONS

### ANALYSIS

Pharmaceutical companies are facing an increasingly competitive environment, with investment decisions based heavily upon maximising shareholder return. Within these financial constraints, allocating resources to anti-tuberculosis drug discovery and development is unappealing. The research is intensive and the payoff, relative to other areas, is paltry. Large pharmaceutical companies may have adequate resources, but are reluctant to delegate them if the project will not enable a lead over competitors. In contrast, smaller pharmaceutical companies are willing to reap lesser gains, but often lack the stability to absorb heavy costs.

Without a perceived increase in market size and commercial opportunity -- or a significant decrease in input costs – companies will never voluntarily initiate anti-tuberculosis drug discovery or development. Without participation by the pharmaceutical industry, however, WHO will have difficulty attaining global tuberculosis-control objectives. This dilemma points to the obligation for increased public and private sector collaboration, with public sector institutions leading the charge, armed with innovative and creative solutions. The burden falls upon the public sector because continued inaction will simply perpetuate the status quo.

The challenge for WHO is to identify mechanisms to stimulate the commitment of the pharmaceutical industry. Actions must be taken that offer industry valid and persuasive reasons to enter anti-tuberculosis drug development *and* to stay. Finding substantive, affordable methods to pull industry into the anti-tuberculosis drug market will be a formidable task, requiring persistent efforts and considerable thinking outside-the-box. Ultimately, WHO will need to change both the market picture and industry's *perception* of the market picture.

### POINTS TO CONSIDER

#### ➤ **THINK REALISTICALLY AND ESTABLISH PRIORITIES**

Optimistically, given development and registration hurdles, a novel anti-tuberculosis agent will not appear for another five to eight years, and most likely in an industrialised nation first. Those companies that have drugs in the pipeline or are currently active remain in formative stages.

These conditions emphasise the need for WHO to focus on measures that provide the greatest hope for improving tuberculosis treatment today. WHO should develop short and long-range strategies for improving tuberculosis drug regimens. Nurturing new drug development is a long-term strategy, so priority should be placed upon advancing other tools. In the short-run WHO should continue taking aggressive measures, among others, to speed the development of once-weekly rifapentine, encourage the development of high-quality, effective fixed-dose combinations, and carefully exploit other existing compounds known to be active. In the longer term, WHO can cultivate its relationship with industry

and encourage national governments to improve their tuberculosis control efforts and overall health infrastructure.

### ➤ **SEND A CLEAR AND CONSISTENT MESSAGE**

Once WHO establishes programme priorities and identifies global needs, the corresponding public message must be clearly and firmly articulated to industry. Organisational priorities should be repeated often, consistently, and with minimal inflammatory rhetoric. WHO should clarify global drug needs and characterise the market by answering such questions as:

- In which countries or markets is the demand for new drugs greatest?
- In what sectors do these potential consumers fall and how can they be reached?
- What characteristics should a new drug have to be used most widely?
- How would new drugs be incorporated into DOTS and national programmes?

Short of overtly endorsing specific products, WHO can make public declarations that influence market dynamics. Because of its political standing, WHO's endorsement of a strategy, method or treatment may induce more countries to demand certain therapeutics, which increases a company's potential to increase sales. Being somewhat 'guaranteed' a market and knowing WHO's priorities, companies may be encouraged to supply the new product, supply more of it, or deliberate ways to supply better versions of it. Wherever possible, WHO should ensure that its public statements remain consistent and definitive,

### ➤ **FOCUS ON PRIMARY INCENTIVES**

To entice companies to enter anti-tuberculosis drug research, WHO should focus on developing primary incentives – either helping companies cut costs or generate more revenue. Companies can decrease costs by limiting the expense of clinical trials or working to find ways to produce compounds in the most inexpensive manner. Companies can increase revenue by expanding their market, charging higher prices or finding new uses for their products.

A measure initiated by the National Institute of Health (NIH), offering to test compounds for *M. tuberculosis* activity in-vitro and in-vivo, is exemplary of a limited corporate incentive. The NIH's free testing supports the initial phases of discovery, which is particularly helpful to companies without Pathogen 3 laboratories. Yet companies are more interested in assistance with development phase efforts, where costs are heaviest. Companies are searching for ways to minimise clinical trial expenses and desire support with registration application procedures. Beyond that, companies are searching for assurances of adequate market size and seek help entering relatively uncharted markets. The NIH programme is beneficial for companies already interested in pursuing tuberculosis – i.e., helping smaller companies cut research costs -- but it does not address the more important hurdles. As summarised by one interviewee, "It's helpful, but no one will start up a tuberculosis programme because of it."

It is important to acknowledge the distinction between *drawing new companies* into tuberculosis research versus *keeping those companies already in*, committed to the field. Companies now engaged in tuberculosis research still perceive risks and remain uncertain if and how they can manoeuvre future hurdles. WHO's attempts to open up and maintain communication with these companies will probably be mutually beneficial. Encouraging other companies to mobilise resources when efforts have already been minimal is more challenging. As one source remarked, "Other companies don't have incentives to come in. Why would you want to be there, unless there were some reasonable incentives that offset the costs? It's a crucial issue."

### ➤ **IDENTIFY ACCEPTABLE STANDARDS**

The clinical evaluation of potential anti-tuberculosis agents is more complex, prolonged and costly than the evaluation of conventional antibiotics. These increased barriers include the lengthy treatment course (requiring a primary endpoint of non-relapsing cure at a 2-year follow-up) and the necessity of combining antibiotics to prevent the emergence of drug-resistant strains. The high cure rate of existing regimens allows a thin margin where the superiority of a new regimen can be demonstrated in a comparative trial. Related to this point, ethical issues exist in testing potentially inferior regimens, even if these regimens offer other advantages, such as convenient dosing. The use of combination therapy in particular complicates the evaluation of novel agents, as it is difficult to detect the relative efficacy of any particular agent when added to a multi-drug regimen or when substituting an existing agent.

WHO should explore ways to simplify the process of new drug development, without comprising drug quality, by addressing some of these issues. One avenue is the careful evaluation of possible surrogate markers for non-relapsing cure. WHO could assess the effectiveness of mechanisms such as biologic or molecular markers of drug activity, early culture conversion, or percent cure after an abbreviated follow-up period. The scientific and ethical appropriateness of limited-duration monotherapy trials or other non-standard trial designs should also be explored and clinical guidelines drafted. Taking lessons from HIV treatment trials, WHO should initiate international discussion over the ethical assumptions underlying tuberculosis trials, the limitations imposed by these assumptions, and facilitate open dialogue over what would be gained or forfeited by altering these core assumptions.

## **ACTIONS TO TAKE**

### ➤ **CONTINUE RELATIONSHIP-BUILDING AND NURTURE PREVIOUS AND NEW CONTACTS IN PHARMACEUTICAL INDUSTRY**

Cross-sectoral collaboration requires trust across parties. Such trust has historically not been strong between WHO and industry. Past interactions have at times been unrewarding, fettered with misunderstanding about each party's motivations. According to one interviewee, "We've often been characterised as the evil empire types." Another stated, "In the past, we've been made the pariah." Breaking away from this 'old-school' thought requires increased efforts at communication building and development toward more sophisticated, transparent dialogue.

While some interviewees spoke of having a good relationship with WHO, others admitted to having virtually no contact with WHO and “no idea what is going on” within the GTB programme. Several expressed curiosity about WHO’s priorities with respect to global drug needs. Questions such as “Does WHO want to have fixed-dose combinations?” and “Would WHO want an active compound that we couldn’t develop?” reflect the need to expand lines of communication.

Several individuals volunteered a desire to maintain contact developed with WHO through this survey, notably from companies currently conducting tuberculosis research. Because these companies do not wish to develop drugs in a vacuum -- and because WHO wants to ensure that new drugs get developed -- it is mutually beneficial to sustain the momentum for relationship-building. The opportunity should not be squandered. If WHO can enter the discovery process early, it can offer valuable technical support during development and build positive relations with a range of companies. The fruitful ‘alliance’ with Hoechst Marion Roussel on rifapentine is an example of this type of successful collaboration.

Not only should WHO build relations with those in the upper ranks of research, but also with those in management. A theme arising from interviews was that new anti-tuberculosis drug discovery is an area that appeals to researchers, but scientific enthusiasm is outweighed by marketing constraints. If WHO can maintain trusting relationships with companies, and be attuned to both research and business dimensions, it will be more effective in its efforts.

WHO should continue working with the pharmaceutical industry to improve public-private sector collaboration. Toward that effort, the Director-General Dr. Gro Harlem Brundtland has appointed Dr. Michael Scholtz, an individual with a career in pharmaceutical management and marketing, as the Director of the Health Technology and Pharmaceuticals cluster. Additionally, she has referred to the need for an Industry Council. Through these high-level executive meetings, the priorities of WHO can be better delineated and expressed, and points of common interest uncovered. . In addressing the WHO staff on July 21, 1998, Dr. Brundtland affirmed, “We need that broader view if we are to deal effectively with the complex field of health technology, drug and vaccine development, and most importantly, how to develop new drugs and make them available and affordable to all.”

### ➤ **TAKE INITIATIVE TO PROVOKE DISCUSSION, GENERATE IDEAS AND DISSEMINATE KNOWLEDGE**

WHO is uniquely positioned to bring together some of the greatest minds in academia, research, government, the donor community and industry and can host round-table discussions to gather expert opinions about how to simulate sustainable, anti-tuberculosis drug development. WHO can serve as an intermediary and create a neutral forum to generate novel ideas, brainstorm solutions for incentive-building, keep relevant participants involved and informed, and perhaps broker the appropriate partnerships. There will no shortage of good ideas on how to approach the problem, and the challenge will be in harnessing energy into actionable items. But until dialogue begins among interested parties and key stakeholders, it will be difficult to identify the highest priorities. Launching this type of initiative runs in parallel with the broader vision Dr. Brundtland has publicly outlined as the mandate of WHO.

Together we can make a difference – by reaching out to each other in the UN family and unite our resources and our knowledge – by engaging more closely with countries in their elaboration of sustainable policies and paths of progress. By building consensus that no country can achieve lasting growth if their people do not enjoy elementary access to health care. By reaching out to the private sector and engage (sic) the immense creative potential of innovation to get new drugs – more affordable drugs – new technologies to safeguard our environment and allow future generations to inherit at least the same opportunities we did.<sup>16</sup>

## ➤ **HELP BUILD, DEFINE AND PROTECT MARKETS**

**PROVIDE PROJECTIONS OF GLOBAL DISEASE BURDEN.** The quantitative data that WHO publishes -- including individual country disease burden and frequency of drug resistance - - influence the pharmaceutical industry's perception of medical need and market size. Companies value information that reflect trends over time, so disease projections are important tools that help define the market today and the potential market five or ten years in time. A couple of interviewees stated that historically, disease numbers have been inconsistent in WHO publications, harming the credibility of WHO figures. WHO should therefore take special care with such estimations and where possible, show transparency.

**ACKNOWLEDGE INDUSTRY VALUES AND ADDRESS ASSUMPTIONS.** One interviewee suggested industry would be better persuaded of sufficient market size if WHO delineated the therapeutics that countries wanted *and* their willingness to pay. The proposal is instructive to the degree that it reveals the 'lens' through which pharmaceutical companies view decision-making. Of the 7 to 8 million new tuberculosis cases per year, companies question what percentage of these individuals are potential consumers and at what price. Many interviewees assumed that the market size for anti-tuberculosis drugs was too small at approximately \$150 million dollars, but it was unclear how this estimate was derived. Most companies believed that individuals in developing nations would and could never pay several hundred dollars for tuberculosis treatment, but that assumption may not be valid. As industry decision-making relies heavily upon indicators such as these, then WHO should re-examine benchmark figures and provide reliable data to counter assumptions that may be inaccurate.

**STRENGTHEN HEALTH INFRASTRUCTURE.** The poor infrastructure and 'fragmented' nature of developing markets was often expressed by interviewees as a corporate frustration. As stated by one representative, "We could use help going in to countries where WHO believes the medicines will actually go for sale." Over time, WHO can build up stronger markets by emphasising the development of health systems and identifying stable mechanisms for drug delivery and dispersal. Through its work with national programmes and implementation of DOTS, GTB/TRS has achieved progress in building up health infrastructure. WHO should continue these activities, which include: working with governments to ensure that medicines are channelled to desired end points,

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<sup>16</sup> Commemorative Ceremony on the Occasion of the Fiftieth Anniversary of the World Health Organization. September 21, 1998.

encouraging the development of accessible health centres for treatment, educating health communities and the public on tuberculosis detection and proper treatment, and supporting the training of personnel to implement national programmes effectively.

**ENCOURAGE GOVERNMENT SELF-SUFFICIENCY.** WHO can further build up markets by strongly encouraging governments – via Ministries of Health or Ministries of Finance – to place value on anti-tuberculosis drugs. In the long term, these governments should be pressured to pay, where possible, for the necessary therapies to cure their own patients. If developing countries depend heavily upon the World Bank or donors for health funding assistance, companies will remain averse to producing drugs primarily for countries that offer no assurance of sustainable financing of products. WHO should develop more creative pricing schemes that allow new drugs to be affordable to needy regions, but at price levels which remain satisfactory to industry. This does not necessarily demand that WHO be a global purchaser, but WHO may be able to effectively price-negotiate or co-ordinate bulk purchases.

**SUPPORT PROTECTION OF PATENTS.** WHO should emphasise to governments the importance of respecting international patent law and discourage the use of generic substitutes that appear before the original patent expires. Indoctrinating this level of respect for patent law will increase the importance of regulatory incentives that might in the future be applicable to new tuberculosis drug development, such as the extension of patent exclusivity by two or more years. If drug companies foresee that potential profits – already perceived as small -- will be cannibalised by illegal generics, it is certain they will never initiate investment in tuberculosis.

### ➤ **FACILITATE JUMPING THE DEVELOPMENT HURDLES**

Without expansive contacts to local hospitals, clinics or research centres, and without close relations with Ministries of Health, many companies feel at a loss of where to turn and how to best structure a trial in the developing world. The absence of strong health infrastructure in these countries leave many companies the impression that they will be tangled in a web of government procedures, with no guarantee that appropriate patients for testing will be found. There is too, the problem of ‘appearance’, where companies in the past have been criticised of exploiting local citizens for drug testing, only to ‘turn face’ and charge exorbitant prices.

WHO can help address this potential barrier, certainly with more ease and technical expertise than most drug companies, including those with multi-lateral experience. WHO can identify clinical trial sites and perform the type of political brokering that is necessary to conduct medical trials of a sensitive nature. This would facilitate one of the bigger logistical obstacles for drug companies, and may also serve the needs of WHO, since sites can be identified where the new drug is most critically needed. Being involved at this level may also provide WHO more leverage in negotiating prices satisfactory to both countries and industry.

Supporting clinical trials, or helping ease the burden of regulatory approval – perhaps by encouraging shorter follow-up periods – are measures that WHO can undertake to dismantle existing disincentives. Yet these actions are more useful to companies already active in tuberculosis research, as their relevant challenges are addressed. These actions are insufficient, however, to entice any company that is not already ‘in’, to enter.

## FINAL GUIDELINES

### ➤ **WORK CONSTRUCTIVELY TO PRESSURE INDUSTRY**

WHO needs to pressure the pharmaceutical industry and heighten awareness of the need for anti-tuberculosis drugs, but engaging in public criticism is counter-productive. In some manner, the industry has to be involved in the drug process – in research, discovery, development or commercialisation. Beyond tuberculosis, WHO needs the continued involvement of industry to successfully combat global health problems, so the relationship needs to be sourced from solution-thinking, rather than blame and criticism. Industry does not need to fulfil the objectives of WHO to be profitable. WHO should avoid alienating potential partners from the drug industry by involving them early in strategic discussions. As summarised by one interviewee, and echoed similarly by others:

By being so righteous, WHO has made itself a tar baby. It hasn't worked for thirty years, there are no drugs and millions are dying. WHO needs to change its approach. People still believe the stick approach works, but it doesn't.

Dr. Brundtland herself has repeatedly affirmed the need to work collaboratively with industry, and industry is encouraged and hopeful for a new working relationship. As she stated in a National Public Radio Address:

And there is a lot of new developments which we need – which then illustrate that we need to reach out to industry to ask them how they can contribute in an even more effective way, to give really equal access to health technologies and drugs. And that's why I have spoken out and announced that I will be inviting industries to work with us...<sup>17</sup>

To keep consistent with the Director General's public messages, WHO should seize the opportunity to redefine old approaches. Industry needs to be pulled into the picture through positive incentives, rather than pushed into it for fear of suffering negative consequences.

### ➤ **ACCEPT INDUSTRY'S NEED TO PRICE AT A PROFIT**

The prices a company can capture for its goods are critical. When WHO emphasises how cheaply medical therapies are or should be, pharmaceutical companies are disheartened. One of the biggest demotivators for a company infusing millions of dollars in product development is to foresee, down the line, strong pressure to price at dollars or pennies a dose. A number of interviewees referred to the fact that with the drugs in a DOTS regimen being available in some cases for as little as \$11, there was little reason to enter the market.

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<sup>17</sup> National Public Radio, Talk of the Nation. August 11, 1998.

In trying to obtain the most affordable drug prices for countries, WHO cannot alienate industry's interest in serving these regions. WHO should continue to acknowledge that there is a real cost to drug manufacturers and create more imaginative pricing and financing schemes that satisfy both industry's profit goals and meet countries' budgetary limitations. For example, simultaneous purchasing/donation plans keep one market price visible, while still allowing countries to purchase drug supplies and stay within budget.

### ➤ **ACKNOWLEDGE THE IMPERFECTION OF DOTS**

For companies that are funding tuberculosis research, public campaigns touting the strength of DOTS raise concerns. If DOTS can cure tuberculosis, management ponders, why is the company squandering money trying to find another cure? The fact that anti-tuberculosis drug discovery is not perceived as a sales 'winner' in the company means that if DOTS continually sounds super-successful in combating tuberculosis, research programmes are at risk of termination.

WHO should take care to present the optimism of DOTS without glossing over the programme's flaws, and the need for new agents to improve treatment should be emphasised. WHO should also highlight that the promotion of DOTS aids countries in strengthening health delivery systems; thus when new drugs are developed, adequate infrastructure will already be in place to support delivery. The message should be made clear that the name DOTS is not synonymous with the existing first-line drug agents and treatment schedule, but a comprehensive medical approach that can be facilitated or expedited with better drugs.

To change this approach obviously raises the predicament of how to distinguish between publications that advocate DOTS to countries -- to encourage programme adoption -- versus DOTS documents disseminated to the wider public. But the issue needs to be addressed, as pharmaceutical companies can and do gain access to either type of publication.

## CONCLUSION

I am not sure how responsive corporate culture is to facilitation by WHO. It depends on the core values of the company and how driven the company is by medical need, curiosity and people within the organisation to support research in particular areas

Interviewee

Few pharmaceutical companies will develop new anti-tuberculosis drugs of their own volition, and this is not likely to be changed by technical breakthroughs such as the genome sequencing of *M. tuberculosis*. But the minimal appeal to researching tuberculosis is not a problem of science, it is a problem of money. Pharmaceutical companies calculate the cost/benefit ratio as too high. Even companies actively involved in tuberculosis research are hesitant to fully commit themselves, for fear of being unable to jump all hurdles.

Unfortunately, the public-sector does not possess the resources to discover, develop and market new drugs on its own. Public-sector institutions must therefore lead the effort to mobilise, coordinate and drive the process forward, developing creative mechanisms to incite and maintain industry interest. WHO is an institution with the proper global mandate and political authority to be an active participant in, if not leader of, this process. WHO can build the means to identify expertise, establish cross-sectoral links and pool resources to finance substantive research and development. WHO can and should use political leverage to help build collaborations among academic centres, research institutes, multi-national donors and drug corporations. To lower some of the market barriers that occur downstream, WHO should encourage country governments to strengthen health infrastructure and build more sustainable health financing mechanisms, additionally working to define and increase the pool of global purchasers. By managing a variety of these 'push' and 'pull' dynamics, WHO can better shape and guide the outcomes in private-sector drug development. Director-General Brundtland recently alluded to her support of this combined upstream/downstream approach:

This is a policy area... for the World Health Organization it has been for many years. And I think both advising governments on drug policies, putting systems and regulations in place, and also working with industries to achieve new drugs, new developments and to look at the pricing and cost situation is really an essential part of our work.<sup>18</sup>

There is much work to be done, and a division solely dedicated to tuberculosis research cannot take on the burden singularly. The problems in the context of anti-tuberculosis drug development are not unique or new, so programmes possessing similar objectives

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<sup>18</sup> National Public Radio, Talk of the Nation. August 11, 1998.

should be identified. Resources and expertise can be pooled together so that momentum can be built.

As an example, the *Medicines for Malaria Venture* initiated by the Special Programme for Research and Training in Tropical Diseases (TDR) has faced similar challenges with industry concerning malaria drug development. Over time, the TDR division has established a network within the drug industry and has nurtured the trust necessary to forge successful partnerships. It is now likely that a private-public sector programme to develop malaria drugs, with potential funding of up to \$30 million per year, will soon be launched. Attempts to increase anti-tuberculosis drug development could be modelled after the *Medicines for Malaria Venture*, incorporating valuable lessons learned in managing cross-sectoral endeavors.

Industry as a whole may not view anti-tuberculosis drug discovery as a wise investment, but there are individuals within corporations who *do* have a personal commitment to the topic. For that reason, WHO should persist in keeping connected with company representatives who have a vested interest in tuberculosis, *particularly within companies who are currently conducting tuberculosis research*. It is important that these ties are not neglected. Forging personal relationships with key pharmaceutical individuals can influence how future agendas are set, so identifying and cultivating allies early in the process will aid WHO in its work.

## **INTERVIEW LIST**

**Abbott Laboratories**  
**Astra India**  
**Bristol Myers Squibb**  
**Chugai Pharmaceutical**  
**Eli Lilly**  
**Glaxo Wellcome**  
**Hoescht Marion Roussel**  
**Johnson & Johnson**  
**Merck & Co.**  
**Novartis**  
**Parke-Davis**  
**PathoGenesis**  
**Pharmacia and Upjohn**  
**Rhône-Poulenc Rorer**  
**Roche**  
**SmithKline Beecham**  
**Stanford Rook**  
**Wyeth Ayerst**  
**Zeneca**

### ***Additional External Interviewees:***

Food and Drug Administration  
NIAID, National Institute of Health  
University of London, St. George's Hospital Medical School  
Centers for Disease Control

### ***WORLD HEALTH ORGANIZATION CONTACTS:***

Richard Bumgarner, GTB/PDC  
Wyn Gutteridge, TDR/TDP  
Tom Kanyok, TDR/TDP  
Mary Ellen Kitler, GTB/NPS  
Kraig Klaudt, GTB/PSP  
Jacob Kumaresan, GTB/NPS  
Fabio Luelmo, GTB/SEP  
Mario Raviglione, GTB/SEP  
Rob Ridley, TDR/TDP  
Sergio Spinaci, GTB,NPS



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# **APPENDIX A**



## APPENDIX A

### The Drug Development and Approval Process in the '90s

It takes 15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

	Early Research /Preclinical Testing	File IND at FDA	Clinical Trials			File NDA at FDA	FDA	15 Total	Phase IV
			Phase I	Phase II	Phase III				
<b>Years</b>	6.5		1.5	2	3.5				
<b>Test Population</b>	Laboratory and animal studies		20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers				
<b>Purpose</b>	Assess Safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use	Review processes/ approval		Additional post- marketing testing required by FDA	
<b>Success Rate</b>	5,000 compounds evaluated		5 enter trials			1 approved			

Source: <http://WWW.phrma.org/charts/approval.html>



# **APPENDIX B**



# New Drugs for Tuberculosis

**Ken Duncan, Glaxo Wellcome Research and Development**

The last new drug for treating *M. tuberculosis* infections was rifampicin, introduced in 1972. Its use led to development of the short-course regimen, which forms the backbone of the highly effective DOTS strategy. But, the DOTS strategy has its problems. Drug toxicity, the long duration of therapy, and the emergence of multi-drug resistant strains of *M. tuberculosis* have highlighted an urgent need for new tools. New drugs that are better tolerated, that permit intermittent chemotherapy, or that affect cure in a shorter time would have a significant impact, making it easier and less expensive to deliver the DOTS strategy. By spending less time on therapy and reducing the number of treatment failures, savings in the cost of providing healthcare can be made.

Three strategies are typically employed to find new drugs, each of which has advantages and disadvantages:

1. Improve existing agents: These provide a chemically tractable starting point and testing is straightforward - direct comparison can be made with the parent compound, and a clear path to the clinic may be envisaged. However, this can only provide an incremental improvement in therapy. It is common for any new agent to be susceptible to pre-existing resistance mechanisms, and therefore ineffective against strains resistant to the parent compound.
2. Develop broad-spectrum antibacterial agents: These can be tested easily and if in clinical use already, are known to be safe for use in man. On the other hand, their structures will not have been optimised against *M. tuberculosis*, so they may have relatively poor activity. Widespread use may encourage resistance to develop, and differential pricing restraints exist.
3. Find new chemical entities: The best long-term strategy is to discover and develop an entirely new class of agent, acting on a completely novel target. It should have better tolerability (lower toxicity) than existing drugs, and would have improved pharmacokinetic properties, in order that intermittent chemotherapy might be feasible. Furthermore, with an improved understanding of the disease, it will be possible to target persisting bacteria and hence reduce the overall duration of the therapy to less than six months. However, identifying and validating such targets requires intensive research effort, lead molecules are difficult to find, and the entire drug development process is both expensive and carries a high risk (many drugs drop out along the way).

Several drugs are currently in development, which have an application in the TB field:

- Long-acting rifamycins: Hoechst Marion Roussel recently obtained approval from the US Food and Drug Administration for marketing Rifapentine, which may be taken twice a week, in place of daily rifampicin. Others of interest include KRM-1648 (Kaneka; licensed to PathoGenesis) in Phase I/II in the US and SPA-S-565 (SPA; licensed to Glaxo India) in Phase I/II in India.

- The oxazolidinones, a novel class of broad-spectrum antibacterial agent acting on protein synthesis, also possess antimycobacterial activity. Pharmacia & Upjohn are reported to be developing U-100480 for use against *M. tuberculosis*.
- In an open-label Phase II trial, PathoGenesis Corp. is testing TOBI (tobramycin solution for inhalation) in patients with pulmonary TB, by delivering the drug directly into the lungs using a nebuliser. It is anticipated that this would be a valuable adjunct to conventional drugs, given over the first few weeks of therapy to rapidly reduce the bacterial load in the lungs and to prevent further spread of infectious organisms.
- PathoGenesis Corp. have also described PA-824 and PA-1343, novel nitroimidazopyrans with activity against *M. tuberculosis*. These compounds have a completely new mechanism of action and are thus active against MDR-TB, but are still at an exploratory stage. PathoGenesis recently received a Small Business Innovation Research Grant from the US National Institute of Allergy and Infectious Diseases to support anti-TB research.

There are other agents that have shown some promise against *M. tuberculosis* in vitro or in early in vivo work which are of interest because of the extensive experience already accrued with these drugs in the treatment of other infections:

- Beta-lactam antibiotics are active against *M. tuberculosis* but are rapidly degraded by bacterial  $\beta$ -lactamases. Experiments using  $\beta$ -lactamase inhibitors or using stable  $\beta$ -lactams have demonstrated both in vitro and in vivo activity. Clinical experience with amoxicillin/clavulanate includes anecdotal reports of MDR-TB treatment as well as an early bactericidal activity (EBA) study suggesting activity superior to most standard TB drugs other than isoniazid. Activity may be limited to actively-replicating, extracellular organisms.
- Several 4-fluoroquinolones are active against *M. tuberculosis*. In clinical trials, both ofloxacin and ciprofloxacin demonstrated fairly good bactericidal activity and have been found useful in the treatment of at least some cases of MDR disease. However, in the largest treatment trial of its kind to date (6HR4ZE vs. 6HR4C), the cipro-containing regimen resulting in slower culture conversion and a greater frequency of relapse than did the traditional 4-drug regimen, especially in HIV-infected subjects. Studies with two newer agents have been disappointing: phototoxicity at higher doses limits the utility of sparfloxacin, and the very low MIC of clifloxacin against purified gyrase does not translate into good in vivo activity. Moxifloxacin appears to be highly active in vitro and has not yet shown phototoxicity. In the mouse, moxifloxacin at 100mg/kg was as active as isoniazid at 25mg/kg.

Following a long period when very little research was carried out on *M. tuberculosis*, there has been a great deal of activity over the past decade in the underlying basic research carried out largely by public sector agencies and private foundations. The recently completed determination of the entire genome sequence of *M. tuberculosis* has transformed our ability to identify and validate drug targets. The free availability of the data improves the working efficiency of researchers everywhere. The mycobacterial cell envelope, which differs significantly from that found in other bacterial pathogens, is a rich source of potential new drug targets. Over the last five years, a very basic understanding of the component parts has been transformed into a detailed working knowledge of the

biosynthetic pathways involved. Many enzymes have been identified. These are being correlated with specific gene products yielding targets for high-throughput screening and for rational inhibitor design.

Expression studies are revealing which genes are essential for the organism's viability at different stages of the infection, suggesting targets that may be inhibited to interrupt the host-pathogen interaction. Advances in molecular genetics are providing the research tools for manipulating the genome of *M. tuberculosis*. The ability to generate both random and specific mutants will allow the function of many more genes to be elucidated.

Academic groups are carrying out much of the underlying basic research into new drugs. Support for this work comes mainly from public research funding bodies, such as the National Institutes of Health in the USA. Few pharmaceutical companies have drug discovery programmes in the TB field. The notable exceptions include Glaxo Wellcome (Stevenage, UK), which has invested £20M in its 'Action TB' Initiative, Astra (Bangalore, India, basic research in target identification), and PathoGenesis (Seattle, USA).

Within the pharmaceutical industry, advances in combinatorial chemistry, coupled with automation of the high throughput screening process, have increased significantly both the diversity and the number of molecules available for testing, thus improving the likelihood that a novel drug lead might be identified. Against this, however, the regulatory requirements for new drug registration have changed dramatically since the first anti-TB drugs were developed, making it much more challenging to bring a new drug to the clinic. Typically, it is likely to be ten years before any significant new medicines become available.

There are a number of constraints that have deterred companies from investing in new drugs to treat TB. The research is expensive, slow and difficult, and requires specialised facilities for handling *M. tuberculosis*. There are few animal models that closely mimic the human disease, particularly if we look beyond drugs with properties similar to those in use today. Development time of any new drug will be long; clinical trials will require the minimum six-month therapy, with a 12-18 month follow-up period. They will be complex since they involve combination therapy, and are made difficult by the fact that the existing therapy is highly effective under tightly controlled clinical trial conditions, thus making it hard to demonstrate that a new agent has benefit over today's drugs. Finally, there is the perceived lack of commercial return. Since over 95% of TB cases worldwide are in developing nations, it will be hard to recoup the estimated \$300M-\$500M cost of developing a new medicine. The NIH has pioneered a possible solution to many of these issues, by investing in the infrastructure for drug discovery and initial development, encouraging companies to submit compound banks for screening against *M. tuberculosis*, then providing access to *in vitro* and *in vivo* models of infection, free of charge. Furthermore, the TB Research Unit at Case Western University provides infrastructure and access to clinical trial sites at lower than normal cost. The NIH, among other institutions, have funded the recent development of molecular and microbiologic surrogate markers for therapeutic response. These surrogates could, if validated, substantially ease the clinical evaluation of new agents. Such public subsidy of the drug development process and the concentration of resources, available to all, lower the barriers to entry considerably. However, no compounds have emerged from this process into future development. Significant disincentives appear to remain for companies to develop anti-TB drugs.

It is important that the WHO continues to drive home the importance of the DOTS strategy, in order that today's drugs are used wisely and effectively. Furthermore, the infrastructure for delivering the DOTS strategy will ensure that new tools are used correctly. In parallel, the WHO must encourage and support the development of new medicines by providing clear and compelling statistics highlighting the need for the new tools. It should work with companies, governments, NGO's, and other bodies to find a way of ensuring that new drugs can be developed, delivered to those in greatest need, and yet provide some return on investment. A necessary first step is a better understanding of the incentives and disincentives for industry to develop new anti-TB drugs.

# **APPENDIX C**



## TOP TWENTY RESEARCH AND DEVELOPMENT SPENDERS WORLDWIDE

1997 (\$ millions)

		Pharma R& D spent	% Pharma Sales
1	Glaxo Wellcome	1,882	14.4
2	Novartis	1,813	18.6
3	Roche	1,760	21.1
4	Pfizer	1,710	16.0
5	Merck & Co	1,684	11.9
6	Eli Lilly	1,382	16.2
7	Hoescht Marion Roussel	1,374	17.0
8	Abbott	1,302	11.0
9	Johnson & Johnson	1,285	16.7
10	SmithKline Beecham	1,272	17.5
11	American Home Products	1,246	16.0
12	Pharmacia & Upjohn	1,217	18.5
13	Bristol Myers Squibb	1,200	12.1
14	Astra	1,146	19.5
15	Bayer	1,134	14.4
16	Rhône Poulenc	1,012	17.7
17	Schering AG	913	20.6
18	Schering Plough	847	12.5
19	Boehringer Ingelheim	833	20.7
20	Zeneca	721	17.2

Source: SCRIIP World Pharmaceutical News.  
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**Appendix D** contains a letter and a questionnaire available on request from:

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