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# **THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG DEVELOPMENT**

Pharmaceutical R&D Policy Project

Dr Mary Moran (Director), Anne-Laure Ropars, Dr Javier Guzman,  
Dr Jose Diaz and Christopher Garrison

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September 2005

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## GLOSSARY

<b>ADME</b>	Absorption, Distribution, Metabolism, and Excretion
<b>AIDS</b>	Acquired Immune Deficiency Syndrome
<b>APC</b>	Advance Purchase Commitment
<b>BIAG</b>	Biomedical Industry Advisory Group
<b>BMS</b>	Bristol-Myers Squibb
<b>CEO</b>	Chief Executive Officer
<b>CRO</b>	Contract Research Organisation
<b>CSR</b>	Corporate Social Responsibility
<b>DC</b>	Developing Country
<b>DFID</b>	Department for International Development (UK)
<b>DNDi</b>	Drugs for Neglected Diseases initiative
<b>EC</b>	European Commission
<b>EDCTP</b>	European & Developing Countries Clinical Trials Partnership
<b>EMA</b>	European Agency for the Evaluation of Medicinal Products
<b>ESAC</b>	Expert Scientific Advisory Committee
<b>EU</b>	European Union
<b>FDA</b>	Food & Drug Administration (US)
<b>FDC</b>	Fixed Dose Combination
<b>FIIM</b>	Fédération Internationale de l'Industrie du Médicament
<b>FT</b>	Fast Track
<b>FTO</b>	Fast Track Option
<b>GCP</b>	Good Clinical Practice(s)
<b>GLP</b>	Good Laboratory Practice(s)
<b>GFATM</b>	The Global Fund to fight Aids, Tuberculosis and Malaria
<b>GMP</b>	Good Manufacturing Practice(s)
<b>GSK</b>	GlaxoSmithKline
<b>HIV</b>	Human Immunodeficiency Virus
<b>HTS</b>	High Throughput Screening
<b>ICH</b>	International Conference on Harmonization
<b>IDA</b>	International Dispensary Association
<b>IFF</b>	International Finance Facility
<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers & Associations
<b>iOWH</b>	Institute for OneWorld Health
<b>IP</b>	Intellectual Property
<b>IRFF</b>	Industry R&D Facilitation Fund

<b>JNJ</b>	Johnson & Johnson
<b>KEMRI</b>	Kenya Medical Research Institute
<b>KPF</b>	Kunming Pharmaceutical Factory
<b>LSE</b>	The London School of Economics and Political Science
<b>LSHTM</b>	London School of Hygiene and Tropical Medicine
<b>MMV</b>	Medicines for Malaria Venture
<b>MNC</b>	Multinational Company
<b>MRSA</b>	Methicillin-Resistant Staphylococcus aureus
<b>MSF</b>	Médecins Sans Frontières
<b>NCE</b>	New Chemical Entity
<b>ND</b>	Neglected Disease
<b>NDA</b>	New Drug Application
<b>NGO</b>	Non-Governmental Organisation
<b>NIH</b>	National Institutes of Health (US)
<b>NITD</b>	Novartis Institute For Tropical Diseases
<b>OECD</b>	Organisation for Economic Co-operation and Development
<b>PFT</b>	Protein Farnesyl Transferase
<b>PK</b>	Pharmacokinetics
<b>PPP</b>	Public-Private Partnerships
<b>PR</b>	Public Relations
<b>PRPP</b>	Pharmaceutical R&D Policy Project
<b>R&amp;D</b>	Research and Development
<b>SAR</b>	Structure-Activity Relationship
<b>SME</b>	Small and Medium-sized Enterprise
<b>STI</b>	Swiss Tropical Institute
<b>TB</b>	Tuberculosis
<b>TB Alliance</b>	The Global Alliance for TB Drug Development
<b>WHO/TDR</b>	UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases
<b>TIPR</b>	Transferable Intellectual Property Rights
<b>UNDP</b>	United Nations Development Programme
<b>UNICEF</b>	United Nations Children's Fund
<b>VC</b>	Venture Capital
<b>VL</b>	Visceral Leishmaniasis
<b>WHO</b>	World Health Organization
<b>WRAIR</b>	Walter Reed Army Institute of Research

## PREFACE

Our fundamental aim is to improve health outcomes for developing country neglected disease patients by increasing the quality and number of *drug* treatments available to meet their needs (we do not examine vaccines or diagnostics). Within this broad framework, we focus specifically on policies and incentives that Western governments could implement to achieve this aim.

We have taken a strongly empirical approach, covering known neglected disease drug Research & Development (R&D) from 1975 to end 2004, with the exceptions noted below. All findings and conclusions are based on a review of existing knowledge, supported by original research and interviews with stakeholders involved in the development and use of new drugs. Strenuous efforts have been made to check primary sources and to verify our data with the relevant groups.

Although we are primarily health-focused, our work is multidisciplinary, and includes analysis of economic, commercial, political, regulatory and intellectual policy implications. We have consulted widely with groups who have a stake in neglected disease drug development – government, public health community and industry – since we believe that solutions supported by all parties are more likely to be successful and feasible. Where possible, we have disclosed full information. However, in many cases we have used pooled data or non-attributed quotes in order to protect confidentiality.

It is important to clarify the limits of this report. Our analysis and conclusions relate only to neglected disease drug R&D and cannot be automatically translated across to vaccines and diagnostics. We have included drug development activity only as it relates to the ten neglected diseases listed by the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR). These are leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, malaria, leprosy, African trypanosomiasis, tuberculosis and dengue. Other developing country diseases, for example, hookworm, roundworm or diarrhoeal illnesses, are excluded although in many cases our conclusions could equally apply to these.

Furthermore, some areas of activity have also been excluded from within the drug development field. Sometimes this was a deliberate choice – for instance, we have not focused on developing country activity since it is unlikely to be amenable to Western government incentives. In other cases, we may have inadvertently excluded activities because of lack of publicly-available information. This includes, for instance, undisclosed academic work at pre-publication stage and private industry projects that were not disclosed to us, available in public literature or on standard industry databases. It was particularly difficult to gain full information on small pharmaceutical companies working independently of public organisations or Public-Private Partnerships (PPPs). Since our scoping research in this area is early, this independent small company activity is excluded, although it is clear that in some disease areas, notably Tuberculosis (TB), it is significant.

Finally, we do not consider two important areas that impact on, but are not directly related to, neglected disease drug development. The first is ‘upstream’ R&D, including broader public/academic basic and exploratory research that is not compound-based eg identification of new drug targets or mechanisms of disease. In this report, public/academic activity is only considered insofar as it directly relates to a drug development project or programme – where drug development is defined as commencing at the drug discovery stage (ie the process of screening compounds against known targets in order to identify ‘hits’ that could become new drug leads). The second area that is not considered in this report is that of ‘downstream’ issues, such as developing country infrastructure, human resource capacity and implementation. Our exclusion of these issues does not detract from their importance: both are crucial to delivery of new treatments for developing country patients. However, we wished to focus this report tightly on the drug development process itself and how it could be improved and expedited.



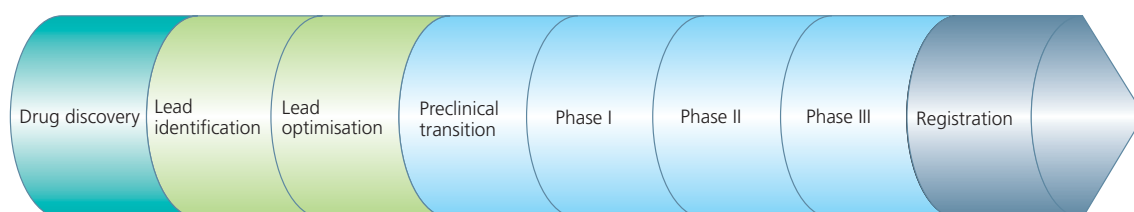
# THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG RESEARCH AND DEVELOPMENT

## 1.1 BACKGROUND

### 1.1.1 Current understandings

Development of new drugs is expensive, lengthy, complex and risky, with most new compounds only reaching patients after a 10-12 year development process (see Figure 1). This has had a marked effect in limiting development of new drugs for neglected diseases (diseases that primarily affect the developing world).

Figure 1. The drug development pipeline <sup>1</sup>



For many decades, governments have attempted to overcome these obstacles by the use of R&D incentives. However, the failure of these policies to deliver more than a handful of neglected disease drugs from 1975 through to 2000 has now led to proposals for new, different and substantially larger incentives.

The starting point for designing these new incentives – and, indeed, for our own research – has been four widely accepted (*although no longer accurate*) understandings. They are roughly summarised as follows:

- only 13 new drugs for neglected diseases have been developed since 1975 (as per a seminal 1999 article);<sup>1</sup>
- neglected disease markets are non-commercial, therefore drug companies are not interested in them;
- drug development Public-Private Partnerships (PPPs) have started, but are unproven; public funds may be invested in the ‘wrong’ PPP, with a resultant waste of money; and the plethora of PPPs is leading to duplication and waste;
- drug development is best left to industry. Therefore, we need to bring multinational pharmaceutical companies, who are the powerhouse of drug development, back into the neglected disease field.

The logical outcomes of these understandings are proposals to stimulate neglected disease R&D activity by making it profitable enough to attract the interest of big companies. For example, the Commission for Africa report, in its discussion of how health and medicines should be prioritised in Africa, stated that: ‘It means giving large pharmaceutical firms incentives to investigate the diseases that affect Africa, instead of focusing on the diseases of rich countries’.<sup>2</sup> Most current thinking suggests this aim would be best achieved by using public funds to create multinational-size ‘markets’ for desired products (eg advance purchase commitments, although these are primarily envisioned for vaccines), or by linking neglected disease R&D to additional returns on Western drugs (eg roaming patent extensions).

<sup>1</sup> Graph adapted from: Nwaka S and Ridley R (2003). ‘Virtual drug discovery and development for neglected diseases through public-private partnerships.’ *Nature 2* (November): 924.

However, our research suggests that these understandings no longer hold true, and therefore different approaches to stimulating neglected disease R&D are needed.

## 1.1.2 Upturn in neglected disease drug development

**1999: There have only been 13 new neglected disease drugs since 1975.**

**2005: There has been a dramatic increase in neglected disease drug development, despite the absence of significant new government R&D incentives.**

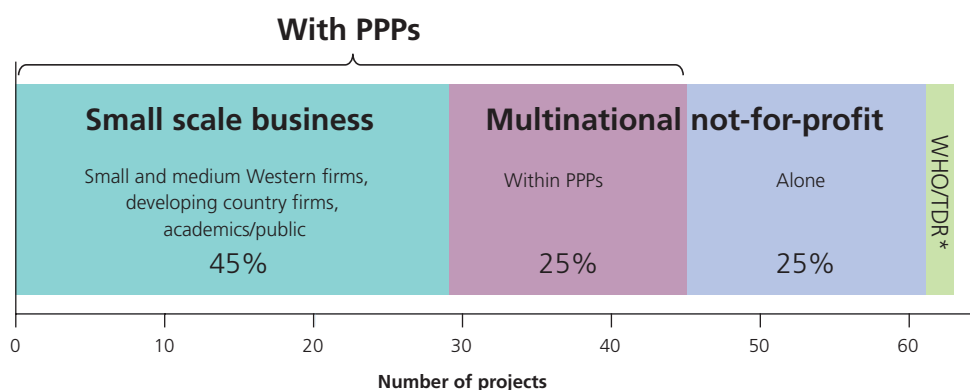
**This increase is a result of recent structural changes in industry and the public sector.**

**Failure to understand these changes may lead to misdirected public policies.**

A review of the drug development field shows that the '13 drugs' figure, which covered the period 1975-1997, does not reflect neglected disease R&D activity in recent years.

- There were over 60 neglected disease drug projects in progress at the end of 2004 (see Figure 2).<sup>ii</sup>
- 18 of these drugs were already in clinical trials (including half at phase III) and two drugs in registration.
- Assuming there was sufficient funding, at standard attrition rates this would be expected to deliver eight to nine drugs within the next five years, even if no further projects were commenced after the end of 2004.<sup>iii</sup>

**Figure 2. The drug R&D landscape for neglected diseases (Dec 2004): 63 active drug development projects**



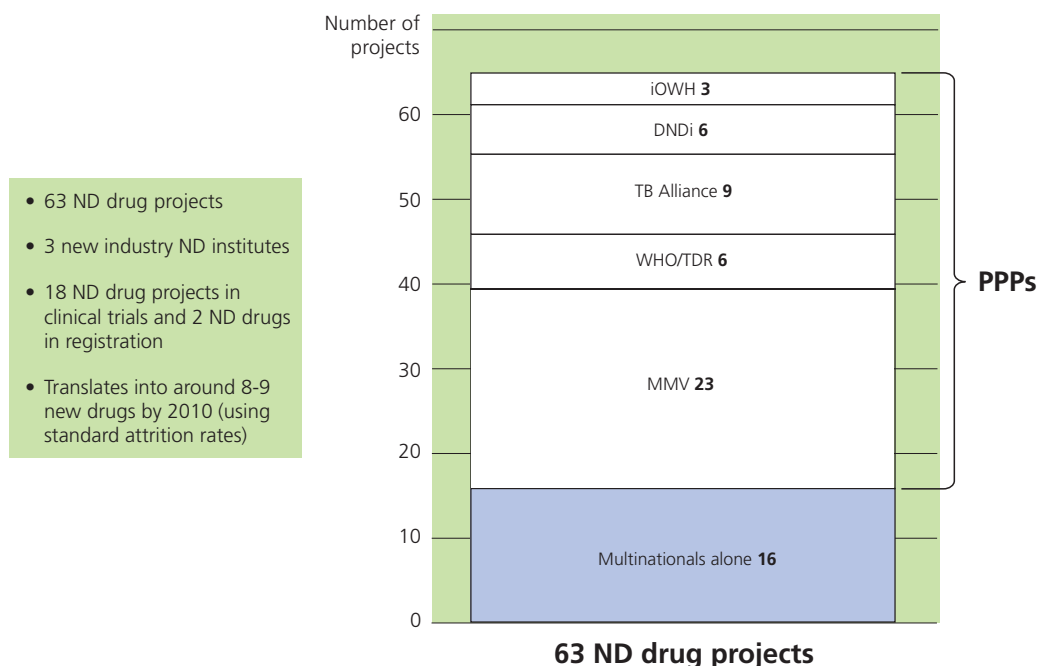
\*Unable to verify details for three WHO/TDR projects.

The breakdown of the current neglected disease activity by type of institution is shown in Figure 3 overleaf. Our figures differ somewhat from published PPP project figures since we have excluded PPP projects that are either not yet agreed, or which have no drug development component (eg treatment protocol trials that are conducted without the intent to pursue a formal label extension or to develop a new product – See Annexe1D).

<sup>ii</sup> This figure excludes independent small company drug development activity and academic basic research, which, if included, would be expected to noticeably increase project numbers.

<sup>iii</sup> DNDi, the TB Alliance and MMV expected yield based on the respective attrition rates proposed by each organisation; other projects (industry and other PPPs) based on Tufts figures (DiMasi J, Hansen R, Grabowski H (2003) The price of innovation: new estimates of drug development costs; Journal of Health Economics 22: 151-185).

Figure 3. Active Neglected Disease (ND) drug R&D projects by institution\* (Dec 2004)



\* Medicines for Malaria Venture (MMV), the TB Alliance, Drugs for Neglected Diseases (DNDi) and the Institute for One World Health (iOWH).

This level of public and private neglected disease R&D interest and activity was unheard of in the past two decades. However, the nature of this increase is more telling than the numbers themselves. It has taken place without commercialising neglected disease markets, and *in the absence of significant new government incentives*.<sup>IV</sup> Rather, it appears to stem from three significant developments:

- **Growing public awareness of the fact that developing country health needs are not being met** is leading to an increased pressure on the pharmaceutical industry and on public donors.
- **Transformations in the pharmaceutical industry sector since the 1980s have resulted in changes for neglected disease R&D over the past five years** (see Section 1.1.3 overleaf).

Pre-2000, newly-merged multinational pharmaceutical companies were actively closing down neglected disease research: ‘Our neglected disease portfolio was at risk of going under in 1995’; ‘We didn’t have a strategy on neglected diseases’ (multinational pharmaceutical company interviews 2004, 2005). Now, however, around one-third of current neglected disease drug projects are conducted in three dedicated institutes set up since 2000 by multinational companies, collectively employing nearly 200 industry scientists.

- **Four new Public-Private Partnerships for drug development have been formed since 2000, financed by an influx of new public, and particularly philanthropic, funds into neglected disease R&D.** PPPs now conduct nearly 50 drug projects, often in collaboration with the specialist industry institutes.

In the long run, we would expect these developments to lead to a significantly higher number of projects and, ultimately, drugs, as these newly formed organisations, and others, continue their work.

By better understanding this current upward trend in activity, and its drivers, governments can develop incentives and policies that build on these promising changes rather than inadvertently replacing or subverting them.

<sup>IV</sup> The European Commission (EC) introduced legislation aimed at European Union (EU) orphan markets in Dec 1999, and the UK Government instituted tax breaks for neglected disease R&D which became active in 2002/3. However, all companies interviewed said these measures had had no impact on their R&D decisions (see Section 1.2.1).

### 1.1.3 Changes in the pharmaceutical industry sector

Since the 1980s we have seen the emergence of 'big pharma'. In 1995, half the global pharmaceutical market was made up by 25 companies, by 2000 this had fallen to 15 companies, and it is now closer to 12. The greatly increased sales base of these 'super companies' has driven them to focus on therapeutic areas offering ever-higher returns, with the typical peak sales threshold for drug R&D candidates increasing to around US \$500 million/year or more. As a result many multinationals have downsized, spun-off or closed down their less lucrative infectious disease divisions, often leading to a significant loss of skills, compounds and knowledge relevant to neglected disease R&D. For example, Roche, Bristol-Myers Squibb (BMS), Abbott, Lilly and Wyeth have done so, although some maintain programmes for diseases such as hepatitis C or HIV/AIDS, which are more commercial.

The in-house commercial R&D model has increasingly moved towards a modular R&D approach, with multinational pharmaceutical companies licensing-in Intellectual Property (IP) from candidate-rich but cash-poor biotechs, small companies and academics, and outsourcing non-core R&D activities to Contract Research Organisations (CROs) including some in developing countries such as India and China. Analysis of company R&D pipelines in 2001 showed that 35 per cent of drugs in Phase III or registration were either licensed-in or derived from collaborative research.<sup>3</sup> Also, according to a study carried out by the Tufts Center for the Study of Drug Development, 'CROs account for about 10 per cent of annual spending by R&D sponsors. ... [They] have experienced a six-fold market increase over the last decade ... and are involved in as many as two-thirds of clinical projects'.<sup>4</sup>

Countries such as India and China are emerging as market opportunities, as well as centres for high-skill low-cost R&D. In response, large companies are increasingly seeking a regional toehold via R&D institutes, partnerships (eg GlaxoSmithKline (GSK)-Ranbaxy in India) and joint ventures (eg Novartis and Kunming Pharmaceutical Factory in China for Coartem®). As JP Garnier, the Chief Executive Officer of GSK noted, 'Globalisation is about arbitrage ... you need to de-aggregate the core processes of the enterprise and reconstruct them so that you get access to the pools of low-cost resources as well as high-value skill sets wherever they are'.<sup>5</sup>

However, developing world markets also pose threats to multinational companies. A September 2004 report by the Pharmaceutical Shareowners Group noted the 'extensive public criticism' industry had faced over the past five years for its 'response to the HIV/AIDS pandemic and the wider public health crisis in emerging markets', and suggested this had 'potential negative impacts on [the industry's] reputation and license to operate'.<sup>6</sup> This pressure on industry has been fuelled by shortages of life-saving vaccines and antibiotics closer to home. While cut-price offers and drug donations for HIV/AIDS and neglected disease therapies have taken off some of the heat, perceived industry neglect of these life-threatening but non-lucrative areas is an ongoing strategic threat to large and profitable companies.

Small pharmaceutical companies – which include biotechs, CROs and, increasingly, developing country firms – have benefited from scientific and technological breakthroughs in bioinformatics, combinatorial chemistry, genomics and proteomics. The increasingly modular approach to R&D has also provided new opportunities for these firms, who often lack 'bricks and mortar' manufacturing capacity, to generate revenue by licensing IP to larger companies or providing them with contract R&D services.

Small companies operate on a quite different scale from large pharmaceutical firms. They often focus on technologies or niche markets, for example, infectious disease and orphan markets, that are of little interest of multinational pharmaceutical companies but well-suited to their smaller scale. We note the preponderance of small firms chasing orphan biologic markets, which had an average annual value of only US \$103 million in 2000<sup>7</sup> (70 per cent of orphan designations went to small firms in the United States in 2001, while this figure reached 85 per cent in the European Union during the period 2000-2004).<sup>8 9</sup>

Because they tend to be 'R&D heavy and commercial/development light', small companies supplement their lack of end-pipeline capacity in various ways. Sometimes, they circumvent their lack of large-scale capacity by targeting smaller markets into which they can sell directly via a specialty sales force (eg orphan markets). In these instances, these companies tend to operate as the manager/integrator, relying heavily on outsourcing to CROs for trials, manufacture and even aspects of preclinical development.<sup>v</sup> By contrast, small firms pursuing larger markets usually team up with bigger partners.

<sup>v</sup> Occasionally small companies may have their own manufacturing capacity; for example, Immtech is setting up a Chinese manufacturing plant for its neglected disease products.

For a commercial indication this is likely to be a multinational pharmaceutical company, while for a less lucrative neglected disease indication, it is more likely to be a developing country firm or a Public-Private Partnership. Many small companies also operate a CRO 'sideline' to finance their core R&D work, particularly if Venture Capital is tight.

These collective changes have paved the way for new interest in, and approaches to, neglected disease drug development.

## 1.2 MULTINATIONAL PHARMACEUTICAL COMPANIES

### 1.2.1 Multinational companies active in neglected disease R&D

**1999:** Multinational companies had very little neglected disease activity, and kept costs and risks down by working slowly and focusing on 'adaptive' products.

**2005:** Four of the top twelve multinational companies now have neglected disease R&D units employing over 200 scientists; three others work on a smaller scale.

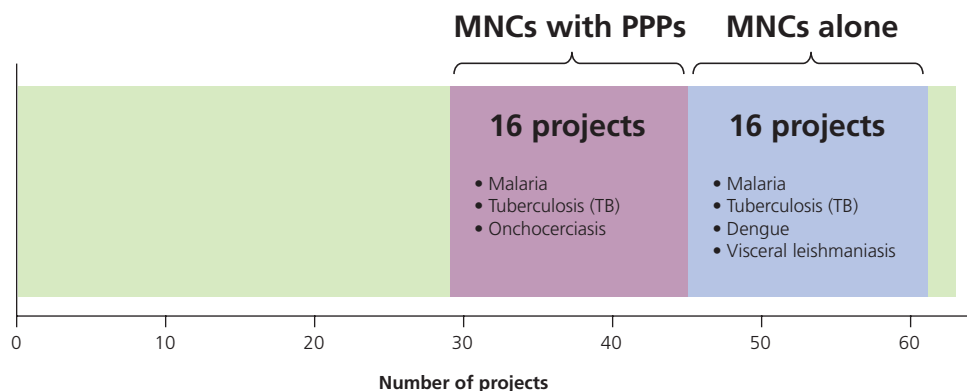
This activity is driven by 'non-commercial' motives (ie by broader business concerns rather than by returns in the neglected disease market) and is conducted under a new 'no profit-no loss' model that provides drugs to developing country patients at cost price.

Structural changes underlie this renewed activity, including an industry move upstream to less expensive, more innovative early-pipeline R&D, and increased reliance on public partners to assist with the more expensive clinical development stages.

#### Activity

A number of multinational pharmaceutical companies have moved back into the neglected disease field, with a substantial increase in their activity since 2000. Seven of the world's top 12 drug companies now conduct around half of the 60-plus neglected disease drug development projects in progress (see Figure 4 and Annexes 1B and 1C). The bulk of this activity is accounted for by the four companies that have formal neglected disease divisions: GlaxoSmithKline, Novartis, AstraZeneca and Sanofi-Aventis. Some of these companies have also expressed interest in expanding into new neglected disease areas, including Chagas disease, sleeping sickness and leishmaniasis, if they can get the right kind of support (company interviews, 2004/05). The remaining three companies have less formal neglected disease activity, conducting perhaps one or two projects each, and generally on a more serendipitous basis.

**Figure 4. Neglected disease drug R&D projects carried out by multinational pharmaceutical companies (MNCs) (Dec 2004)**



European-based multinationals are particularly well represented, accounting for 90 per cent of current projects and all of the structured neglected disease activity. This reflects historical company involvement in tropical diseases as well as Europe's long-standing links with Africa.

## Motivations

All of the captured R&D activity by multinationals is on a *not-for-profit* basis, with all the companies stating that they are not motivated by commercial returns in the neglected disease market, but rather by longer-term business considerations (which stem from the changing pharmaceutical landscape outlined previously). Company motivations are:

- Corporate Social Responsibility (CSR)/ethical issues;
- minimising reputational risk stemming from failure to address developing country needs;
- strategy – for example, positioning themselves in emerging developing country markets by setting up neglected disease joint ventures (eg Novartis' Coartem® partnership); building access to low-cost, high-skilled developing country researchers (eg AstraZeneca's first Asian R&D centre is its neglected disease institute in Bangalore, India); or having an eye to possible spin-offs for disease families that may have developed country market pay-offs.

Individuals within companies are also often motivated to contribute to the global health problems posed by neglected diseases. They may act as 'champions' within a company, encouraging senior management to support this R&D (eg Marion Merrell Dow's TB drug, Priftin® – rifapentine), or they may 'smuggle in' neglected disease projects alongside their commercial work. The latter approach is particularly tenuous, since unmotivated firms can and do decide to stop the R&D once it comes to their attention, while others may take it up on a formal basis (eg Johnson and Johnson's new TB drug, diarylquinoline R207910).

## Business models

### The Intellectual Property (IP) setting

The way in which multinationals view R&D has a great deal to do with intellectual property (eg patents), which is in many ways at the heart of the pharmaceutical industry R&D model.<sup>VI</sup> Patents allow a company to maximise its profits by excluding competitors during the patent period.<sup>VII</sup> These revenues are then used to recover the costs of R&D (including cost of capital and cost of failures), to fund further R&D and to provide financial rewards to the innovator and its investors. In other words, patent profits drive the R&D cycle. During the patent-protected period, society pays a higher monopoly price for the patented invention than if there were free competition, when the product price would be driven down towards marginal cost of production. However, this has generally been seen in the West as an acceptable price to pay to stimulate invention of new products for public health.

The IP-driven innovation model has some limitations. There is no public control over industry's R&D agenda, which, being commercially driven, may not coincide with the areas of greatest public health need. Limited public control over the pricing of the final product, when this occurs, can also result in reduced patient access if purchase funds are tight since less product can be purchased at the higher monopoly price than at the lower competitive price. Although this is more commonly a problem in poor markets (eg the case of anti-retrovirals), there have also been cases where Western authorities have sought to limit patient access in order to control costs (eg 'postcode prescribing' in the UK). Additionally, commercial R&D tends to be more secretive than collaborative, since companies have a strong interest in guarding their valuable IP.

<sup>VI</sup> IP rights do not refer only to patents; they also include trade secrets / confidential information, data exclusivity, orphan exclusivity and, perhaps to a lesser extent here, trademarks and copyright. Patents are designed to provide a limited market monopoly to prevent others from actions such as making, using and selling the patented invention without the patent owner's permission. They have classically been used in the pharmaceutical industry to assure in-house end-to-end control over the whole pipeline (although, as noted above, many multinational companies are taking an increasingly modular approach, including buying in IP from third parties, such as biotech firms, for subsequent development). The usual way this control has been exercised has been with a view to profit maximisation.

<sup>VII</sup> The degree to which competition may in fact be suppressed will also depend on such factors as whether or not there are other (substitutable) products falling outside the scope of the patent that can compete with the patented product.

Lastly, it is important to note that the IP-based R&D model is intrinsically linked to the value of the final IP-protected market – for which IP rights are a cipher – to the company. In general, larger potential profits (more valuable IP) generate greater industry activity. Conversely, low potential profits such as those generally expected from neglected disease markets, render IP of little or no value to multinational pharmaceutical companies and therefore stimulate little activity.<sup>VIII</sup> However the upside is that, when multinationals do have low-value IP relevant to neglected disease applications, this may allow them to be more flexible in their approach. Since there is little at stake and little point in exerting maximum control, large companies are often willing to provide such IP for not-for-profit use and to work collaboratively on its development, thereby opening the door to IP agreements with PPPs, as discussed below. We note that commercialising low-value neglected disease markets, for example, through the use of advance purchase commitments or roaming patent extensions, is likely to increase industry activity (particularly by small companies), but at the cost of curtailing these positive behaviours and returning R&D to the more secretive and non-collaborative approaches that are characteristic of commercial R&D.

### The pre-2000 model

Until 2000, it was difficult for industry to respond to the strategic threats and opportunities of neglected diseases even if they wanted to – and many did not. Companies who persisted with neglected disease R&D largely bore the cost and risk themselves, often helped by subsidised technical and clinical input from WHO/TDR (although rarely direct financing). They balanced the equation in a number of ways:

- by focusing on less-expensive and less risky ‘adaptive’ R&D, such as label extensions of veterinary drugs to humans, new combinations or formulations of existing drugs, or re-registrations of existing developing country drugs to Western standards (see Section 2.3 for a fuller discussion of the value of this approach);
- by working slowly, as staff and funds were prioritised to more commercial programmes;
- by picking up externally developed drug candidates (eg from public groups or small companies) and taking them through late-stage clinical development, although this more expensive approach was less common.

Investment in high-cost/high-risk R&D, such as development of truly novel neglected disease drugs, was minimal and often linked to a commercial market, such as traveller’s malaria (eg mefloquine) or AIDS opportunistic infections (eg atovaquone).

Some firms still use these approaches, particularly adaptive work. For example, Pfizer is developing a new antimalarial by combining existing drugs (eg azythromycin-chloroquine), and Sanofi-Aventis has worked on several antimalarial combinations or reformulations, including co-blisters, injectables, and paediatric and rectal formulations. However, since 2000, such strategies have become increasingly less common (see Section 2.3).

### The post-2000 model

Over the past five years, there has been a sea change in both the level of neglected disease R&D carried out by multinationals, and in how it is conducted. Activity has dramatically increased, with *all* neglected disease drug development projects now being conducted under a not-for-profit approach, or, as one company calls it, a ‘no profit-no loss’ model.

This alternative strategic model differs significantly from the traditional commercial approach, under which a company receives substantial profits from sales of a drug in order to cover the cost and risk of developing that drug. Under the ‘no profit-no loss’ model, companies reduce their R&D costs to a minimum (no loss) thereby allowing them to deliver neglected disease products at low or no markup (no profit). By doing so, they can reduce reputational risk and address corporate social responsibility issues for a minimal investment of company funds, thus protecting their commercial position in the long term. Similar models may be useful to companies in other commercially less interesting areas where public pressure for vigorous new R&D programmes is also high, for example, drugs for Methicillin-Resistant *Staphylococcus aureus* (MRSA).

<sup>VIII</sup> We note that the definition of ‘less valuable’ differs between multinational companies, who may see a US \$200 million market as uninteresting, and small companies, who may see such markets as their core business.

The keystone of the ‘no profit-no loss’ model is a company’s ability to cut R&D costs. This is achieved by focusing in-house investment on early-stage R&D and/or by entering into PPP partnerships for further clinical development, registration and dissemination to developing country patients, although in practice the two go hand in hand, as discussed below.

### Early pipeline R&D

Companies can significantly reduce R&D costs by re-focusing in-house activity from late-stage clinical development to early-pipeline R&D, which requires a significantly smaller investment. It is notable that 80 per cent of current multinational neglected disease projects are now early-pipeline R&D, ie discovery of new drugs up to the point of identification of a robust development candidate (see Annexes 1B & 1C). Early-pipeline costs can be cut even further by locating R&D outside the OECD<sup>ix</sup> or using existing infrastructure, as is the case with all the industry neglected disease institutes (see Box 1).

#### Box 1. Neglected disease industry institutes

- GSK’s Tres Cantos Drug Discovery Unit (Spain – use of existing infrastructure) (malaria and TB)
- AstraZeneca Research Facilities (Bangalore, India – use of existing infrastructure) (TB)
- Novartis Institute For Tropical Diseases (NITD) (Singapore) (TB and dengue)

This approach leaves the open-ended question of who will do late-pipeline clinical development of these industry products, which is where partnering with PPPs come in.

### Working with PPPs

The most common approach to cutting company R&D costs is increasingly to partner with PPPs at some point in the R&D process. Half of current multinational projects are already conducted within PPPs, including projects at all stages of the pipeline from drug discovery to clinical. And many companies who now work alone in the early R&D pipeline noted at interview that they already intend, or are considering, partnering for the more expensive clinical development stages. (Eg one company is already working to PPP drug-specifications with a view to possible future collaboration.) Taken together, this means that the majority of neglected disease drug development carried out by multinational companies is either already, or soon will be, conducted under a partnering model.

The trend to partnerships is based on two key PPP inputs: funding and skills.

PPP funding is crucial to industry’s ‘no profit–no loss’ model – particularly when products enter large-scale clinical trials, at which point the public partner may need to cover virtually all direct R&D costs. As one company said, ‘PPPs are the strongest ‘push’ incentive as they directly and substantially contribute to minimising R&D costs’ (company interview, 2005). Instead of covering full development costs of a New Chemical Entity (NCE), multinational companies can now focus on cheaper early-stage innovation in the knowledge that public partners are available to collaborate on and fund further drug development to registration. The result is not only sharply increased multinational company activity in neglected diseases but also a change in the type of this activity, with more early-stage R&D as noted above. It is therefore perhaps not surprising that as early as 2001, after the Medicines for Malaria Venture (MMV) and the TB Alliance had been set up, industry was already proposing formation of an additional PPP focusing on African trypanosomiasis, Chagas disease and leishmaniasis as ‘an appropriate way forwards’.<sup>10</sup>

Multinational companies also partner because they need public skills to deliver neglected disease drugs that developing countries will use. Very few companies have sufficient in-house experience to do this alone, with most needing to secure public input in one way or another. They may seek to achieve this by, for example, contracting work out to public institutes, hiring staff with relevant experience (eg as Novartis did in its Singapore Institute), or, most commonly, by entering into PPPs – which have the advantage of providing these inputs to industry free of charge. Companies identified public input as ‘very important’ in several areas, including:

- technical, scientific and clinical neglected disease expertise;
- access to facilities that multinational companies no longer have (eg parasite houses, developing country clinical trial sites);

<sup>ix</sup> Organisation for Economic Co-operation and Development.



- knowledge of developing country product profiles and markets and experience in developing country clinical trials and dealing with developing country regulatory and health authorities;
- ‘guarantees’ of public demand, with public involvement seen by all companies as essential for developing country implementation and use of new products. This aspect is very difficult for a company to address without a public partner.

Companies have different preferences as to the timing and nature of their partnerships, although all envision playing a role right through to manufacture and distribution of the final products to developing country patients. For instance, while some companies routinely partner from the earliest discovery stages (GSK); others prefer to conduct and fund R&D alone up to the point of Phase I and Phase II trials, in order to keep greater control and protection over proprietary knowledge (Sanofi-Aventis); while yet others take a mixed approach (Novartis).

Multinationals also envision greater or lesser levels of participation, particularly at the clinical trial stages. For example, some plan to take the R&D lead during clinical development of their products, with the public partner essentially being a funder; others envision co-conduct of clinical trials; and yet others are satisfied for the public partner to take the lead on trials, while the company provides data management and regulatory support. Likewise, while all multinational companies plan to conduct manufacture and distribution of the final neglected disease products, some plan to do so in house while others say they may license this out to developing country generic firms. (This depends to a degree on whether the relevant firm has developing country distribution networks.) As noted above, these products are then provided to developing country patients at not-for-profit prices.

Nevertheless, companies contemplating these partnerships continue to face a number of obstacles. The majority have little or no experience of partnering, and complain that the options are unclear. Potential partners can include PPPs where these exist (there is no funded PPP for industry’s dengue projects),<sup>x</sup> governments, and other external funders, such as the Gates Foundation.<sup>xi</sup> Different partners also offer different inputs and levels of funding, and can vary widely in competence – this can require companies to conduct lengthy ‘due diligence’ to determine the best and safest partner. The uncertain funding of public partners was also cited by all companies – experienced and otherwise – as a significant disincentive to embarking on R&D. As one company noted, ‘we could blow it if high costs force us to drop a product at the clinical stage, but it’s very expensive to do in-human trials alone – we need to find a way’ (company interview, 2004).

Overall, however, PPPs were seen as a very helpful innovation for multinational companies working in the neglected disease area and a key component of the ‘no profit-no loss’ model. Several companies estimated that the combined use of the approaches outlined above – relocating to developing countries, using existing infrastructure, focusing on early-pipeline R&D, and partnering – has allowed them to reduce both the overall costs of their neglected disease activity, and their per-project costs. For instance, several firms estimated at interview that the total direct cost of their neglected disease early R&D portfolios was less than US \$20 million per year, excluding infrastructure, overheads and cost of capital.

Therefore, although multinational companies can now choose among many approaches – partnering, late-stage pick-up of external drug candidates, in-house adaptive work, or full in-house drug development – they have a clear preference for the first of these strategies. Most R&D-active companies now prefer to partner with a PPP either throughout the R&D process, or by conducting early-stage R&D in house and subsequently moving to a partnered model for clinical development. This approach allows companies to see their new product through to registration (their preferred ‘start-to-finish’ approach) but without incurring the full cost, risk and liability of doing so. Companies were less enthusiastic about picking up externally developed drug candidates and taking them through late-stage clinical development, both because of the cost implications and the difficulties associated with developing someone else’s product.<sup>xii</sup> The least favourite option was to develop neglected disease products in house alone to the point of registration, with a typical response being: ‘We have neither the expertise nor the desire to do this’ (company interview, 2005). Multinational companies’ dislike of the last two options is unsurprising, given that these require industry to undertake riskier and far more expensive late-stage clinical development, and require a degree of developing country experience that these companies rarely have.

<sup>x</sup> WHO/TDR covers dengue but has very limited funding for partnering.

<sup>xi</sup> For products with some commercial potential, companies also envisaged partnering with other multinational companies, small companies or CROs.

<sup>xii</sup> Nevertheless, this does occur occasionally. For example, GSK is developing sitamaquine, which it picked up from Walter Reed Army Institute of Research (WRAIR) at Phase II.

## 1.2.2 Multinational companies that do not do neglected disease R&D

**1999: We need a big commercial incentive to bring multinational pharmaceutical companies back into the neglected disease field.**

**2005: Multinationals who have left the neglected disease field say quite clearly that big commercial incentives will not bring them back.**

**These companies want other ways of contributing to R&D (eg helping others).**

### Activity

Five of the top 12 multinational companies do not conduct any neglected disease drug R&D.

### Motivations

The companies we interviewed said they do not want to, and will not, go back into neglected disease R&D no matter what incentives are offered. Typical comments were: 'It's not possible for governments to provide incentives that would encourage neglected disease R&D by multinationals – I wish you could make the government understand this ... the company has to have decided to go in for other reasons'; 'Neither cash nor good PR are going to be enough to drive us back into structured neglected disease R&D'; 'Ever-bigger incentives are just painting us into a corner'; and 'Governments should do more to incentivise small companies, rather than focusing on big pharma'.

Virtually all these companies were nevertheless keen to help if they could find an acceptable alternative to in-house R&D, particularly one that gave them control over their degree of input. A frequent comment was that companies were disincentivised from doing any neglected disease R&D, or even publicising in-house leads that might be of neglected disease interest, by the knowledge that discovery of a new product inevitably meant pressure on a company to sign up for the expensive job of bringing that product to registration and distribution. By taking an 'all or nothing' approach to R&D, policy-makers may be inadvertently stifling companies who have other contributions to make.

### Models

Companies who hold these views have typically re-structured their activities to focus on a small number of commercially rewarding therapeutic areas. As most have cut loose from non-core commercial disease areas, as well as infectious disease and veterinary divisions, it is difficult to imagine that any incentive – 'unless ridiculously large', as one company put it – would be sufficient for them to make a commercial U-turn and re-open an active neglected disease division. One imagines that at best they could work on ad hoc products.

Even if these companies did commence limited R&D, for example on ad hoc products, they may not be optimal partners. The loss of infectious disease and veterinary expertise, skills and compounds has made them less attractive neglected disease drug development partners – as one commentator noted, 'good drug-making skills are 70 per cent *generic*, and 30 per cent specific to the disease or even compound family'. Many also lack African distribution networks and have no experience of developing country trials and regulatory processes, or of markets consisting largely of national health and disease control programmes.

What these companies can offer is access to '*generic*' drug-making skills and commercial libraries. Many have already provided PPPs with targeted inputs, for example, access to company compounds (eg Abbott, BMS, Schering Plough, Roche) or provision of experts for Scientific Advisory Committees (eg Merck, Roche, Eli Lilly).

Individual scientists within these companies also play a prominent role, with a surprising number of PPP projects benefiting from their expert advice (eg BMS's Vice-President of Drug Discovery and two other chemists assisted academics to synthesise analogues of PFT inhibitors; Roche medicinal chemists assisted academics in developing MMV's synthetic peroxide). These contributions although minimal in terms of cash value can nevertheless be very valuable in terms of R&D impact.

## 1.2.3 Overall multinational companies' needs and preferences

When queried as to preferred incentives, all companies made similar requests:

- clear partners to work with and a clear mechanism for partnering. Lack of partners was described by several companies as a strong deterrent and 'major concern', as was the need to build ad hoc partnerships for each new project. As a recent submission by the Biomedical Industry Advisory Group (BIAG) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) noted: 'Industry supports PPPs for neglected diseases because they link up most relevant skills and capacities of different players and there is a clear division of labour between public and private sectors. Governments might consider fiscal incentives to encourage a larger number of companies to collaborate with these PPPs';<sup>11</sup>
- 'suitable' R&D partners, ie those with:
  - a pure R&D focus, as opposed to mixed goals (capacity building, technology transfer, improved regional collaboration);
  - industry experience: 'They should understand industry';
  - sufficient funding to be a viable long-term partner, as again noted by BIAG/IFPMA: '[PPPs] increasingly face costly final clinical development, and thus their long-term viability needs to be addressed more securely, so that they can actually serve as a sustainable supplement to the pharmaceutical industry's sole R&D facility.'<sup>11</sup> Tenuously-funded partners represent a major reputational and financial risk to large companies;
- improved clinical trial capacity in developing country settings;
- better guarantees that newly developed neglected disease products will be used in developing countries. For example, industry is seeking a new purchase fund for the drugs they are developing – perhaps in the form of a Global Fund for Tropical Diseases as an extension to the Global Fund for AIDS, TB and malaria (GFATM). (This is not to be confused with an Advanced Purchase Commitment (APC), which aims to stimulate R&D by creating a public 'market' profitable enough to attract commercially-driven R&D by multinationals).
- a high-level reputational prize: 'The key is to get a better reputational return on our investment'.

Most companies were not seeking additional direct funding for early R&D, describing their in-house spend on this as 'a sunk cost' and 'not an issue'.<sup>XIII</sup>

All neglected disease R&D-active companies said however that they would willingly accept a commercialisation approach if governments offered it and indeed some companies were actively promoting this. We queried companies on their support for large commercial incentives, which are self-evidently incompatible with the 'no profit-no loss' model or the reputational/altruistic approach. Some said that commercial incentives such as APCs would not make them pick up new neglected disease R&D, but might change their existing neglected disease R&D priorities towards an incentive-linked disease; others distinguished between how they would treat a drug with commercial potential (probably in house) and one with no commercial potential (partnered); while others had a more confused position, with the company supporting both a strategic partnering model and a commercial model. Companies also intimated that they would preferentially conduct adaptive work (rather than innovative R&D) in response to an APC, for example, the IFPMA noted that APCs were most relevant 'in areas where most needs can be met through adaptive research'.<sup>12</sup>

Some companies were refreshingly honest, saying that they simply 'asked for Paradise' or, as another company described it, 'took a shopping list approach' to incentives. For instance, industry's proposed Tropical disease Drug Act '...would include both research incentives (R&D tax credits, research grants, lower regulatory fees, fast-track approval) and market incentives (eg advanced purchasing commitments) – although this combination of incentives was seen as most likely to stimulate 'smaller companies to conduct early research projects'. We note in passing that these different incentives are not all compatible and that some may crowd out desired activity generated by alternative incentives.

<sup>XIII</sup> One company mentioned that additional direct public funding would be helpful if the company wanted to build infrastructure capacity to expand into a new disease area.

By contrast, R&D-inactive companies were seeking *alternatives* to in-house R&D. Several supported the idea of a structured platform for them to share skill and expertise with other groups making neglected disease drugs, including PPPs. For example, in May 2005, companies proposed that ‘industry could structure collaborations that combine different disciplines and expertise, to facilitate understanding of difficult diseases and to accelerate the discovery of promising new mechanisms and compounds.’<sup>13</sup>

### 1.2.4 Policy-reality gap

At interview, all multinational companies engaged in neglected disease R&D stated that current government incentives had played no role in their decision to commence this R&D. They believed that additional new incentives were unlikely to shift the behaviour of firms who had disengaged from neglected disease research, and saw the main role for any new incentives as being ‘to support companies who had already decided to do neglected disease R&D for other reasons’.

There is a clear disjunct between these views and current government thinking which, as noted previously, is focused on ‘commercialising’ R&D (ie creating return opportunities) on a scale large enough to bring ‘big companies back into the field’. For instance, by using very large ‘pull’ incentives, governments hope to entice more companies to commence development of neglected disease products.<sup>xiv</sup> This policy approach is built firmly on the four understandings outlined at the start of this report – beliefs that held in the pre-2000 world of neglected disease drug development, but are no longer accurate. Consequently, government policy-thinking is now significantly out of kilter with the current industry neglected disease drug landscape.

A key problem of the commercialisation approach is that it is designed to encourage companies to undertake late-stage clinical development. This is a significantly more expensive approach than the alternative early-pipeline model that most companies have chosen. By encouraging/incentivising companies to move back down the pipeline towards late-stage clinical development, governments are unwittingly increasing company risks and costs, and therefore the amounts of public funding needed to reimburse and motivate them.

It is also somewhat unclear who is being targeted by proposals such as APCs. Multinational pharmaceutical companies say APCs are unlikely to bring them back into the field, apart perhaps from adaptive work, while small companies, who are interested and more likely to respond, are particularly weak in the end-pipeline and would presumably need a bigger partner in any case. If they are designed to support and encourage multinational companies that are already active, then APCs seem very likely to ‘work’. However, this offer of temptingly large commercial incentives – for activities that companies now willingly conduct for free or very cheaply – seems highly likely to shift current company activity from a strategic/altruistic approach to a for-profit model, at an additional and probably unsustainable cost to the public purse of many billions across all neglected disease products.

By contrast with the high level of policy debate aimed at creating new ‘commercial’ incentives suited to large companies, there are no government initiatives to support multinational companies’ flourishing ‘non-commercial’ neglected disease activity (ie in the sense that companies are not seeking profits from their neglected disease drugs in developing country markets, although they will naturally have broader business considerations in mind). Companies have largely pursued this new approach unaided and it now represents more than 30 new projects. Unless public support rapidly increases, however, companies are unlikely to continue these activities, which are rapidly moving to the point at which public partnering will be crucial. There are also no policies designed to suit R&D-inactive companies who wish to contribute in other ways. This perhaps explains the popularity of PPPs, which are currently the only ‘incentive’ tailored to industry’s current approaches to neglected disease drug development.

<sup>xiv</sup> In essence, pull mechanisms such as Advanced Purchase Commitments and Transferable Intellectual Property Rights use public funds to create a neglected disease ‘market’ roughly equivalent to normal Big Pharma markets (ie peak sales of around US \$500 million or more) to entice companies back into the field. Although originally designed for use in vaccine R&D, which has a very different cost/risk/benefit profile to drug development, these incentives are often considered for drug development, for instance in US Project Bioshield II legislation.

Overall, there is a mismatch between multinational company neglected disease activity and the policies that governments are now proposing. Governments are offering:

- 'commercial' incentives ... although companies currently have largely non-commercial motivations in the neglected disease market itself;
- policies designed to suit competitive commercial in-house R&D ... although most companies prefer (and sometimes need) collaborative partnerships, particularly in less familiar neglected disease areas;
- policies premised on companies picking up or conducting expensive and risky late-pipeline development to registration ... although multinational companies have expressed a strong preference for working in the cheaper, less risky early-pipeline and partnering for later R&D.

## 1.3 SMALL COMPANY ACTIVITY

### 1.3.1 Small companies overall

**1999: Neglected disease markets are non-commercial; therefore pharmaceutical companies are not interested.**

**2005: Some small companies are already targeting neglected disease markets on a commercial basis, but need help overcoming barriers to entry.**

**'Add-on' neglected disease R&D can make good business sense for small Western-focused companies if public funders can strike the right deal.**

**Contract Research Organisations see public/PPP neglected disease R&D as a growing niche market.**

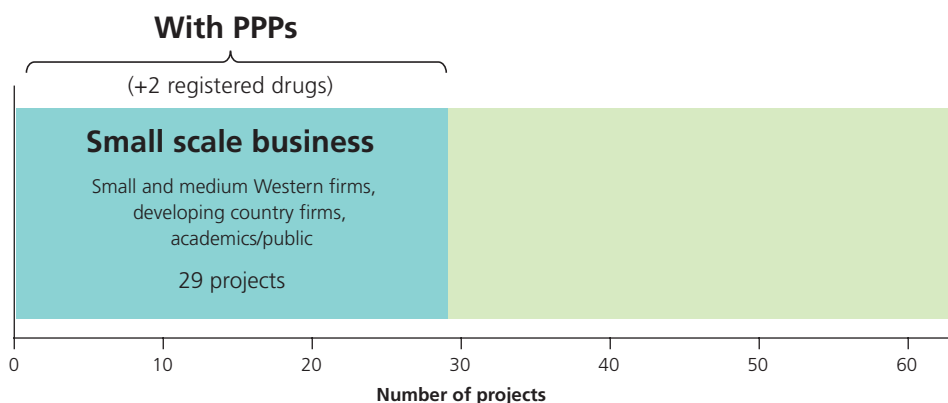
#### Definitions

By 'small scale' business, we refer to companies who are substantially smaller than multinational companies, and who may be motivated by far smaller returns, for example, by markets of less than US \$200 million in peak sales. This includes small and medium-sized pharmaceutical enterprises – virtually all the identified companies had less than 80 employees – and both small and large Contract Research Organisations since, irrespective of size, these firms will still pursue relatively small contracts.

#### Activity

Around half of the identified 63 neglected disease drug projects, plus an additional two registered drugs, were conducted within PPPs by small-scale commercial firms and academics/public groups working on a fully paid basis (see Figure 5).

**Figure 5. Neglected disease drug R&D projects carried out under the small scale business model (Dec 2004)**



- Almost half of the identified 63 neglected disease projects are conducted on a commercial or fully paid basis.
- Five of these drugs are in clinical trials (DB-289, synthetic peroxide, pyronaridine-artesunate and dihydroartemisinin-piperaquine for malaria; PA-824 for TB).
- Two projects additional to these 29 have resulted in registered drugs since 2000 (Artemotil® – β-arteether for malaria; Impavido® – miltefosine for visceral leishmaniasis).

Within this sample, we concentrate specifically on the activity of Western small companies and CROs, since incentives and policies for Western commercial firms are the focus of this report. Commercial or cash-driven activity with developing country firms or academic/public institutions will therefore not be further discussed in this context.

Only eight of these 29 projects are simple one-to-one partnerships between a PPP and a Western company. The others are an often complex mix of paid R&D contracts with CROs, developing country firms, public groups and contract academic researchers, plus academic drug development grants. The Western commercial component of this activity (excluding all contracts or grants with academic/public institutions) is therefore perhaps better quantified as share of total PPP spend, rather than simply by project numbers. In value, this activity represents around one-third of overall R&D PPP spending – with PPP payments to small commercial firms being approximately equal to PPP payments to multinational companies.

Finally, the projects identified here include the activity only of small scale companies working within PPP partnerships. As a result our conclusions apply only to this PPP-small company model. Other small companies are working independently on neglected disease research outside the PPP model – examples being Sequella and Fasgen in the US, developing drugs for TB, and Palumed in France, developing compounds for the treatment of malaria. We will not comment on these here, as we are still scoping activity in this sector (these firms are more difficult to track down). We note, however, that the views of these ‘independent’ firms, as expressed in interviews to date, have so far been consistent with those presented below.

These companies are defined as ‘commercially driven’ since, in all cases and unlike multinational companies, they were motivated to conduct neglected disease R&D by the prospect of shorter-term private returns in the neglected disease market or a related Western market rather than by altruism or long-term strategic concerns.<sup>xv</sup> These returns may come from:

- neglected disease markets themselves (eg small companies focused on neglected diseases);
- parallel Western disease markets, which the neglected disease R&D can support (eg small companies focused on Western diseases);
- subcontracts from groups conducting neglected disease R&D (eg Contract Research Organisations).

### 1.3.2 Small companies focused on neglected diseases

This includes only four projects (as noted above, additional independent activity exists but has not been fully quantified). Two of these projects have already resulted in registered drugs (Impavido® by Zentaris and Artemotil® by Artecef/Ace Pharmaceuticals) and one is in clinical trials (DB-289, by Immtech).

#### Motivations

This small but interesting group of firms differs from all other projects discussed in this report, in that they see neglected diseases as a potential commercial niche market. For instance, Dr Mathias Pietras of Zentaris, who recently registered Impavido® for leishmaniasis, noted that ‘while such a market would be negligible for a big pharmaceutical company, it has a good economic scale for us’ (company interview, 2004).

<sup>xv</sup> Although longer-term strategic considerations are also aimed at improving overall company profit position (in the longer term), this is quite different from the shorter-term returns that small companies are seeking.

Numbers are too small to draw strong conclusions; however we note that all firms managed the borderline commercial nature of these markets by adopting profit maximising and risk management strategies, including:

- partnering with PPPs;
- targeting both developing country and non-developing country (middle-income/Western) markets for the neglected disease indication (eg Impavido® is also registered for cutaneous leishmaniasis in Colombia, with proposed extension to other Latin American, Middle Eastern and US army markets);
- considering other potential Western indications for their primary neglected disease technology. For instance, Immtech is a company explicitly focused on neglected diseases but is also exploring use of its technology platform in hepatitis C and certain cancers.

Perhaps a more relevant question here, given the small numbers, is not why these companies find the neglected disease market worthwhile, but rather why so many other small companies do not. It is clear that poor expected returns compared to other commercial markets are a major disincentive for many neglected diseases. But this cannot be the whole reason since even larger neglected disease markets such as TB and malaria, which offer returns equal to, or greater than Western orphan markets, are still neglected.

In practice, these markets feature a number of additional disincentives for small companies. They are often poorly quantified, with most small companies having little idea of their potential value. Western small companies are also rarely familiar with neglected disease science, as opposed to more commercial disease indications. Finally, and perhaps most importantly, neglected disease markets have far higher barriers to entry for small firms than orphan markets. Small companies are more easily able to address high margin-low volume orphan markets (both in terms of manufacture and marketing) that may consist of only a few thousand target patients centred around a handful of specialist medical centres. Whereas large, disseminated neglected disease markets require capacity for large-scale clinical trials, manufacture and distribution – areas in which small companies do not have a comparative advantage. It is these issues – not just market value – that need to be addressed if these markets are to become more commercially attractive to small companies.

## Partnership model

The key driver for these small companies is the expectation of profit from sales of the final product to the neglected disease market itself.

Therefore, even without PPP funding, these companies will still seek to develop products for neglected disease markets. Most have their own private and public funding sources in addition to PPP funding, and expect future sales revenues to cover their development costs and generate a profit. Some are also actively building their own capacity to address developing country markets. For example, Zentaris has an Indian development and distribution partner (German Remedies) and Immtech has a planned joint venture with a manufacturing and packaging plant in China and is also developing its own developing country trial capacity.

Despite their relatively independent stance, all these companies sought and welcomed PPP input, although, as noted, in a supportive rather than a catalytic role. PPP input can:

- **improve the small companies' cost-benefit equation** (helpful in borderline markets) through providing top-up funding, and access to PPP volume discounts:
  - Zentaris received substantial in-kind assistance from WHO/TDR for the development of Impavido®, while Immtech received around 50 per cent of its funding from public sources, including MMV and the Gates Foundation, before it raised a further US \$45 million of private financing through an initial public offering;
  - Immtech received access to MMV discounted rates from Quintiles (the CRO that assisted with clinical trials) and from the Swiss Tropical Institute (STI) for its parasitology services;
- **provide scientific and technical input** to assist small companies on the steep learning curve to making a successful neglected disease drug – eg:
  - assistance with developing country trials (eg Zentaris in India, Immtech in Thailand);

- provision of technical tropical disease skills and developing country market knowledge;
- **help with market entry** via contacts with international organisations, such as WHO and UNICEF, and developing country health and regulatory authorities. This was seen as particularly valuable although difficult to achieve (eg Zentaris and Artecef/Ace Pharmaceuticals both failed to secure this, although for different reasons – see Zentaris case study below).

Because their investment in neglected disease R&D is conditional on making a profit from the target developing country market, neglected disease-focused companies seek to maintain full control over their Intellectual Property (IP), including manufacturing and marketing rights, and take an equally hard-line approach to protecting it as multinational companies do with their valuable IP (see IP discussion in Section 1.2.1).<sup>xvi</sup> One potentially negative aspect of this is that the public partner has less control over the distribution and marketing of the final product, which can leave ultimate decisions – and their public health impact – down to the company.

Neglected disease-focused firms will also seek to price the final product up to the developing country market's capacity to pay, rather than taking a cost-of-goods approach, as many multinational companies do within PPP partnerships (eg one small company sought a 15 per cent mark-up). This is to some extent mitigated by the need to reach both public and private markets to maximise overall profit, with the former yielding quantity-driven, low margin returns (given the very modest purchasing power of developing country public markets), and the latter returning higher margins through higher prices, but at much lower quantities (see case study on Zentaris below).

In return for PPP assistance, however, these small companies can be willing to reach agreements that include cut-price deals in order to secure access to larger public markets – this is particularly the case if the PPP has provided substantial input, in kind or otherwise. However, we also found a number of firms who had refused to sign PPP deals on the grounds that they saw the PPP's pricing, production and/or distribution terms unreasonable (eg Sequella).

#### Box 2. Case study: Zentaris

**Impavido® (miltefosine)** was originally looked at by Wellcome plc for leishmaniasis in the mid-1980s. However, it was later developed as an oral anticancer agent by Asta Medica and since 2001 by its spin-off biotech company Zentaris AG (now Zentaris GmbH, Frankfurt), in collaboration with the Max Planck Institute and the Göttingen University Hospital. Oral cancer development was discontinued after poor Phase I and II trial results in the late 1980s and early 1990s. In 1995, the company signed an agreement with WHO/TDR to pursue an anti-leishmanial indication after academics demonstrated good oral activity against *Leishmania sp.*

The company noted at interview that they saw this R&D as attractive for several reasons. The decision by WHO and the Government of India to try to eliminate leishmaniasis on the Indian subcontinent by 2010 was seen as an immediate market opportunity. The limited geographical market was attractive, with over 90 per cent of cases of visceral leishmaniasis being concentrated in five countries (India, Bangladesh, Nepal, Sudan, and north-eastern Brazil<sup>14</sup>) and India alone bearing 50 per cent of the global burden. Finally, Impavido® is one of Zentaris' few marketed products: the company has 15 products in development but only two on the market as yet, namely Impavido®, and Cetrotide® for in vitro fertilisation. This is a significant achievement for a company of Zentaris' size, and a big asset in terms of their profile.

A second important feature was the availability of public assistance, including substantial in-kind public input from WHO/TDR. The international organisation set up a joint public-private steering committee for the project, provided specialist leishmaniasis and developing country input, helped develop trial protocols and sponsored clinical trial monitoring. Indian public research groups helped the company conduct four Phase I and II trials in India between 1997-2000, and a large Phase III trial in adults and children in 2002 that showed a 95 per cent cure rate. Quick registration of Impavido® in India was made possible by the

<sup>xvi</sup> The level of IP protection available in the target market, in this case developing countries, will likely differ from that in the OECD. Developing countries have to balance their need to access affordable versions of medicines against the need for R&D incentives and so may choose less extensive protection than rich countries provide – although the WTO/TRIPS agreement now mandates minimum standards. In those countries where the desired IP protection is not available, a degree of control may nevertheless be secured in other ways – for example, if they strike an exclusive distribution agreement with the relevant health authorities.



close contact between WHO/TDR and the government of India during the pre-registration studies, and Zentaris was able to secure development and distribution partners, including an Indian firm (German Remedies).

Overall, Zentaris estimates its capitalised development costs in the double-digit millions. It was hoping to distribute Impavido® to developing countries at a WHO-agreed price of between US \$60 and US \$85 for an oral 28-day treatment for the public/NGO market. At face value, this is more expensive than alternative generic antimonials (US \$13 per patient). However the latter are more toxic, already demonstrate widespread resistance and require a month's hospitalisation, with additional cost implications. Once treatment costs are taken into account, Impavido®, if available at the lower US \$60 public price, will be both cheaper and substantially easier for patients and healthcare staff (no hospitalisation is required).<sup>xvii</sup> Impavido® is already sold in the Indian private market at US \$145 for a 28 day treatment.<sup>15</sup> The European price is expected to be between US \$6,000 and US \$12,000 for the roughly 1,000 European cases of leishmaniasis, providing a sensible example of using Western markets to cross-subsidise the developing country price.

While the public-private collaboration led to the successful development of Impavido®, some problems remain. Impavido® was originally developed for cancer; therefore the drug profile is not optimal for leishmaniasis: the month-long treatment makes patient adherence difficult and precautionary contraception must be given to female patients of child-bearing age because of potential teratogenicity.

Most importantly, the partnership has so far failed to achieve any positive outcome in the roll-out phase of the drug. Three years after registration of Impavido® in India, WHO has still not completed the price deal, and the government of India has still not implemented a public distribution programme of the drug. WHO/TDR is, however, now conducting large Phase IV field trials in order to test miltefosine's suitability for broader use, for example as part of India's eradication programme for visceral leishmaniasis. The very slow implementation by the public partners in effect means that Zentaris is still unable to access the public market and that consequently the drug is not available to the poorer patients who need it. The company has decided in the meantime to make the drug available on the Indian private market, thereby increasing the risk that it is being given to pregnant women and possibly increasing the risk of rapid development of resistance due to patients taking incomplete treatment courses (see Section 2.2 for health assessment).

### 1.3.3 Small companies focused on Western diseases

Only four small company-PPP projects are included under this heading; three additional deals between Western-focused companies and PPPs failed to reach agreement.

#### Motivations

These small companies are primarily focused on Western disease markets, and are under continual pressure from their venture capital financiers and their board to remain so. They do not see developing country markets as interesting, with one firm noting that, '... if a drug cannot project US \$300-500 million sales in the US then it will do very little in the Third World, so the developing country market is not an attractive one to focus on' (ActivBiotics).

However, if a PPP can construct a deal that makes good business sense to these firms, they may agree to develop a neglected disease indication for one of their compounds alongside their commercial work. When such an agreement is possible, companies can be very positive about neglected disease work. If it is not, companies will generally ignore the neglected disease opportunity altogether or may re-target it towards Western markets (eg ActivBiotics did not pursue development of rifalazil analogues for developing country TB after failing to reach a deal with the TB Alliance).

<sup>xvii</sup> Overall cost of treatment for the different regimes, including delivery costs, has been assessed as US \$95-US \$135 for oral Impavido® (depending on where in the US \$60-100 bracket the final price falls), compared to US \$125 for antimonials (SSG).

We note also that many small companies have commercial compounds that may have neglected disease interest, which have not yet been exploited, for example, companies focusing specifically on infectious disease R&D, or companies that have inherited such compounds from multinational spin-offs eg Basilea from Roche and Novexel from Sanofi-Aventis.

The two key factors in constructing an attractive deal are that the neglected disease work must be cost-neutral to the company; and that it must additionally enhance their primary commercial activity (ultimately increasing their overall profits) by providing one or more of the following:

- *generation of neglected disease data that can be cross-applied to core commercial compounds:* for example, Paratek's malaria tetracycline resistance studies, carried out with MMV, provided valuable insights into their commercial anti-bacterial research: 'We will pursue it if it supplements our primary research as well as fulfilling a greater good';
- *extension of the company's compounds into secondary neglected disease indications,* with modest commercial gains from royalties. For instance, ActivBiotics entered negotiation with the TB Alliance on this basis for the development of rifalazil analogues for TB in developing countries;<sup>xviii</sup>
- *'proof of concept' for a technology with both neglected disease and wider commercial applications.* This can apply to existing companies or to start-up companies at proof-of-concept stage (or to academics hoping to start new companies). In the case of start-ups – where PPP or public funding arrives before Venture Capital (VC) financing has been sought – PPP financing has the considerable advantage of being non-dilutive, and therefore highly attractive to a small company that will likely later seek VC funds;
- *Other interests* – in one case, a larger small company sought a strategic developing country partnership in China.<sup>xix</sup>

Western-focussed companies appear to be closely balanced between being interested in neglected disease work and just finding it too much trouble. This is not only due to pressure from the small firms' VC financiers and board, who tend to frown upon activities they see as distracting these companies from their short-term commercial focus, but is also linked to a high level of anxiety over protecting their commercial IP.<sup>xx</sup>

For these companies, the protection of their Western IP – their key commercial asset – is a primary concern. Unlike multinationals, many small biotechnology and pharmaceutical firms have no sales revenues and a relatively small number of commercial compounds. Protecting this IP, and the future profits it represents, is therefore vital to their survival. In this context, companies will only enter PPP deals if they can be absolutely confident that by doing so they do not put their commercial IP at risk. One venture noted that 'licensing IP rights specifically for an indication for someone else to develop is risky because improper trials, use and distribution can harm our primary assets and our commercial opportunity' (company interview, 2005).

The perceived risk associated with licensing rights to a compound for a neglected disease indication was heightened by the fact that the target market is developing countries. Companies expressed fears that parallel imported or locally licensed generic versions of their drug could flow back into the West from developing country markets, thereby compromising the value of their IP. Indeed, most firms said they would not offer their lead compound for a neglected disease indication, but would prefer to give related molecules in order to protect their primary IP assets. These fears are genuinely held and need to be addressed; however, sometimes they did not fully take into account the fact that there are already powerful IP and regulatory mechanisms in place in the OECD to deter illegitimate drug importation (of the company's own drug, or of a generic version or counterfeit product).

<sup>xviii</sup> This project is not counted in our quantitative analysis as no agreement was reached.

<sup>xix</sup> This small company prepared regulatory dossiers and filings in return for a business relationship with a Chinese firm and royalties from commercialisation of the finished product in Europe, Asia and Africa (trials are managed by MMV and the developing country partner).

<sup>xx</sup> Additional IP issues can exist when developing TB drugs, since the TB indication itself may 'muddy the waters' for the Western commercial market (for example, for use as a broad-spectrum antibiotic).

## Partnership model

For small companies focused on Western diseases, PPP input plays a vital role in catalysing neglected disease activity that these companies would otherwise not undertake on their own. This input is in the form of both funding and technical/scientific assistance, with Western-focused firms likely to require greater amounts of both than their neglected disease-focused brethren.

### Funding

Most PPPs, for example MMV, cover all direct R&D costs but exclude overheads (estimated at 10-15 per cent of costs). Others cover R&D project costs only, but do not cover the cost of additional staff needed to conduct the neglected disease work. The latter can be a strong disincentive to companies, since their VC funders generally object strongly to staff being diverted from commercial to neglected disease work. PPP funding is usually short-term (for example, one to two years), and is generally provided in a combination of up-front and milestone payments.

The amount of funding varies depending on the type of firm being funded. Funding to support R&D within *existing* firms is in the order of US \$1 million over two years for preclinical work (consistent with current National Institutes of Health [NIH] grants). Funds to support a start-up *firm* or technology would be significantly higher, on a par with 'round one' VC financing. For example, Amyris received around US \$12 million over five years (heavily front-loaded for the first three) through a deal with the Institute for OneWorld Health (iOWH) and academic partners, funded by the Gates Foundation. Both of these approaches are nevertheless cheaper than fully commercial R&D, since funds cover only direct R&D costs (for example, excluding cost of capital) and scientific synergies between the commercial and neglected disease portfolios can be leveraged.

### Operations

All these firms had little or no experience of neglected disease work or of developing country markets. They were happy to hand over much of the clinical development process to the PPP partner provided they could sufficiently protect their commercial interests, for example, protecting their reputation through ensuring product quality, and controlling against IP infringements.

The PPP support generally includes technical tropical disease input and assistance with clinical development. It may also include assistance at the manufacturing stage, although companies had different views on this. Although some mentioned the possibility of manufacturing themselves, most were content for development and manufacture to be outsourced to a developing country partner, provided they could monitor trial safety results and final manufacturing quality; others simply wanted some influence over choice of developing country manufacturing partner. 'The only way to be sure of a drug's quality is for us to conduct or directly oversee production ourselves' (Paratek).

In return for these PPP inputs of cash and skills, these small companies normally licensed the relevant compound to the PPP solely for the neglected disease indication in developing country markets, and agreed to sell the drug either at cost or for modest royalties (3-5 per cent).

**Box 3. Case study: OneWorld Health-Berkeley-Amyris Partnership**

*'Amyris' partnership with private and public institutions to develop a production process for the antimalarial drug artemisinin exemplifies our progressive business model. We will take no profit from the sales of this product to the developing world. However, the 'plug and play' nature of our platform technology ensures that the techniques perfected in artemisinin production will translate into any isoprenoid biosynthesis process, allowing us to pursue a range of commercial opportunities in the pharmaceutical and fine chemicals industries.'*<sup>16</sup>

As part of their synthetic biology work in the environmental, energy and health fields, University of California, Berkeley, developed a new method of microbial drug production. In 2004, this technology was licensed out royalty-free to a PPP (iOWH), and to a spin-off company (Amyris) for the development of a large-scale low-cost commercial drug production process.

In December 2004, iOWH received US \$42.6 million funding from the Gates Foundation to work with Berkeley and Amyris to develop this process to produce artemisinin, the key component of new antimalarials. Amyris itself will receive US \$12 million over five years through up-front and milestone payments. The new process could potentially cut the cost of artemisinin-based therapies to as little as 10 per cent of their current prohibitive price (artemisinin-combination therapies now cost around US \$2.40 per adult malaria treatment).

UC Berkeley will continue research to perfect the process for artemisinin; Amyris will develop the large-scale industrial fermentation process needed for commercialisation; and the PPP (iOWH) will perform the drug development and regulatory work to demonstrate bioequivalence of the microbially-produced artemisinin with the original natural product. Once the technology for large-scale production is fully operational, Amyris will transfer it royalty-free to iOWH, who will probably licence a developing country company to manufacture and provide the product at-cost to those who need it (eg for use in combination therapies). Amyris will provide ongoing consulting support to iOWH and make future technical improvements from their commercial programme available to iOWH and the developing country manufacturer.

This approach is allowing Amyris to develop its commercial technology by working on a publicly-funded neglected disease project. The non-dilutive public grants will help their company valuation and improve their appeal and viability for future VC funding, while keeping them oriented towards public needs: 'We were very close to going down the traditional VC route, after which time our technology would likely have been blocked from being applied towards antimalarials' (interview, 2005).

### 1.3.4 Contract Research Organisations

Pharmaceutical Contract Research Organisations (CROs) provide R&D services for a commercial fee. They cover the entire R&D value chain, from discovery through to registration.

Over one-third of the 47 PPP projects within our dataset used Contract Research Organisations to support the R&D process. On some projects, *all* drug development is subcontracted to CROs (eg the TB Alliance's development of PA-824), although it is more common for a CRO to be contracted by the PPP to provide supplementary services to other partners, including academics, small companies and developing country firms. CROs working with PPPs include large firms, such as Quintiles and Covance, as well as a myriad of smaller ones.

#### Motivations

After experiencing considerable growth in the past ten years the CRO sector is now starting to consolidate, with leading players employing more than 10,000 staff and having multiple offices around the world. Within this sector, some CROs are increasingly targeting public markets as a way of differentiating their services and supplementing revenues. These firms see the public market – including PPPs – as a growth sector, and as sufficiently attractive for some to set up dedicated sales forces (in particular those who have offices and experience in developing countries). One interviewed company mentioned that their target public sector revenue for 2005 is around US \$100 million, with one-third of this expected to come from (drug and vaccine development) PPPs.

## Partnership model

Examples of CRO contracts with PPPs include the following:

- The TB Alliance has contracted out the entire development of PA-824 to CROs (from preclinical to Phase I);
- CROs were contracted to assist in management of the discovery phase of MMV's synthetic peroxide project, and subsequently for clinical trials;
- On its Protein Farnesyl Transferase (PFT) project, MMV hired CROs to support the collaboration between the partnering academic partners (University of Washington plus Yale University), and to assist with *in vivo* animal work, ADME (absorption, distribution, metabolism, excretion), Pharmacokinetic (PK) and toxicology studies;
- Drugs for Neglected Diseases Initiative (DNDi) has used CROs to support its public and developing country partners (for example, training of local clinical investigators and trial monitors).

CROs run a commercial business and expect their clients – whether these be multinational companies, small companies, biotech companies, public health groups or PPPs – to pay full commercial rates. That said, some CROs may provide discounted rates to PPPs on a volume basis and/or to establish a business relationship (as they do with companies).

The nature of the relationship between the PPP and CRO is transactional. Unlike small companies who partner with a PPP to develop one particular compound, CROs do not remain involved in a project outside the specific service they were contracted to perform (eg toxicology). Hence, they do not have/gain any stake in the final product being developed. As one CRO IP policy states, 'You pay for it, you own it. Period'.<sup>17</sup>

The interest of CROs in the PPP niche market is nevertheless somewhat dampened by the inability of PPPs to commit funds in the long term. For instance, CROs are sometimes hired to manage expensive clinical trials without PPPs having secured funding for the full length of the trial process. PPPs may also pressure CROs to provide discounts; while CROs complain that cash-strapped PPPs 'try to do everything on the cheap' (CRO interview, 2005).

### 1.3.5 Small companies' needs and preferences

None of the small companies we spoke to had commenced neglected disease R&D in response to existing incentives. They viewed orphan drug legislation as largely irrelevant, saying that US or EU neglected disease markets were too small, and that US orphan exclusivity protection offered no significant advantages over patent protection except as a possible 'stamp of approval' (noted by ActivBiotics, Immtech, Paratek and Amyris). R&D tax breaks were viewed equally poorly, although some firms suggested they could act as an additional incentive to investors (in this context, however, they are 'a bonus but not a deal-maker or deal-breaker').

When queried as to preferred incentives, small companies focused on Western diseases had common requests:

- better information on sources of public financing and social VC – 'We don't know all the questions to ask, or who to ask, especially in Europe' (US firms); 'we were unaware that MMV could offer funding' and 'it's hard for small companies who have no contacts inside grant bodies';
- sufficient funding to ensure that neglected disease R&D remains cost-neutral to the company. This funding should be provided as ongoing capital *during the R&D process* rather than at the end of the pipeline, it should be for a *minimum two year commitment* to allow longer-term planning and staff security (short-term funding was seen as a disincentive) and it should cover *all direct R&D costs* related to the neglected disease project, including the costs of any additional staff needed to conduct the neglected disease work;

- ‘round one’-type public or PPP funding for ‘start-up’ companies with promising products that have overlapping neglected diseases and Western commercial applications. This approach could also be very helpful to academic groups who may spend years trying to secure traditional private financing for promising but unproven technologies;
- alternatives to conducting further R&D, including licensing preclinical compounds to PPPs in return for up-front and milestone payments, with further development to be conducted either by the small company or under the auspices of the PPP by others, including possibly developing country firms. Quite small amounts were mentioned by several firms, for example, a US \$1 million up-front licensing fee, milestones up to a total of US \$5 million as the project moved to completion, first option on the Western rights, and split royalties, with the small company taking 5 per cent of developing country royalties and providing a stream of royalties back to the PPP from Western neglected disease sales.

Neglected disease-focused firms additionally sought:

- regulatory reliefs and assistance, including fee reliefs and fast-track registration;
- greater assistance with market entry, including possible centralised purchasing and easier access to public markets.

### 1.3.6 Policy-reality mismatch

Current government industry incentives are poorly designed to meet small company needs and capture small company activity. They provide:

- very limited funding for start-up activity and early-pipeline R&D, where small company activity is concentrated;
- very limited technical partnering support for the late-pipeline, where small companies often need most help;
- insufficient help with lowering barriers to neglected disease market entry, for instance, help with implementation, regulatory assistance and consolidated procurement.

Unlike the case of multinational companies, PPPs are less helpful in supplementing public R&D policy gaps for small companies for a number of reasons. Although the funds required to support small company activity are relatively small, PPPs can find it difficult to provide these in their current constrained financial situation. Some PPPs also lack sufficient experience and understanding of small company bottom lines to structure attractive deals with these commercially focused and IP-protective firms. This is particularly relevant when all or most PPP staff come from non-industry backgrounds. Companies complain that ‘they don’t seem to understand that we *do* need to make a profit (overall)’. Main points of contention over the three documented failed deals were always linked to a mismatch of financial expectations between PPP and small companies (eg the PPP requiring a neglected disease-focused company to offer their final product at cost-price, with essentially no mark-up). We note, however, that some small companies also have unrealistic expectations – with at least one deal failing due to unreasonably high demands from the company. The mixed performance in this area is witnessed by the relatively small number – eight – of small companies/PPP projects. These problems may apply equally to other public funders of small company activity.

## 1.4 DEVELOPING COUNTRY FIRMS

### 1.4.1 Developing country pharmaceutical firms and the new landscape

Developing country pharmaceutical firms are not a subject of this report and are discussed here only in the context of their role within the neglected disease projects we studied. We are aware that several developing country companies are developing new drugs for neglected diseases (for example, Lupin – India – has reached clinical development of Pyrrole LL-3858 for TB) but for the reasons stated, these do not form part of our analysis (see Annexe 1D).

#### Activity

Nearly one-quarter of the documented 47 PPP neglected disease projects and the three drugs registered after 2000 involved developing country firms as either the main or subsidiary partner.

**Table 1. Activity of developing country firms in PPP R&D projects**

Project	Disease	Western partner	DC firm	Country	Role
DB-289*	Malaria	Immtech MMV	Discussion in progress	China	Small company manufacturing partner
Dicationic back-up compounds	Malaria	MMV	Discussion in progress	China	Small company manufacturing partner
Artekin® (DHA/ piperazine FDC)	Malaria	Sigma-Tau MMV	Chongquin Holley	China	Small company manufacturing partner
Artemisinin- production technology	Malaria	Amyris iOWH	Planned	–	Small company manufacturing and distribution partner (not yet secured)
Gatifloxacin* FDC	TB	WHO/TDR EC OFLOTUB Consortium	Lupin	India	PPP manufacturing partner Possible development partner
Paromomycin*	Leishmaniasis	iOWH/IDA WHO/TDR	Company name not known	India	PPP manufacturing partner
Impavido®	Leishmaniasis	Zentaris WHO/TDR	German Remedies	India	Small company development and distribution partner
Synthetic peroxide*	Malaria	MMV	Ranbaxy	India	Main industry partner: development, trial manufacture, and likely final manufacture and distribution
Pyronaridine- artesunate* FDC	Malaria	MMV	Shin Poong	South Korea	Main industry partner: development, manufacture and distribution
Artesunate- mefloquine FDC	Malaria	DNDi WHO/TDR	Far Manguinhos	Brazil	Main industry partner: development and manufacture

\* Clinical trial stage

## Motivations

The developing country firms in our survey were largely motivated by the prospect of technology transfer as part of the drug development process. For example, Ranbaxy was interested in the process of conducting clinical trials and preparing regulatory dossiers to US Food and Drug Administration standards – skills useful in developing its own in-house drugs as it moves into innovative R&D; while other firms were able to bring their manufacturing process up to International Conference on Harmonization (ICH) standards with the assistance of the Western partner eg Chongquin Holley with Sigma Tau.

A number of these companies worked *pro bono* and sought no share in newly generated IP, on the basis that the technology transfer they received was ample reward (similar to the strategic position of multinational companies, as discussed above). Others were additionally motivated by a desire to contribute towards meeting global health needs, or were able to do so because of public support from their national government. For example, Shin Poong and Far Manguinhos both provided free or discounted R&D to the relevant PPP, while Far Manguinhos will also provide the final drugs on a not-for-profit basis in developing countries and is offering a non-exclusive licence and technology transfer to potential Asian producers. Large developing country companies, on the other hand, eg Ranbaxy, may expect to operate on a purely commercial basis, including seeking full coverage of direct R&D costs, a share in foreground IP and profitable markets as the price of their involvement.

## Models

Most developing country pharmaceutical companies are not R&D-based, instead focusing on large-scale manufacture and distribution of generic versions of existing drugs for both national and international markets. As a result, many have a comparative advantage in the end-pipeline, including:

- formulation chemistry, for example, Shin Poong developed a cheaper and better synthetic route for MMV's pyronaridine project, duplicating its earlier success in improving and cutting the cost of BayerHealthCare's Biltricide® formulation (see Section 2.2.3);
- low-cost scale-up and good manufacturing practices;
- distribution in disease endemic countries.

This skills base means that, within PPP projects, developing country firms generally play the role of manufacturing and distribution partner for a small company or PPP lead (see Table 1 on previous page), in the same way that multinational companies act as end-pipeline partners for small companies in Western markets.

However, developing country industry activity is now beginning to change, both generally and within PPP projects. Several large developing country companies are now moving into R&D either alone or in partnerships with Western multinationals (eg Lupin and Ranbaxy in India) and an increasing number of developing country CROs have sprung up to offer cheap, skilled R&D services to Western pharmaceutical companies. Likewise, in four of the ten PPP projects listed in Table 1, the developing country firm is the *main* industry partner and is participating in clinical development as well as manufacture and/or distribution.

An interesting feature of all the listed projects is that their modular approach mimics Western pharmaceutical pipelines but on a smaller and significantly cheaper scale:

- drug discovery and preclinical development work is conducted by a small player (small company or academic);
- clinical trial and regulatory dossier preparations are conducted by the industry partner (small or developing country company), although usually with substantial CRO and public assistance to reinforce the generally weaker skills of these firms in this area;
- manufacture, scale-up and distribution are conducted by a larger partner (developing country pharmaceutical company).



The potential of this alternative pipeline as a cheaper source of commercially developed neglected disease drugs is interesting, particularly as it has already delivered one drug (Impavido®) and has several others at the clinical trial stage (asterisked in the Table above). This seems to be an area worth pursuing through further research.

As a final point, we note that the cost-savings generated by using a developing country-based firm are slightly offset by the higher level of 'hand-holding' and substantial CRO assistance that these can require to stay on track. Larger developing country companies, on the other hand, may make easier partners and require very little input, although, as noted, they generally operate on a purely commercial basis. However, it may not be very long before these larger firms can no longer be tempted to pursue neglected disease markets: as noted by the head of Biocon: 'In India, we are in a quandary about being mercenary and being missionary.'<sup>18</sup>

## 1.5 PUBLIC-PRIVATE PARTNERSHIPS

### 1.5.1 The new landscape of Public-Private Partnerships

**1999: Public-Private Partnerships (PPPs) are unproven; public funds may be invested in the 'wrong' PPP, with a resultant waste of money; the plethora of PPPs is leading to duplication and waste.**

**2005: There are now four new drug-development PPPs, plus WHO/TDR.**

**These PPPs are responsible for three-quarters of neglected disease drug R&D.**

**PPPs do not conduct drug development themselves. Their main functions are to:**

- **integrate and co-ordinate multiple industry and academic partners and contractors along the drug development pipeline;**
- **allocate philanthropic and public funds to the 'right' kinds of R&D projects;**
- **manage neglected disease R&D portfolios.**

**PPPs receive very little public funding and are largely supported by philanthropy.**

**PPPs substantially reduce public expenditure and risk in funding neglected disease R&D.**

**The term 'Public-Private Partnership' no longer accurately reflects PPP activity.**

#### Definition

We define PPPs as public health driven not-for-profit organisations that drive neglected disease drug development in conjunction with industry groups. Using this definition, some groups who consider themselves PPPs are excluded from our analysis<sup>xxi</sup> – for instance, we do not classify the Novartis Institute for Tropical Diseases (NITD) as a PPP since its public partner, the government of Singapore, is neither primarily focused on public health nor the main driver (we note, however, that NITD itself was set up by Novartis as a not-for-profit organisation). We also include groups who do *not* define themselves as PPPs. For instance, the Drugs for Neglected Diseases initiative (DNDi) – which sees itself as a primarily public group – and the Institute for One World Health (iOWH) – which defines itself as a not-for-profit private company – are both included since they meet all the above criteria.

On the basis of these criteria, there are five neglected disease drug development PPPs:

- one for malaria (the Medicines for Malaria Venture (MMV), founded in late 1999);
- one for TB (the TB Alliance, founded in late 2000);

<sup>xxi</sup> We have included individual projects between public and private groups (for instance, the GSK-WHO/TDR-DFID Lapdap® (chlorproguanil/dapsone project) as 'projects' not as 'partnerships', since these are one-off partnerships rather than formal organisations.

- one with a first focus on the kinetoplastid diseases (the Drugs for Neglected Diseases initiative (DNDi), founded in mid-2003);<sup>xxii</sup>
- the Institute for One World Health (iOWH), founded in 2000, which addresses a range of diseases from malaria to diarrhoea, and including drugs, vaccines and technologies;
- the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR) is also included, since it has operated as a de facto PPP since the mid-1970s.

All these groups have greater similarities than differences, but nevertheless vary in some aspects. For instance, unlike most other PPPs, the TB Alliance supports platform initiatives that may benefit the whole TB R&D community (for example, studies of TB latency). In addition to its primary drug-making enterprise, DNDi is alone in seeking to stimulate developing country technology transfer as part of its core mission, and has a focus on strengthening existing capacities in disease endemic countries. iOWH operates in a very similar way to the other PPPs, but has positioned itself as a private firm, including building and maintaining an IP portfolio and conducting some aspects of R&D in house (regulatory aspects, as opposed to laboratory work or manufacture). MMV, with 23 projects, plays an active portfolio management role, selecting and terminating projects within this portfolio on the basis of their relative merits. WHO/TDR promotes and manages partnerships with industry, but rarely finances these and has less freedom to operate than the other four organisations. Additionally, the organisation has a strong focus on Phase IV field trials of registered products to ensure safe developing country use, rather than simply on drug development and registration. WHO/TDR's role as the 'mother' of some PPPs should be highlighted, with its efforts being central to the formation of MMV, and helpful in the foundation of DNDi. (Although WHO/TDR is included in our project analysis, it is excluded from the funding and expenditure analyses since – unlike other PPPs – it could not provide us with per-project budget information or full information on how these funds were spent.)

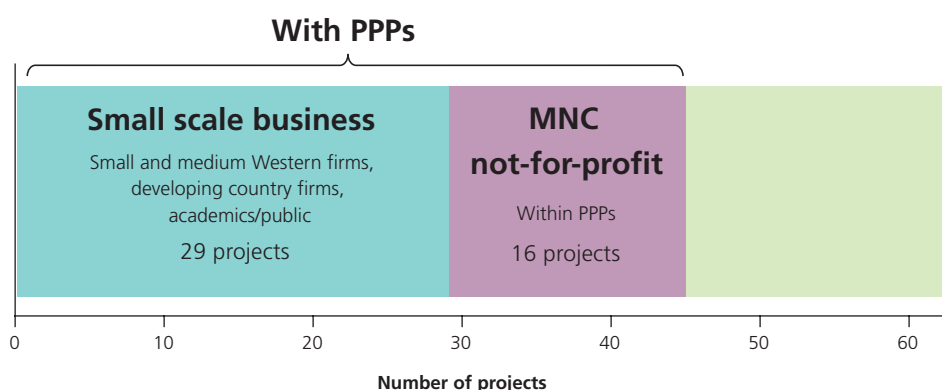
Finally, we raise our doubts about the use of the term 'Public-Private Partnership'. As seen from the discussion below, many Public-Private Partnership projects for drug development have neither public funding nor private partners, and many fall outside any reasonable definition of partnership. We do not have a better term to offer, but suggest this is an area where more accurate nomenclature could help to dispel a number of mistaken beliefs.

### Activity

PPP now manage *three-quarters* (47) of all identified neglected disease drug development projects. Nearly one-third of these projects (13) are at the clinical trial stage, including six drugs now in Phase III trials. A further two products are in the registration stage (rectal artesunate by WHO/TDR, and paromomycin by iOWH).

Based on standard attrition rates, this combined portfolio would be expected to yield six to seven new neglected disease drugs within five years.

Figure 6. Neglected disease drug R&D projects carried out by PPPs (Dec 2004)



<sup>xxii</sup> The kinetoplastids are a group of parasites that cause a family of diseases including leishmaniasis, sleeping sickness and Chagas disease. DNDi is also involved in two malaria projects inherited from its parent group, Médecins Sans Frontières (MSF), but after these are completed it will have no antimalarial activity.

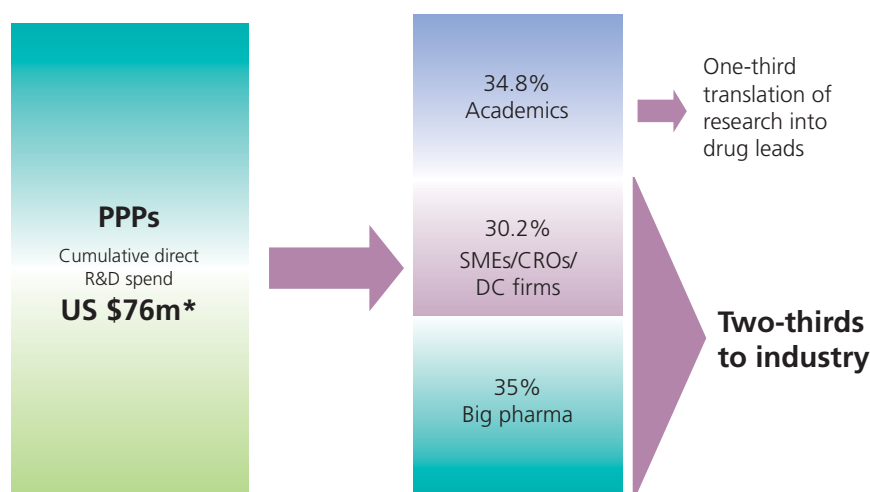
## The role of PPPs

PPPs do not conduct drug development themselves, that is, they do not have their own laboratories, manufacturing plant or distribution networks, although they may manage or conduct some aspects in house, for example regulatory work. In practice, PPPs fulfil three main functions:

- when developing non-industry compounds, PPPs integrate the development process across multiple partners and/or subcontractors. This is similar to the role played by multinational companies in a modular commercial pipeline;
- PPPs act as a fund manager or resource allocator, sourcing philanthropic and public funds for neglected disease drug development, and channelling these funds to industry and public institutions for the 'right' kind of projects ('right' from a public health perspective);<sup>xxiii</sup>
- as PPPs mature, they begin to function as portfolio managers, with projects spanning the spectrum of R&D from drug discovery to late-stage clinical trials.

The importance of PPPs as resource allocators is seen in an analysis of PPP budgets since 2000. (See Figure 7.) These show that two-thirds of PPPs' direct spend on R&D projects goes directly to industry (almost equally divided between large and small companies), while a further one-third goes to public and academic groups for translational work, converting basic research into new drug leads (WHO/TDR is excluded from these figures).

**Figure 7. PPP: a resource allocator**



\* – Covers period 2000-2004

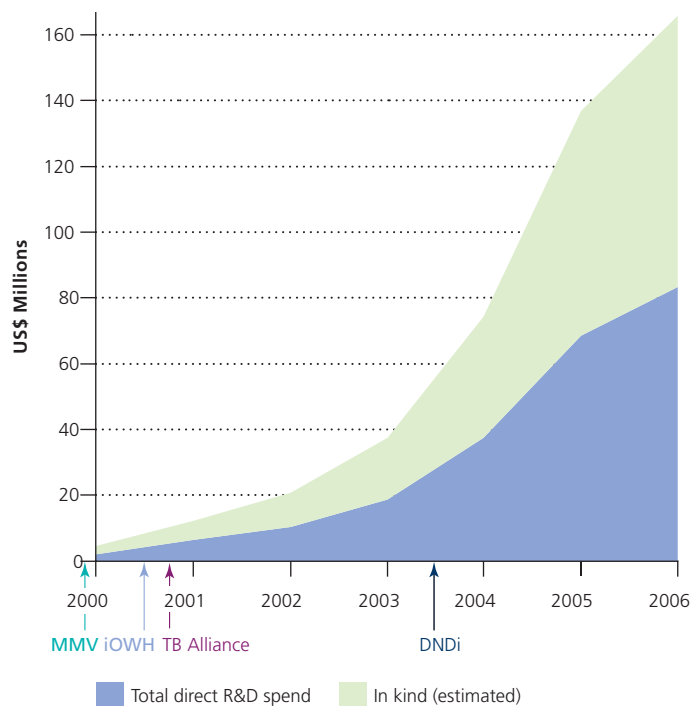
– PPP R&D spend only (total PPP spend was US\$112 million)

– WHO/TDR figures are excluded

SMEs: Small and Medium-sized Enterprises, CROs: Contract Research Organisations, DC: Developing Country

By virtue of their resource-allocation activities, PPPs are creating a rapid-growth niche sector in the neglected disease field, particularly for industry. This growth has accelerated as new PPPs have entered the field and established projects have reached the clinical trial stage. For instance, PPP direct R&D expenditure doubled between 2003 and 2004 (see Figure 8 overleaf).

Figure 8. PPP direct R&D spend (including projections to 2006)



## Models

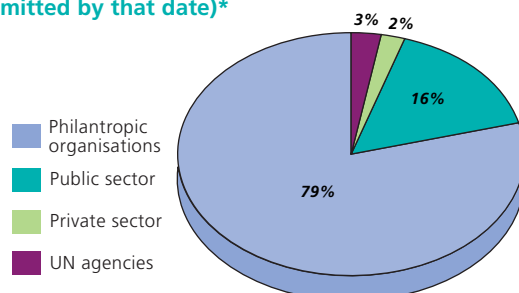
The classical model of a 'Public-Private Partnership' is of a publicly-funded organisation that provides funds to private industry partners to conduct drug development for neglected diseases. This model is usually seen as being based on a one-to-one partnership between a public group and a private pharmaceutical company (often a multinational company, and usually taken to mean a Western firm), where both contribute resources (funds from the public partner and skills from the private partner) and where both have a stake in the final product. Closer examination, however, shows that this classical model is often far from the reality.

### Public funding

PPPs in fact receive very little public funding and are largely supported by private grants from philanthropic organisations (see Figure 9).

OECD governments collectively provide only 16 per cent of PPPs' total budgets, with a further 3 per cent coming from UN agencies. The 30 OECD members, with a collective GDP of nearly US \$30 trillion in 2004<sup>19</sup> have contributed only US \$43 million to PPPs over the past five years. Of these, 26 member countries contribute nothing at all, while the EC contributes only 0.6 per cent of total PPP funding (see Table 2 below). PPP budget predictions for 2005 rise to around US \$85 million as projects go into human trials; however only US \$50 million in public and private funds have been pledged to date (around a 40 per cent shortfall). As noted, WHO/TDR figures are excluded.

Figure 9. Total cumulative PPP funding by type of funder (as of April 2005, including forward funding committed by that date)\*



\* Excludes WHO/TDR

**Table 2. Breakdown of cumulative philanthropic and public funding to drug PPPs (as of April 2005, including forward-funding committed by that date)\***

Donor	Total funding (US \$)	Per cent of total
<b>Philanthropic</b>		
Bill and Melinda Gates Foundation	158,757,717	58.9
Médecins Sans Frontières (MSF)	29,738,133	11.0
Rockefeller Foundation	20,300,000	7.5
The Wellcome Trust	2,827,504	1.1
<b>Sub-total</b>	<b>211,623,354</b>	<b>78.5</b>
<b>Public</b>		
US government	16,000,000	5.9
UK government	10,909,468	4.1
Netherlands government	10,489,255	3.9
Swiss government	4,422,285	1.6
European Commission	1,554,150	0.6
<b>Sub-total</b>	<b>43,585,077</b>	<b>16.2</b>

\* Excludes WHO/TDR

### The IP setting

IP issues play as vital a role in how PPPs structure and manage partnerships and projects as they do in the multinational company models discussed above.<sup>xxiv</sup>

In order to achieve their mission, PPPs will often want to develop existing compounds into new drugs, and to provide these drugs to developing country patients at affordable prices. They may therefore need to gain access to compounds held by companies or academics (background IP) and they will need to decide how to treat any new products developed under the PPP programme (foreground IP), based on mission considerations such as affordability and accessibility of that product. It is important to note that where PPPs have IP control they will use it to forward their public health mission, rather than for profit maximisation as is the case with commercial companies. For example, instead of excluding all others, as in the classical pharmaceutical industry monopoly model, a PPP can use IP rights to select optimal partners to work with, for the development process itself and/or for production and distribution of the final product.

The degree of PPP control over – and responsibility for – development, production and price of newly developed products will depend heavily on their degree of control over both foreground and background IP, or otherwise their ability to influence those who do have this control. This, in turn, will depend on who owns the original compounds and on how the PPP chooses to develop them. Different choices require, and allow, quite different models.

### Classical partnerships

The classical approach is most common when a PPP works in partnership with a small or large pharmaceutical company to develop an in-house company compound, for example, Wyeth's filariasis project with WHO/TDR (moxidectin) or MMV's antimalarial project with the small company Paratek (tetracycline). A variation is where the PPP brings external compounds to a company for further development: for example, the TB Alliance brought a series of PA-824

<sup>xxiv</sup> PPP IP issues are discussed only in outline here. For a fuller discussion see, for example, 'Public-Private Management of Intellectual Property for Public Health Outcomes in the Developing World: The Lessons of Access Conditions in Research and Development Agreements', Taubman A, Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, June 2004.

back-up compounds to Novartis to take advantage of their medicinal chemistry know-how. Taken together, these approaches represent less than half of all PPP projects.

As would be expected under this classical model, the primary role of the PPP in these partnerships is to provide the company with funds and any technical support they may need. The level of PPP input needed will generally depend on the size of the company and its developing country experience. For example, multinational companies usually (but not always) minimise the need for PPP funding by providing substantial in-kind services, whereas small companies may often seek full cost-recovery on their neglected disease work. Likewise, technical support may be modest for a neglected disease-focused firm (eg assisting with trial partners), but can range up to conduct or co-conduct of clinical trials for less experienced small companies and multinationals, or even require the PPP to take responsibility for manufacture and distribution in some partnerships with small companies.

In the classical PPP category the IP situation will largely be out of the PPP's hands.<sup>xxv</sup> This lack of IP control could pose problems for PPPs whose main aim is to secure affordable and timely access to the new products for those in need.

However, ownership of IP is only a means to an end – control – and if that control can be exercised in another way then that may suffice. PPPs generally deal with this issue by including binding contractual obligations on price and delivery in their agreements with companies. As noted above, these agreements can be easier to conclude with multinational companies, for whom this IP is low-value, than with small companies, for whom it may represent their only source of profits. Nevertheless, under current PPP agreements, *the great majority of partners agree to provide the final product at a not-for-profit price or at a low mark-up (3-5 per cent) to neglected disease patients in developing countries.* This includes all multinational company partners (around one-third of PPP projects), small companies focused on Western diseases, and the great majority of academic partners. The small number of companies who see the developing country market as commercially interesting tend to be less flexible, seeking larger margins (for example, up to 15 per cent in public developing country markets) or, as noted above, refusing to sign PPP deals that they feel would put their profits under pressure.

### New models

A different approach arises when the PPP has more control over IP issues relating to the compound, for example, because the compound being developed is already in the public domain (so no-one has background IP rights), because it has been licensed to the PPP by an academic or a company (so the PPP has the rights it needs for its mission), or because the PPP owns the relevant background IP (so the PPP owns all the rights).

In these cases, the PPP takes full responsibility for developing the product, but it also has far greater control over issues such as price, production, registration and distribution to developing country patients.

PPPs manage this responsibility in a number of ways. PPPs may:

- choose to work with no partner, by simply subcontracting out R&D to multiple industry and academic/public groups;
- develop the compound itself, using academic or industry subcontractors for preclinical work, but bringing in an industry partner or subcontractor (in some cases a developing country firm) at a later stage to assist with regulatory work, manufacture and distribution;
- forgo industry input altogether, with R&D being conducted solely by public partners or public subcontractors. This happens particularly with early-stage projects (although industry input would be expected further down the development line), but sometimes also with late-stage registration projects.

The most important aspect of these varied approaches is that they allow and stimulate different models of drug development. For instance, they allow PPPs to develop compounds from many different sources, even if there is no interested industry partner, for instance leads from academics or shelved industry compounds. Alternatively, active pairing of small Western companies (or academics) with developing country manufacturers can sustain a neglected disease pipeline that is far cheaper than the traditional commercial approach.

<sup>xxv</sup> For the most part the company in question will want to retain total control over the relevant IP (both the background IP and the new, foreground IP).

Irrespective of which model is chosen, none of these projects is conducted on a one-to-one basis, since there is no obvious 'one' who could conduct the entire drug development process. Instead, PPPs develop these products using industry's 'modular approach', where the relevant IP is derived from external sources, and development work is outsourced on a paid or unpaid basis to a range of partners with different skills, some or all of whom may have no stake in the final product.<sup>xxvi</sup>

The various approaches are illustrated in the following examples:

- PA-824, a new TB drug, is being developed by the TB Alliance **without a partner**, with the Alliance responsible for designing and managing the entire development process. PA-824 is protected by a PathoGenesis patent family, subsequently acquired by Chiron. Chiron have provided a worldwide exclusive licence to the TB Alliance for PA-824 and all its analogues, in return for a modest one-time licensing fee (modest compared to the industry average of US \$1-3 million) and yearly threshold R&D investments by the Alliance to ensure rapid progress. All preclinical R&D on PA-824 is subcontracted to commercial CROs (paid by the TB Alliance), and project management (paid by the NIH) is conducted by the Research Triangle Institute, a not-for-profit organisation that conducts contract research for the NIH and others. If and when development is successful, Chiron has the option of buying back the OECD rights by reimbursing the TB Alliance for all development costs.<sup>xxvii</sup> The TB Alliance would retain rights in all developing country markets, and the deal includes 'an expansive commitment' to affordable pricing
- Synthetic peroxide, a new antimalarial, is being developed by MMV using **a mixed approach**. Up to the preclinical stage, R&D was conducted by MMV and its academic partners (University of Nebraska, Monash University, Swiss Tropical Institute), assisted by expert advisers from Roche. An Indian pharmaceutical company (Ranbaxy) was subsequently brought in as a partner to conduct formulation chemistry and scale-up manufacture. The academic inventors (who did not want to bear the costs of applying for and maintaining patents) passed their rights to MMV, who now own this patent family, which is in turn licensed to Ranbaxy. These academic partners are now working on 'next generation' synthetic peroxides, which it is hoped will out-perform the current compound. New IP generated under the development work will be shared between MMV and Ranbaxy. (Roche offered in-kind assistance, in particular expert advice, during early development but did not conduct the R&D and does not have a share in the final rights.)
- Paromomycin, for African visceral leishmaniasis, is being developed by DNDi under a **purely public model** (paromomycin is a public domain drug).<sup>xxviii</sup> DNDi is covering all R&D costs and conducting regulatory work in conjunction with WHO/TDR. R&D is carried out by public groups on either a paid or in-kind basis: clinical trials are being conducted in Ethiopia, Kenya and Sudan by Médecins Sans Frontières and the Kenya Medical Research Institute (KEMRI); clinical trial investigators and monitors were trained by WHO/TDR; and the International Dispensary Association (IDA), a Dutch not-for-profit foundation is packaging and shipping trial drugs. DNDi will provide the final drug at cost in developing country markets. (We note that some work is now being repeated using paid industry Contract Research Organisations, eg training of trial monitors).

#### Box 4. Key points regarding PPP projects

- There may be little or no public funding
- There may be no private partner
- There may be no 'partnership' and no stakeholders outside the PPP itself
- Industry input is just as likely to be from a developing country firm, CRO, not-for-profit company or small Western company (or some combination of these), as from a multinational firm.

<sup>xxvi</sup> The choice of development partner will determine the ownership of any new IP; for example, if the PPP chooses to develop a compound using sub-contractors then the PPP will be likely to own the new IP, whereas if the PPP chooses to develop it with a partner then the IP will be likely to be shared in some way between the two.

<sup>xxvii</sup> The agreement has a grant-back clause that allows Chiron to re-enter the TB drug development process, within a specific window of time, in wealthy countries and includes manufacturing options for the company.

<sup>xxviii</sup> We note that iOWH is also developing paromomycin for registration in India.

## 1.5.2 Needs and preferences

The success of PPPs in developing new drugs depends on having their needs met. However, since one of their central functions is as a resource allocator, it also depends on their ability to meet the needs and preferences of the stakeholders who provide and receive these funds. These are ideally public funders on the one hand (although philanthropic funds are currently holding the fort), and drug developers on the other. In a best-case scenario, where a PPP is able to closely match stakeholder needs, the outcome is a large diverse portfolio that moves efficiently towards delivery of new neglected disease drugs.

### PPP needs

Public-Private Partnerships have significant gaps between their needs and what is available to them. The chief of these are lack of sufficient funding, incomplete access to potentially interesting industry compounds in both small and large companies, lack of sufficient developing country trial sites equipped to conduct clinical trials to the standards needed to secure regulatory approval, and imperfectly integrated trial, registration, purchase and distribution systems.

### Public needs and PPPs

Governments choosing between different R&D approaches have many, and often conflicting, wants and needs. Although they may want to foster development of new products for neglected diseases, they may also want to protect the interests of their own industries (including protecting the patent system that delivers their own drugs) and to foster increased translation of academic research, which they heavily subsidise, into useful products. Most governments also want to keep public expenditure on neglected disease drug development to a politically acceptable level.

The governments and public bureaucracies who make and manage these decisions also have internal needs. Inevitable scrutiny of their funding choices – including by the media, interest groups and political adversaries – means they may prefer approaches that minimise their level of risk and responsibility. This may lead them, as Stephen Maurer pithily observes, to favour approaches that ‘produce visible benefits, hide costs and obscure responsibility for failure, over those that do not’.<sup>20</sup> In other words, policy-makers must often make a choice between more expensive solutions that reduce their own choice and risk, and more cost-effective solutions that place the responsibility for success or failure squarely in their court.

From this perspective, PPPs in many ways present an ideal solution for governments and policy-makers, since they increase the cost-efficiency of government R&D expenditure and reduce government risk/choice.

The drug development PPP approach to date has required far lower public expenditure than commercial alternatives; for instance, total PPP expenditure from 2000 to 2004 was just US \$112 million, to progress over 40 drug development projects, including ten at the clinical trial stage, four of which are already in Phase III, plus one in registration (these figures do not include WHO/TDR as accurate costs were not available). These costs will, of course, increase substantially as more projects enter large-scale Phase III trials. PPPs use these funds more efficiently since they do not have to cover cost of capital or provide investor profits in most cases, and can use public funds to leverage substantial in-kind industry input. Final purchase (if the public sector intends this) is also more cost-efficient since, in the majority of cases, the resulting drugs are provided at a not-for-profit or low-profit price to developing country patients as part of the original PPP development agreement.

By virtue of the PPPs’ role as a resource allocator, the burden/risk of picking winners is shifted from government policy-makers to PPPs. From a public health perspective, PPPs are far better placed to select optimal R&D projects than government officials or most Western-focused pharmaceutical companies. Their choices are guided and monitored by the senior pharmaceutical industry figures and neglected disease experts who participate in PPP Expert Scientific Advisory Committees (ESACs), and who are generally leaders in their field. Public risk is further reduced since public funds are spread across a PPP portfolio rather than allocated to individual projects.



The PPP approach also fits neatly with other government priorities. It matches the interests of industry, particularly large multinational companies whose views may count more heavily with policy-makers, and is an active avenue for translation of academic projects into neglected disease drugs, with nearly one-third of PPP projects falling into this category. As noted above, the bulk of PPP funding goes directly back to industry and academic/public partners. A final aspect of potential interest to governments is the high level of PPP transparency and accountability, with PPPs providing their public sponsors with full information on R&D pipelines, including progress, successes, failures and budgets.

However, many potential donors consider the PPP model is still unproven (although industry with WHO/TDR input has delivered eight new neglected disease drug registrations) as newer PPPs have not yet had time to establish a track record in drug delivery. This, beyond all other considerations, makes governments wary of funding them. Indeed if 'track record' is only measured by the number of registered drugs, then newer PPPs will need years to establish this; however, if 'track record' is judged by their performance to date then our data show that PPPs collectively perform well (see Section 2). PPPs now conduct the majority of neglected disease drug projects, have the majority of drugs in clinical trials (including at Phase III) and are likely to have registered several products within the next few years. This is an excellent outcome for a very modest annual investment of philanthropic and public funds.

The final risk/choice is for governments to decide which PPP to fund, with potential public losses if the chosen PPP collapses or fails to deliver. The lack of empirical data on PPPs has made this choice particularly difficult (although we attempt to address it with this paper). Therefore, it may be easier to structure a funding solution that avoids the need to choose between PPPs (see Section 3.2.1 for one such proposal).

## Industry needs and PPPs

The needs of large and small companies are discussed at length in Sections 1.2.3 and 1.3.5 respectively, and are therefore summarised here only briefly.

Multinational companies primarily seek funding to mitigate their costs, particularly at the clinical trial stage, but also welcome technical help in conducting developing country trials, registration and implementation. PPPs are able to closely match these needs in a way that other public policies and incentives do not, and have therefore rapidly become a preferred multinational company approach – indeed, as noted above, PPPs are probably essential to industry's 'no profit-no loss' model of neglected disease drug development. The central role of PPPs is evidenced by the increased number of multinational company PPP partnerships. More are expected as in-house projects carried out by these multinational companies move to partnering for the clinical stage.

Small firms, who operate on a commercial basis, may seek full cost-coverage of their neglected disease R&D activities, and may need substantial technical assistance in development, manufacturing and implementation, particularly if they are primarily focused on Western markets. Overall, the PPP approach is less well adapted to these companies. Most PPPs lack the funds to meet small company financial needs, and some additionally lack the experience to conclude deals with small profit-driven companies, who can be very tough on IP issues. However, when PPPs do meet these requirements, they play a vital role in progressing neglected disease projects that small companies would otherwise have shelved and a helpful role in expediting projects that small companies already intended to pursue. We do not discuss the needs of developing country firms, since these are unlikely to be met through OECD R&D policies and incentives, which are the focus of this report.

### 1.5.3 The policy-reality gap

Given the importance of PPPs as industry neglected disease partners, their role in growing neglected disease R&D as an industry niche sector, and their potential high value to public neglected disease funders, it is surprising that there are currently no policy incentives in place to support PPPs directly, or to specifically underwrite industry participation in PPPs. Indeed, many current proposals seem designed to encourage industry away from PPPs and towards profit-driven in-house neglected disease drug development.

The gap between current public funding policies and PPP activity is now restricting the ability of PPPs to establish industry contracts and partnerships, and constraining them to adopt a variety of counter-productive practices that divert or reduce commercial business and dis-incentivise industry involvement. This approach impacts particularly heavily on small companies, making borderline commercial markets even more borderline and neglected disease work even less competitive with other small commercial markets. Examples of counter-productive cost-cutting practices include:

- restricting paid industry contracts;
- limiting the number of new projects picked up;
- reducing costs by contracting public groups in areas where industry works best (see Section 2.4 below);
- making short-term funding commitments, which are difficult for small companies to manage and incompatible with multinational companies' long-term strategic planning;
- pressuring small companies for discounts or in-kind services, thereby making neglected disease R&D even less attractive;
- excluding payment of overheads and management time from small company contracts (estimated at an additional 15 per cent of total cost);
- negotiating in-kind services rather than commercial deals;<sup>xxix</sup> eg one PPP estimated that it negotiated an average US \$1.2 million in free services on one project in one year alone. Over-dependency on in-kind services can be counterproductive, eg it can reduce PPP control over lead times and quality of outcomes;
- slowing down R&D;
- delaying projects while waiting for grant funding;
- conducting studies sequentially rather than in parallel.

Continued lack of public support, while PPP development costs are increasing, is likely to lead to the collapse of PPPs, leaving governments with little recourse but to fund more expensive industry activity from start to finish or to consider building alternative public drug-making capacity.

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<sup>xxix</sup> We are not suggesting that *all* in-kind contributions given by multinational companies be substituted with small commercial contracts, since some free input by multinationals is desirable from the public, company and PPP perspective, as discussed above.

# PERFORMANCE METRICS

## 2.1 INTRODUCTION

Good public policies should not only match the activity and needs of different players, but also encourage approaches that deliver maximum cost-efficiency on public investment and optimal public health outcomes. The different approaches – industry, PPPs, and public sector – have therefore been assessed across all documented neglected disease drug projects since 1975 using a range of metrics (standard industry metrics where available). As primarily public drug development is rare, data on this category is limited.

Metrics examined include:

- health value for developing country patients:
  - safety
  - efficacy
  - suitability
  - affordability
- level of innovation;
- capacity (ability to make drugs);
- development times;
- cost and cost-efficiency.

## 2.2 HEALTH VALUE FOR DEVELOPING COUNTRY PATIENTS

The most important overall metric is the health impact of the final product for the target developing country patients. Health value can only be measured for 21 projects that to date have led to the registration of a finished product<sup>xxx</sup> (all other documented projects are in development). 13 of these projects were conducted by industry alone and eight through collaborations between industry and WHO/TDR.<sup>xxxi</sup> We are not aware of any registered drugs that have, as yet, been fully developed in the public sector.

### 2.2.1 Methodology

In consultation with neglected disease experts and after an extensive review of the neglected disease literature, a series of independent metrics for safety, efficacy, affordability and suitability of neglected disease drugs for developing country target patients were developed.<sup>xxxii</sup> An ideal drug would receive a maximum score on all criteria (we recognise that such drugs rarely exist but this nevertheless continues to be the goal of drug development), while a drug with low scores on all criteria would represent a very poor product.

<sup>xxx</sup> We note that Coartem® was registered twice, and therefore both registrations were considered as separate projects. (The second registration was a label extension to suit developing country needs 5 years after the initial registration).

<sup>xxxi</sup> Mectizan® (ivermectin) is difficult to classify. The drug was largely developed to registration by Merck alone; however WHO/TDR subsequently conducted the extensive trials needed to establish the safety of mass-administered Mectizan® for eradication or control purposes. Mectizan® is therefore classified as a joint industry–WHO/TDR drug, rather than an industry-alone drug.

<sup>xxxii</sup> Literature review references are shown in Tables 3 and 4 below.

Existing neglected disease drugs were then assessed for their performance against these metrics by one to three medical experts in each disease; these assessments were supplemented by further literature review and by company data on price and registration where available, and then cross-checked with public health experts, both from Western and developing countries (see Annexe 2 for the list of experts contacted). On the basis of the scores provided by this exercise, products were then classified as *below average* (less than or equal to half the maximum score for an ideal drug) or *above average* (more than half the maximum score) on each metric (see Annexe 3 for a sample score sheet).

The four metrics against which the health value of each product was assessed are as follows:

### Efficacy

Resistance is the enemy of efficacy when treating parasitic and infectious diseases, as witnessed by the case of chloroquine in malaria treatment; therefore efficacy has been measured for both the short term (cure rates) and the long term (likelihood of rapid development of resistance). Efficacy metrics were also tailored to each disease; for example, schistosomiasis treatments were assessed for whether they were active against all common strains and species, and lymphatic filariasis treatments were assessed for activity against both larval and adult worms (microfilariae and macrofilariae).

### Safety

A drug that can be safely administered to individual patients in a Western setting may have a different safety profile in a developing country setting. Safety assessment was based both on the incidence and severity of adverse effects (as usually experienced and reported) and on the degree of risk incurred in settings where over-the-counter and non-prescription use is high, where mass administration may take place, and where the safety nets of adverse-event reporting or post-marketing studies do not exist.

### Suitability for developing country use

Suitability was assessed against several indices, including:

- ease-of-use for patients and health care workers – for example, dosing intervals, length of treatment required, availability of oral formulations;
- appropriateness to developing country health systems – for example, requirement for cold chain, or for hospital-based administration;
- percentage of the affected patient group covered by the therapy – for example, adults and children, or only adults; all patients, or only second-stage or severely ill patients. This index was also tailored to each disease; for example, TB treatments were additionally assessed for their usefulness in HIV/TB co-infected patients, while antimalarials were additionally assessed for usefulness in pregnant women and paediatric patients, who make up the majority of malaria mortality figures.

## Affordability for the target developing country patients

Purchasing power (and therefore affordability of drugs to individual patients) varies widely both within and between developing countries. Some products will never be affordable to very poor patients, no matter how cheap; therefore we assessed affordability by comparing the cost of the new treatment to the cost of existing treatments for each disease, ie 'will this drug make treating the disease cheaper or more expensive?' For instance, an antimalarial at US \$5.00 per adult treatment would receive a low score, since this is well above the price of existing malaria treatments, but an anti-leishmanial drug at US \$5.00 per adult treatment would score highly, since this is well below the cost of existing alternatives. Prices were sourced from company interviews, published literature and commercial suppliers (see Tables 3, 4 and 5). Although we collected data on availability where possible – that is, whether a drug was registered and distributed in endemic countries – many firms classified this information as 'commercial' or 'confidential', making the final 'availability' dataset too patchy for inclusion.

Efficacy and safety metrics are shown, but are not further discussed here on the grounds that poor performance against these metrics generally reflects scientific gaps rather than poor performance by the drug developer. For example, there is limited knowledge of the mechanism of action of end-stage Chagas disease, or of what 'switches on' latent TB in some patients. The main purpose of including these efficacy and safety metrics is to highlight the impact of decades of under-investment in applied neglected disease research and the gap that still exists between therapeutic needs and therapeutic realities for these diseases.

A key point before continuing is to note that poor performance on any one metric will greatly devalue the overall health value of the final product. For instance, a drug that performs well on the safety, efficacy and suitability metrics will nevertheless be of little use if few patients can afford it. Likewise, cheap, safe, appropriate drugs are pointless if their effectiveness is low, for example, chloroquine for *P. falciparum* malaria in much of the world.

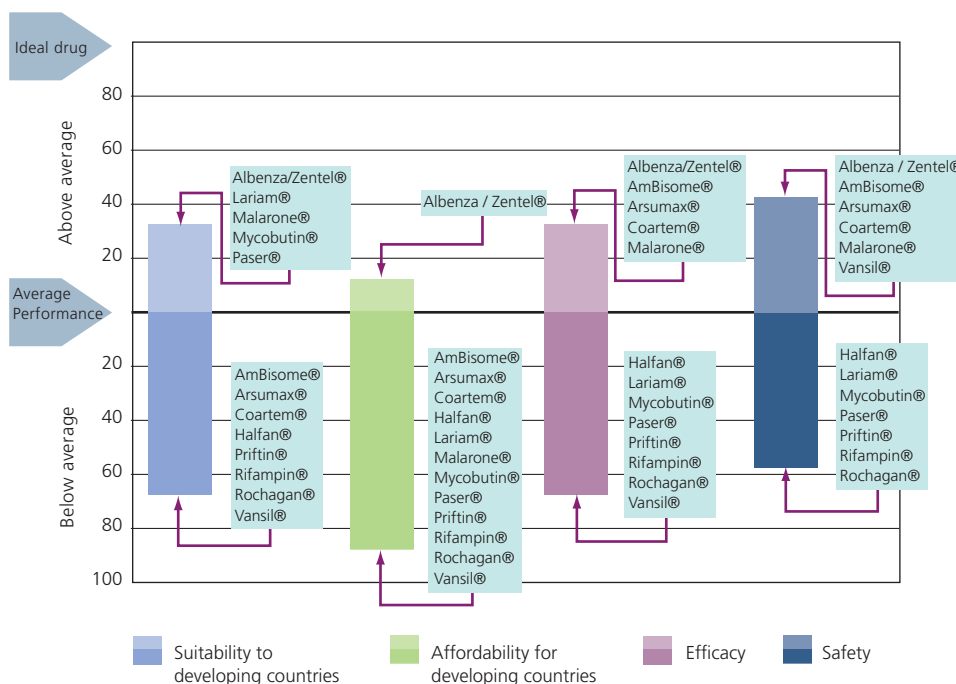
## 2.2.2 Industry products

Metrics show that virtually all of the 13 neglected disease products developed since 1975 under the industry-alone model have a low overall health value to developing country patients. This is unsatisfactory from a public health perspective and a substantial waste of industry effort, resources and goodwill. Policy-makers need a better understanding of what lies behind this poor performance if they are to design incentives that will achieve optimal R&D outcomes.

Performance of each industry-alone drug against each metric is set out in Figure 10. We note again that poor performance on *any one metric* will greatly devalue the final product; drugs that perform poorly on more than one metric play very little role in developing country patient treatment. Only one drug – Zentel® (albendazole) – performed well in all categories and is widely useful in managing neglected diseases of the developing world.

Overall, the single greatest obstacle to developing country use of these industry-developed drugs is poor performance against the affordability metric (see Figure 10). In many cases this stems from the choice of a lead compound that is unlikely ever to be affordable in a developing country setting because of the high cost of the active pharmaceutical ingredients or high formulation costs. This can be due to inattention to developing country relevant concerns, or because companies choose and design leads for overlapping Western commercial markets where safety and efficacy, rather than cost or ease of use, are the main drivers. For example, companies may target travellers' and military malaria, AIDS opportunistic infections, and the US market for TB or HIV-associated TB. Even if the resulting drugs are offered at cost price or cut price they are still too expensive for many developing country patients and health systems. Some companies have sought to address this issue by setting up donation programmes; however, while helpful in the short-term, these do not address the underlying problem.<sup>xxxiii</sup> Likewise, although tiered pricing to match developing country capacity to pay is a sound approach, its impact will always be limited if products are intrinsically expensive.

**Figure 10. Health performance metrics of industry-alone neglected disease drugs**  
(Drugs are listed alphabetically within each category – no ranking is implied)



Many of these industry-alone drugs are not only too expensive, but also poorly suited to developing country use, for instance, because they require hospital administration or cannot be used by key patient groups such as children, HIV-positive patients, or patients with severe diseases, eg hepatic or renal insufficiency. (See Table 3 for the list of main obstacles to wider use.)

Examples of new neglected disease drugs poorly adapted to developing country needs include:

- Priftin® (1998), a new TB drug. Priftin® was developed with the US market in mind. Priftin® trials, conducted at 10 North American and 29 South African sites, were designed to exclude HIV-positive patients (as noted by the company at an FDA hearing).<sup>21</sup> The US Centres for Disease Control and Prevention (CDC) notes that because 'the safety and effectiveness of Priftin® have not been established for patients infected with HIV ... administration of rifampentine to patients with HIV-related TB is not currently recommended'.<sup>22</sup> This view was confirmed by the FDA, who advise that 'rifampentine should be used with extreme caution in patients with HIV' on the grounds that 'limited data are available'.<sup>23</sup> It is worth noting that national surveys show that 55 per cent of South African TB patients are now HIV-positive, with HIV being the greatest driver of increasing TB cases.<sup>24</sup> As a result of the trial design, Priftin® cannot be used to treat these patients, or indeed any TB patients in high HIV-prevalence developing countries. A public group is now planning trials of rifampentin for HIV-infected TB patients.
- Coartem® (1999) is a new, safe and effective antimalarial based on a Chinese artemisinin therapy, which was originally developed and registered by Novartis in a 4-dose combination for patients weighing over 10kg. Although well suited to OECD needs (where it is marketed as Riamet®), the 4-dose combination was associated with higher relapse rates in endemic settings and the 10kg limit excluded use in small children, the main contributors to developing country malaria mortality. Novartis subsequently partnered with WHO/TDR to re-register Coartem® tablets in 2004 in a 6-dose formulation and for children down to 5kg, thereby greatly increasing its relevance and usage in Africa (see WHO/TDR Section). The company is now developing a paediatric syrup formulation with MMV and discussing trials in pregnant women with WHO/TDR.
- AmBisome® (1996) is a new anti-fungal, registered in the UK in 1991 for AIDS opportunistic infections, and subsequently shown by public studies to be safe and almost 100 per cent effective against visceral leishmaniasis. In 1996, the FDA allowed the company to use public data 'from studies done abroad and relevant historical controls'<sup>25</sup> to register AmBisome® as an orphan drug for visceral leishmaniasis. However, only public data on the Mediterranean

strain were included, while 'data supporting the clinical efficacy of AmBisome as treatment of leishmaniasis caused by other species and from other geographic foci were not provided by this NDA (New Drug Application)'.<sup>26</sup> AmBisome® works well in Western AIDS settings but is difficult to use in developing country settings since it requires a cold chain, it must be given intravenously in hospital for seven days over a three-week period, and its complex formulation makes it prohibitively expensive even at the public preferred price. Public groups are now conducting trials to determine whether shorter (and therefore cheaper) treatment courses may be equally effective.<sup>27</sup>

Key factors explaining the poor health performance of industry-developed drugs are: industry R&D choices based on primary Western priorities (safety and efficacy); insufficient focus on additional developing country issues such as suitability and likely end price; pressure on companies to balance the cost-benefit equation by maximising the Western market for their products (eg focusing on Western strains and needs); lack of company knowledge; lack of public input; and the need for companies to limit risk and liability, for instance, by excluding paediatric patients and pregnant women. The recent move towards a public-partnering model of neglected disease drug development (at least by large companies) mitigates these factors, and is therefore likely to lead to improved outcomes.

**Table 3. Health value of drugs developed by industry alone from 1975 to December 2004**

Brand name® (first registration for the neglected disease indication) Generic name	Health value in developing country settings
<b>Malaria</b>	
Coartem® (1999) Artemether/lumefantrine	Safe and effective but... <ul style="list-style-type: none"> <li>• Price US \$2.40 per adult treatment at the preferential public price (&gt;2x price of existing treatments)<sup>28</sup></li> <li>• Not registered for paediatric cases and pregnant women – the main mortality groups in malaria (refers to the initial registration, not the subsequent registration conducted in conjunction with public partners)</li> </ul>
Arsumax® (1996) Artesunate	Safe, effective and suitable but... <ul style="list-style-type: none"> <li>• Price US \$3.08 per adult treatment<sup>29</sup></li> <li>• Monotherapy, not recommended combination therapy</li> </ul>
Malarone® (1996) Atovaquone/proguanil	Safe, effective and suitable but... <ul style="list-style-type: none"> <li>• Price US \$12.00 per adult treatment<sup>30</sup></li> <li>• Data lacking on use in pregnant women<sup>31</sup></li> </ul>
Halfan® (1988) Halofantrine	<ul style="list-style-type: none"> <li>• Price US \$5.00 per adult treatment<sup>32</sup></li> <li>• Not for paediatric use (&lt; 10 kg) or for pregnant or breastfeeding women<sup>33</sup></li> <li>• Susceptible to rapid development of resistance<sup>34 35</sup></li> <li>• Fatal cardiotoxicity in some risk groups<sup>36 37 38</sup></li> <li>• Monotherapy, not recommended combination therapy</li> </ul>
Lariam® (1984) Mefloquine	Suitable but... <ul style="list-style-type: none"> <li>• Price US \$2.60 per adult treatment<sup>39</sup></li> <li>• Common severe side-effects (neuropsychiatric adverse reactions)<sup>40 41</sup></li> <li>• Susceptible to rapid development of resistance<sup>42 43</sup></li> <li>• Monotherapy, not recommended combination therapy</li> </ul>
<b>Tuberculosis</b>	
Mycobutin® (1992) Rifabutin	Suitable for developing country settings but... <ul style="list-style-type: none"> <li>• Price US \$2,300 per adult treatment<sup>44</sup></li> <li>• Severe side effects (blood disorders) can occur<sup>45</sup></li> <li>• Not registered for TB in many developing countries<sup>46 47 48</sup></li> <li>• Not for use in children and pregnant women<sup>49</sup></li> <li>• Cross-resistance with rifampin occurs<sup>50</sup></li> </ul>
Paser® (1994) Aminosalicylic acid	Suitable for developing country MDR-TB settings but... <ul style="list-style-type: none"> <li>• Price US \$2,700 per adult treatment at the preferential public price<sup>51</sup></li> <li>• No improvement in poor efficacy of original (1950s) formulation<sup>52</sup></li> <li>• Difficult in developing country settings: needs cold chain<sup>53 54</sup></li> </ul>

continued

Brand name® (first registration for the neglected disease indication) Generic name	Health value in developing country settings
Priftin® (1998) Rifapentine	<ul style="list-style-type: none"> <li>• Price US \$400 per adult treatment<sup>55</sup></li> <li>• Has to be preceded by a high fat meal<sup>56</sup></li> <li>• Not for use in HIV-positive TB patients, which represents up to 70 per cent of TB patients in some sub-Saharan Africa countries<sup>57 58 59 60</sup></li> <li>• Registered only in the US and Puerto Rico<sup>61</sup></li> </ul>
Rifadin® (1989) Rifampin IV	<ul style="list-style-type: none"> <li>• Has to be given in a hospital setting (intravenous formulation)<sup>62</sup></li> <li>• Not registered in many endemic countries</li> </ul>
<b>Chagas Disease</b>	
Rochagan® (1981) Benznidazole	<ul style="list-style-type: none"> <li>• Price US \$15-30 per adult treatment<sup>63</sup></li> <li>• Only for early stages of active disease and variable efficacy (cure rates between 60 and 90 per cent)<sup>64 65 66</sup></li> <li>• Potential cross-resistance with the only other Chagas treatment (nifurtimox)</li> <li>• Severe adverse reactions including blood disorders</li> <li>• Poor suitability: long treatment course (1-2 months); not for use in patients with severe disease associated with Chagas (eg hepatic or renal insufficiency), although well tolerated in children<sup>67</sup></li> </ul>
<b>Schistosomiasis</b>	
Vansil® (1975) Oxamniquine	<p>Safe but...</p> <ul style="list-style-type: none"> <li>• Price US \$20.16 per adult treatment<sup>68</sup></li> <li>• Only effective against one of the three species of schistosome that infect humans<sup>69 70</sup></li> <li>• Treatment failures have been documented, but as yet unclear whether these are due to appearance of resistance</li> </ul>
<b>Visceral leishmaniasis</b>	
AmBisome® (1997) Amphotericin B liposomal	<p>Safe and effective but...</p> <ul style="list-style-type: none"> <li>• Price US \$350 per adult treatment at the preferential NGO price<sup>71</sup></li> <li>• Treatment requires one-month hospitalisation (trials of shorter treatment now in progress) and cold chain<sup>72</sup></li> <li>• Slower response and high relapse rates in HIV patients<sup>73</sup></li> </ul>
<b>Lymphatic filariasis (helminths)</b>	
Zentel® (1981) Albendazole	<p>Safe, effective, suitable and cheap in helminth treatment<sup>74</sup></p> <p>Safe, suitable and cheap in lymphatic filariasis: effective in removing microfilariae when combined with diethylcarbamazine or ivermectin (important to reduce transmission). But...</p> <ul style="list-style-type: none"> <li>• Role in individual treatment (elimination of microfilariae – key to cure of infection) still needs to be clarified</li> </ul>



## 2.2.3 Products with WHO/TDR input

Although WHO/TDR drug development projects are usually PPPs involving industry, academics and developing-country partners, this organisation is not a representative PPP since it does not provide direct R&D funding to companies and is limited by the political, legal and structural constraints intrinsic to all publicly funded multilateral organisations. WHO/TDR also has broader objectives beyond development and registration of new products. In particular, it focuses strongly on field trials of new drugs in order to ensure their safety for use in the 'non-prescription' settings that often typify developing country use. Its performance is therefore not entirely representative of newer PPPs founded since 2000.

Eight registered neglected disease drugs were developed with public input from WHO/TDR. Data shows that more of these drugs performed well against more metrics than industry-alone drugs, although only one (Mectizan® – ivermectin) performed well in all categories. (See Table 4) WHO/TDR input is associated with improved access, including through negotiating lower public sector prices or free donation programmes (eg Mectizan® and Coartem®, although the latter is still expensive).

In particular, through conducting Phase IV trials, WHO/TDR's input allows these new drugs to be safely and widely used in developing countries, and adopted by country disease-control programmes. As a consequence of these activities, several WHO/TDR-industry and WHO/TDR-academic collaborations have contributed significantly to reducing global health problems:

- Mectizan® is being used to eradicate river blindness (onchocerciasis). Onchocerciasis is a worm infestation that causes severe itching and skin lesions; it is the second biggest infectious cause of blindness globally. Mass administration of donated Mectizan®, combined with vector control, has approximately *halved the global burden of onchocerciasis* between 1990 and 2000, from 884,000 to 498,000 cases and there have been virtually no new cases of blindness in Onchocerciasis Control Programme areas in West Africa.<sup>75</sup>
- Biltricide® (praziquantel) is effective in a single dose against all species of schistosomiasis (a worm infection leading to liver, spleen and kidney damage and bladder cancer). Generic praziquantel use has *controlled schistosomiasis in Brazil, the Mahgreb region, the Middle East, China and the Philippines*,<sup>76</sup> and a global control plan is now in progress. This was made possible by the use of a simpler formulation developed by a South Korean company (Shin Poong), which brought the cost of treatment down tenfold. For instance, the cost of a child's treatment was reduced from US \$2.25 (1994 WHO-reduced price of Biltricide®) to only US \$0.20 with the new formulation.<sup>77</sup>
- The label extension of Coartem® for African and paediatric use has provided Africa with its *first safe, effective, suitable new antimalarial* for many years (although both the US \$2.40 per adult/treatment cost and US \$0.90 per child/treatment require substantial public subsidy, without which broader use would be very difficult).

WHO/TDR's record on other aspects is less positive. The Programme has assisted several companies to develop intravenous and intramuscular drug formulations that fill an extremely useful medical niche but cannot provide the broader benefits of an oral drug, eg Paluther® (intramuscular artemether) and Artemotil® for malaria, and Ornidyl® for sleeping sickness.

Several WHO/TDR-industry drugs have also run into the sand due to conflict with other aspects of developing country health policy. For instance:

- Impavido® (miltefosine) was developed and registered for leishmaniasis in 2002 with WHO/TDR assistance, despite its potential teratogenicity, in the belief that it was nevertheless a useful new anti-leishmania drug. However, WHO subsequently declined to include Impavido® in its Essential Drugs List (EDL) which guides developing country treatment policy and purchasing decisions, noting that 'toxicity and teratogenicity are even more risky taking into account the target population, the real price and the trend to develop resistance'.<sup>78</sup> Failure to conclude a WHO preferential price agreement (offered by the company) or to regulate distribution of the drug mean that miltefosine is being sold over the counter, an approach that leads experts to fear that resistance may emerge relatively quickly.<sup>79</sup>
- Lapdap® (chlorproguanil–dapsone) was developed and registered in 2003 as a new cheap antimalarial drug for Africa by GSK, the University of Liverpool, Liverpool School of Tropical Medicine, London School of Hygiene and Tropical Medicine, DFID and WHO/TDR. However in 2003, WHO noted that 'to what extent Lapdap® will, by itself, find use in the treatment of malaria is uncertain. WHO strategy is to use new antimalarial drugs in combination with an artemisinin derivative' (Lapdap® does not contain an artemisinin).<sup>80</sup> This change in policy has led to delays in implementing Lapdap®, which is being re-engineered by GSK/MMV as Lapdap®-artesunate, at a significant cost in time and resources. WHO/TDR is also conducting Phase IV field trials and pharmacovigilance studies of Lapdap® to assess its scope for use.
- Artemotil® (β-artether injectable) was developed and registered for use in malaria in 2000 by Artecef (a Dutch company) with WHO/TDR assistance. However, it was subsequently rejected for inclusion in WHO's Essential Drugs List (EDL) on the grounds that 'WHO does not recommend the unconditional use of injectable formulations for the management of uncomplicated malaria since effective oral formulations exist to treat this condition. Other injectable formulations of artemether and intravenous quinine ... are currently included in the EDL ... the addition of other antimalarial drugs ... can only be justified if the formulations are more effective, safer, easier to use and more affordable [than these]'.<sup>81</sup> A major factor in these difficulties was that this was a 'tied' project, with the Netherlands government providing WHO/TDR with R&D funding to specifically support it.

Overall, WHO/TDR-industry collaborations have had a better health outcome than industry-alone projects, with three of the resulting eight drugs having a major impact on global health problems once pricing issues were addressed – particularly in those cases where Phase IV implementation studies were conducted as a prelude to wider roll-out. However, WHO/TDR's health performance has also been rather mixed. This partially reflects their practice of coming in late to support clinical development rather than being an early and active driver of suitable R&D choices, but appears also to stem from their constrained funding position and somewhat opportunistic approach to compound selection and development. This provides useful lessons for the design of improved R&D incentives.

**Table 4. Health value of drugs developed by industry with public input from WHO/TDR from 1975 to December 2004**

Brand name® (first registration for the neglected disease indication) Generic name	Health value in developing country settings
<b>Malaria</b>	
Artemotil® (2000) β-artether	Safe and effective but... <ul style="list-style-type: none"> <li>• Intramuscular</li> <li>• Potential cardiotoxicity issues<sup>82</sup></li> <li>• Developing country price still not agreed<sup>83</sup></li> <li>• Does not match WHO recommended treatment protocols<sup>84</sup></li> </ul>
Paluther® (1996) Artemether	Safe and effective but... <ul style="list-style-type: none"> <li>• Price US \$24.65 per adult treatment<sup>85</sup></li> </ul>
Coartem® tablets (2004) (paediatric label extension ) Artemether/lumefantrine	Safe, effective and suitable but... <ul style="list-style-type: none"> <li>• Price Children 10-14 kg = US \$0.90 per treatment (&gt;2x price of existing treatments)<sup>86</sup></li> </ul>
Lapdap® (2003) Chlorproguanil/dapsone	Suitable and very cheap: US \$0.08 per child treatment/ US \$0.29 per adult treatment <sup>87</sup> . But... <ul style="list-style-type: none"> <li>• Potential for cross-resistance with a commonly-used malaria treatment (sulfadoxine-pyrimethamine)<sup>88</sup></li> <li>• No longer matches WHO malaria treatment policy (policy changed while drug was in development)<sup>89 90</sup></li> <li>• Safety uncertain in G6PD deficiency (a not uncommon African health problem)<sup>91</sup></li> </ul>
<b>Schistosomiasis</b>	
Biltricide® (1982) Praziquantel	Safe, effective and suitable but... <ul style="list-style-type: none"> <li>• Price US \$2.25 per child treatment (eradication programme uses generic praziquantel, costing US \$0.20 per child treatment)<sup>92</sup></li> </ul>
<b>Visceral leishmaniasis</b>	
Impavido® (2002) Miltefosine	Safe, effective in males and children, suitable but... <ul style="list-style-type: none"> <li>• Potentially teratogenic, therefore can only be given to women with child bearing potential if contraception is guaranteed<sup>93</sup></li> <li>• Cheaper than existing therapies but still expensive. Price US \$145 for a 28-day treatment at Indian private sector price. (Low public sector price still in negotiation)<sup>94</sup></li> <li>• Prone to rapid development of resistance<sup>95 96 97</sup></li> <li>• Long treatment (one month) although oral</li> <li>• Lower efficacy in patients with HIV co-infection<sup>98</sup></li> </ul>
<b>Trypanosomiasis (sleeping sickness)</b>	
Ornidyl® (1990) Eflornithine IV	Effective in some strains, safer than existing alternatives and a free five year donation programme, but... <ul style="list-style-type: none"> <li>• Two weeks, four times a day intravenous treatment in hospital</li> <li>• Not effective against all African strains<sup>99</sup></li> <li>• Not recommended in HIV/AIDS patients<sup>100</sup></li> </ul>
<b>Onchocerciasis (river blindness)</b>	
Mectizan® (1987) Ivermectin	Safe, effective, suitable and free (donation programme), but... <ul style="list-style-type: none"> <li>• Does not kill the adult worm so requires long-term treatment<sup>101 102</sup></li> <li>• Individual treatment requires dosing once to twice a year for up to ten years (in the absence of reinfection) while control programmes are required to be longer.</li> </ul>

## 2.2.4 New PPPs

All post-2000 PPPs are highly focused on suitability and access for developing country markets, as well as safety and efficacy. For instance, the TB Alliance focuses on oral therapies to reduce TB treatment from the current six-eight months to four months or less, and MMV includes in its mission statement the goal that new antimalarials for uncomplicated malaria be oral regimens of three days or less. Most PPPs also have a portfolio of early-pipeline projects, which allows them to direct R&D (including R&D by industry partners) towards cheap, suitable leads. Projects also appear to be chosen or discarded on cost and suitability criteria, as well as efficacy and safety. The impact of this approach can be seen when comparing industry and PPP project choices in the field of malaria (eg their focus on cheaper artemisinin combinations than Coartem®).

**Table 5. Price of antimalarials**

Developed by	Drug name	Price (US \$) per adult treatment	Source
Sanofi-Aventis	Paluther® (artemether IM)	<b>24.65</b>	**
GSK	Malarone® (atovaquone/proguanil)	<b>12.00</b>	**
GSK	Halfan® (halofantrine)	<b>5.00</b>	^^
Sanofi-Aventis	Arsumax® (artesunate)	<b>3.08</b>	**
Roche	Lariam® (mefloquine)	<b>2.60</b>	** ^
Novartis	Coartem® (artemether/lumefantrine)	<b>2.40</b>	^^^
<b>Public health target price: One dollar per adult treatment</b>			
MMV-GSK *	Artekin® (DHA-piperazine)	≤ <b>1.00</b>	^^^
MMV-Shin Poong-Uni Iowa *	Pyronaridine/artesunate	≤ <b>1.00</b>	^^^
DNDi-Sanofi Aventis *	Artesunate/amodiaquine	≤ <b>1.00</b>	^^^
WHO/TDR-GSK	Lapdap® (chlorproguanil/dapsone)	<b>0.29</b>	***

\* Drugs still in development. Target price (depends on changing cost of raw artemisinin)

\*\* Drug prices obtained from pharmaceutical companies.

^ Baird J.K. (2005) Effectiveness of Antimalarial drugs. *New England Journal of Medicine*. 352: 1565-77

^^ WHO (2001b) The Use of Antimalarial Drugs: Report of a WHO informal consultation, 13-17 November 2000. WHO/CDS/RBM/2001.33

^^^ Drug prices obtained from PPPs.

\*\*\* Pinock S. (2003) Drug company to offer new malaria drug cheaply in Africa. *BMJ*. 327(7411):360

^^^ WHO (2001) WHO and Novartis join forces to combat drug resistant malaria. Press release. Geneva.

The performance of newer PPPs cannot be more fully assessed until the clinical trials now underway are completed and any resulting drugs are registered and implemented (ten trials in progress at end 2004 plus one drug at the registration stage).

## 2.3 LEVEL OF INNOVATION

It is important to distinguish between innovation from a drug development perspective and innovation from a health perspective. Low innovation products from an R&D perspective may nevertheless be both valuable and innovative from a health perspective. For example, adaptations that make treatment compliance easier are welcomed both by patients and by health professionals seeking to slow the advent of resistance. Some examples are fixed-dose anti-retrovirals for AIDS, paediatric syrups (eg MMV's paediatric Coartem® formulation) and simpler formulations that replace multiple dosing (eg DNDi's artesunate-amodiaquine project with Sanofi-Aventis). Extensions of existing drugs to new disease areas can be even more valuable (eg AmBisome®, an anti-fungal, proved to be highly effective in visceral leishmaniasis), while higher-innovation products, such as follow-on New Chemical Entities in the same class, can also offer improved safety and efficacy over existing treatments.

However, unlike with other types of drugs, in the field of anti-infectives and anti-parasitics, a key requirement is the ability to outwit bacteria or parasites that will inevitably develop resistance to existing therapies – ie it is the bug rather than the patient that is being targeted. Diseases where microbe or parasite resistance to current treatments is already high include TB, sleeping sickness, leishmaniasis and malaria (although in the case of malaria a new class of drug, artemisinins, is having a dramatic impact). This means that, in addition to improving existing therapies, we must also develop new classes of product if we are to have successful treatments for the future. This aspect was recently highlighted by industry in an FIIM<sup>xxxiv</sup> IFPMA report, which noted that: '...perhaps more important than the total number of projects is the level of breakthrough innovation'.<sup>103</sup>

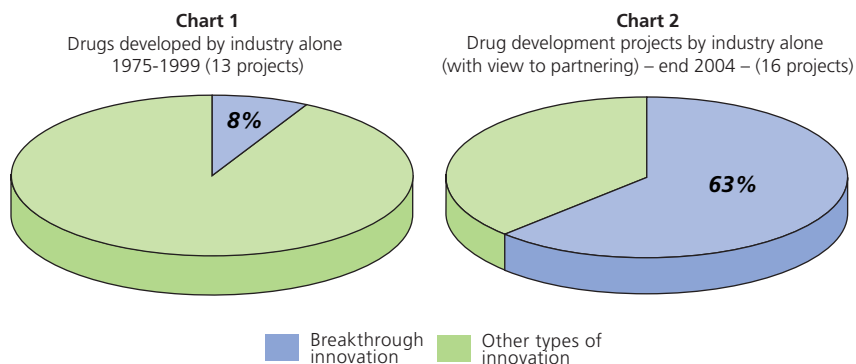
*Breakthrough innovation* is defined in this report as a New Chemical Entity (NCE) *in a new class*, ie a compound which is not only new in itself, but also targets the disease in a completely new way. Breakthrough innovation can sometimes occur by serendipity – for example, when an existing drug is found to have a new method of action in another disease (eg miltefosine, originally developed for cancer, was found to be highly effective in visceral leishmaniasis). However, if we are not to rely on serendipity alone, then we need to foster R&D that is focused on developing new classes of NCE that will overcome the problems of resistance. These innovative products are both more risky and more expensive to develop than other types of drug, since the sponsors have to bear most of the cost from drug discovery through to registration, and must do so in an environment where the target, mechanism of action and proof of concept are not well established.

We note that the majority of public neglected disease research is highly innovative blue skies and basic research, much of which is 'breakthrough' in nature. We acknowledge the vital role this plays in generating new ideas and approaches for industry and others; however this research is excluded from the scope of this report, as noted in the preface. This report includes public activity only insofar as it pertains to active neglected disease drug development (eg drug discovery, lead identification and optimisation, or preclinical and clinical development of new products for registration). Although we found a handful of drug development projects where the public sector worked alone, eg the antimalarial projects of the Walter Reed Army Institute of Research (WRAIR), these were too few to draw reliable conclusions as to level of innovation – and, in any case, moved to a partnered model for final development. Levels of public innovation are therefore not assessed in this Section.

### 2.3.1 Industry

Data show that only 8 per cent of drugs developed by industry working alone between 1975 and 1999 were in the breakthrough category, with companies tending to focus on less costly label extensions, reformulations and re-registrations (we note that no industry-alone drugs were registered after 1999). However, there has been a marked reversal since 2000, with over 60 per cent of industry projects now in this breakthrough category (see Figure 11).

**Figure 11. Level of innovation of industry alone products**



We note that Chart 1 and Chart 2 cannot be directly compared since the first is based on data for registered drugs while the second plots a portfolio of ongoing drug development projects. Given that R&D of breakthrough NCEs is associated with higher attrition rates, the profile of *finished* drugs coming out of the project portfolio described in Chart 2 is likely to include fewer innovative products (since more will have failed during the development process than products in less innovative categories).

This alone, however, cannot account for the much higher share of breakthrough innovation in Chart 2. Rather, the key explanation for this difference is that *there has been a major shift in industry neglected disease R&D strategy since 2000*, where the serendipitous approach that characterised the past 25 years has given way to one that is specifically focused on breakthrough innovation – in particular, the formation of specialist industry neglected disease institutes exclusively focused on drug discovery. (As noted in Section 1.2.1, this new approach relies heavily on the presence of potential partners for subsequent clinical development). In the long term, this approach can only deliver high-innovation products, irrespective of attrition rates, since these industry institutes focus solely on discovery of novel compounds, ie failed *discovery* projects are always replaced by further *discovery* projects.

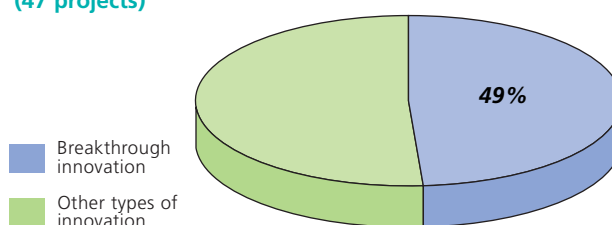
Industry activity therefore seems likely to remain at promisingly high levels of innovation, provided that partnership routes are maintained and that new policies do not inadvertently encourage companies towards lower-innovation 'adaptive' R&D.

## 2.3.2 Public-Private Partnerships

Nearly half of PPP projects (49 per cent) are breakthrough R&D (see Figure 12 below).

This project mix reflects a transitional stage in young PPP portfolios. At initial formation, most PPPs move to capture 'low-hanging fruits' in their disease area, for example, completing registration of almost finished neglected disease drugs (eg paromomycin) or developing fixed-dose combinations of existing drugs to fill an immediate disease need (eg DNDi's antimalarial combinations). However, PPPs also actively focus on discovering novel early-stage compounds to supply their drug development pipelines (although high early attrition rates mean that much more needs to be done). For instance, MMV's first Call for Proposals specifically sought drug discovery projects; the TB Alliance's second Call for Proposals restricted those responding to lead identification projects; and DNDi picked up four new drug discovery projects from its first Call. This high-innovation pattern seems likely to increase as the handful of low-hanging fruits are picked, and PPPs increasingly rely on discovering new compounds to supply their early and mid pipelines.

**Figure 12. Level of innovation of PPP drug development projects at the end of 2004 (47 projects)**



## 2.4 CAPACITY (ability to make drugs)

We define capacity as a group's ability to make good drugs, ie to pick good leads, to optimise them to improve druggability, and to know when something is not working and act accordingly. This does not measure the suitability of the final drugs to neglected disease settings (see Section 2.1 previously) but only the intrinsic capability of each approach to make and register new neglected disease products. Our analysis shows that different groups – multinational companies, small companies and academics – have different comparative advantages at different parts of the drug development pipeline, and suggests that the most successful projects use approaches structured around these comparative advantages.

### 2.4.1 Industry

Pharmaceutical companies both large and small are clearly able to make drugs. Multinational companies are competent in all steps of the drug-making process, while small companies are stronger in the preclinical pipeline (lead identification, lead optimisation and preclinical) and generally need assistance in clinical development, regulatory work and large-scale manufacture and distribution. In virtually all cases, both large and small firms will need additional public skills in R&D tasks that require neglected disease or developing country knowledge, for example: screening against parasites, knowledge of parasite biology and enzyme targets, availability of suitable developing country trials sites, and knowledge of developing country health protocols and regulatory processes.

DC firms are particularly strong in process formulation, scale-up and large-scale manufacture and distribution, but often weak in clinical development and regulatory skills. Developing country manufacturing processes may also need to be brought up to Good Manufacturing Practices (GMP) standards in some cases (eg Sigma Tau assisted Chongquin Holley, Rhone-Poulenc Rorer assisted Kunming Pharmaceutical Factory, and Sanofi assisted Guilin Pharmaceutical Factory, People's Republic of China).

## 2.4.2 Public

Most pure public drug development activity is concentrated on basic and drug discovery research. However, as noted in the preface, we have only discussed public R&D activity insofar as it relates directly to neglected disease drug development projects (basic research is excluded). Public involvement also occurs in later development stages, but this is generally in the context of partnerships, or provided as contract research to other groups, and is therefore discussed under the PPP Section below. An important point to note is that these two different areas require very different skill sets.

Public and academic groups perform strongly in drug discovery research. Many are leaders in their field and are used by companies for these skills; for instance, Texas A&M is a world expert in X-ray crystallography of the Fab1 enzyme used in both MMV and commercial projects. Public institutions and academics are also skilled in parasitology and the science of neglected diseases (eg the Swiss Tropical Institute and the London School of Hygiene and Tropical Medicine) and some (eg Monash University in Australia and Mahidol University in Thailand) are competent in performing preclinical pharmacokinetic (PK) studies, toxicology or ADME studies. Although these academic laboratories do not usually operate to Good Laboratory Practice (GLP) standards they can nevertheless provide these services cheaply and effectively at earlier stages of the drug development pipeline. Many are highly motivated to work on neglected disease projects and offer very competitive rates compared to CROs.

### Box 5. Some public strengths

- Structural genomics and proteomics
- Target identification
- Assay development (although not always HTS assays)
- X-ray crystallography
- Elucidation of Structure-Activity Relationships (SARs) to guide drug modelling
- Parasitology, including the *in vivo* and *in vitro* studies needed to determine the efficacy of a compound against the target parasite
- Some aspects of developing country clinical trials (see below)

## 2.4.3 Public-Private Partnerships

There is a wide variation in effectiveness of PPP projects, with the major correlates of success being early industry input to the public partnership, and appropriate use of the respective skills of the public and industry partners.

### PPP drug development with industry input

Overall, drug development projects conducted with both industry and public partners perform well. This is irrespective of whether the industrial input comes from a small or a large company, a developing country firm, or a contract research organisation.

The chief proviso is that each group carries out the tasks in which they are most skilled. As noted above, this can involve public researchers in the drug discovery stage, or as providers of specialist skills that require neglected disease knowledge. Public groups also provide vital assistance to industry partners at the clinical development stage, by virtue of their knowledge of developing country health protocols and regulatory processes, and experience in running medical trials in developing countries (as distinct from clinical trials needed to support regulatory approval of new drugs, where public groups are often inexperienced). Industry groups, on the other hand, perform well on identifying and optimising 'druggable' leads, and have greater experience in conducting trials for regulatory purposes (including data management and preparation of regulatory submissions). However, they are often inexperienced in targeting this work to developing country needs, and generally have little experience with developing country regulatory and health systems. (CROs who specialise in developing country trials are the exception).



There are many projects where using each contributor in their area of strength leads to increased capacity to deliver a good product efficiently. Examples include:

- Preclinical development of the TB Alliance's PA-824 project is fully outsourced to (largely) US CROs experienced in ADME, toxicology and PK studies, with project management by Research Triangle Institute (RTI) International, a not-for-profit group linked to the NIH.
- The MMV synthetic peroxide project is based on a public lead developed by academic partners, but with in-kind industry advice from Roche. It has Ranbaxy (India) as a development partner, and supplements their relative inexperience in clinical trials and regulatory submissions by use of a subcontracted Western CRO (Quintiles). A partner drug for combination therapy is being sought and this will probably bring in another public or private partner.
- The iOWH artemisinin production project is based on a new method of microbial drug production developed by academic synthetic biologists at the University of California, Berkeley, and scaled-up into an industrial fermentation process by Amyris (a small US company).
- The MMV-GSK-University of Liverpool isoquine project is based on a lead developed by the University of Liverpool, which conducted 15 years of research into the action of 4-aminoquinolones leading to identification and synthesis of isoquine as a simple, low-toxicity lead compound for malaria. Subsequent GSK input built on this work by identifying a different but related compound with better drug performance.
- The MMV-GSK-University of Bristol lactate dehydrogenase inhibition project developed a pharmacophore based on Bristol's X-ray crystallography and Structure-Activity Relationship (SAR) studies; it screened 0.5 million GSK compounds, used the SAR and screening results to guide synthesis of a range of potential leads (GSK), and quickly discovered that no potent compounds resulted from that line of enquiry. The project progressed rapidly and was terminated efficiently within the space of two years.

Although difficulties can arise from cultural clashes between the academic and industry approaches in these partnerships (eg academics may seek to continue projects that the industry partner believes should be killed), we found no cases where these were unresolvable.

### **PPP drug development with public partners (no industry input)**

These projects have very mixed performance.

Projects that build on academics' comparative advantages (particularly drug discovery work) tend to perform well. Examples of these include DNDi's High Throughput Screening (HTS) project against whole cell trypanosomes with Harvard Medical School Institute of Chemistry and Cell Biology and their HTS screening project against trypanothione reductase with Harvard University and the University of Dundee.

Later stage projects conducted without industry input appear to have a lower capacity to deliver good new drugs efficiently. Public groups are less effective in selecting and optimising suitable drug leads (an area in which industry has long experience), for instance, in synthesizing improved new compounds based on existing leads and optimising these to improve druggability. Although many academics have medicinal chemistry skills, they tend to have a non-industrial focus and may therefore have difficulty in keeping focused on druggability (ie what works in the patient, rather than what works in the laboratory) or in managing the process to conclusion. For instance, they may fail to define and stick to milestones and may have trouble terminating projects that are failing. Many public groups also have limited experience of designing and monitoring trials to ensure they meet regulatory standards, as opposed to non-Good Clinical Practice (GCP) or protocol trials in which most have extensive experience. Some, however, such as WHO/TDR, have experience in both.

As a result, once PPP projects move to lead identification and optimisation stages, failure to include industry expertise tends to lead to a fall-off in performance. Late-stage regulatory work also appears to be more difficult if industry (large and small) experience is absent, eg if there is no subcontracted or partner firm to assist with trial design, data management and regulatory submissions. Below are a number of examples where additional industry input could have expedited or improved R&D outcomes (these are not identified by name for confidentiality reasons):

- a project where assessment of the additional data needed to register an existing product for a new neglected disease use was conducted by public groups, but subsequently had to be repeated to meet EMEA standards;
- training of clinical trial investigators and monitors to GCP standards that was conducted by a public group (at a relatively high cost), but had to be repeated by a CRO to meet regulatory standards;
- many synthesis projects that failed to deliver compounds with increased activity: 'The researchers weren't focused on druggability and lacked milestones'; 'It was terminated due to lack of the industrial skills needed to identify potent compounds'; 'The academics lacked milestones and tended to keep running along just synthesising more compounds in the hope of eventually hitting on the right one';
- a project progressed by academics, despite an assessment by a multinational company that it was unlikely to be a fruitful line of enquiry (terminated due to failure two years later);
- academic development of a potential new antimalarial up to Phase I, but whose complex synthesis process meant that the costs to produce the first kilo reached nearly one million dollars and could never translate into commercial production for malaria (this product may still be useful in other OECD contexts);
- a project delayed by the absence of the principal investigator on one year's sabbatical leave. Other projects are delayed while public academics have to undertake other duties (lecturing, writing, conferences) or, in the case of WHO/TDR or WRAR, by tours of duty in the field;
- a public drug development project that conducted two PK and efficacy studies that delivered poor results (80 per cent combined treatment failure and relapse rates) possibly due to insufficient dosing levels, followed three years later by further Phase II trials at up to 3 times the original dose. This group already had access to company data suggesting that higher dosing levels might be needed and demonstrating the compound's poor oral performance (no linearity).

PPPs may choose to use academic/public input rather than industry services in order to keep costs down or for philosophical reasons. If this choice is based on academic comparative advantages then all is well, since outcomes are optimal and costs are reduced. However, substitution of less skilled academic/public services for skilled industry inputs slows down drug development and decreases the likelihood that a successful drug will result, with negative consequences for developing country patients. Efforts should be made to address these cost and philosophical issues in other ways.

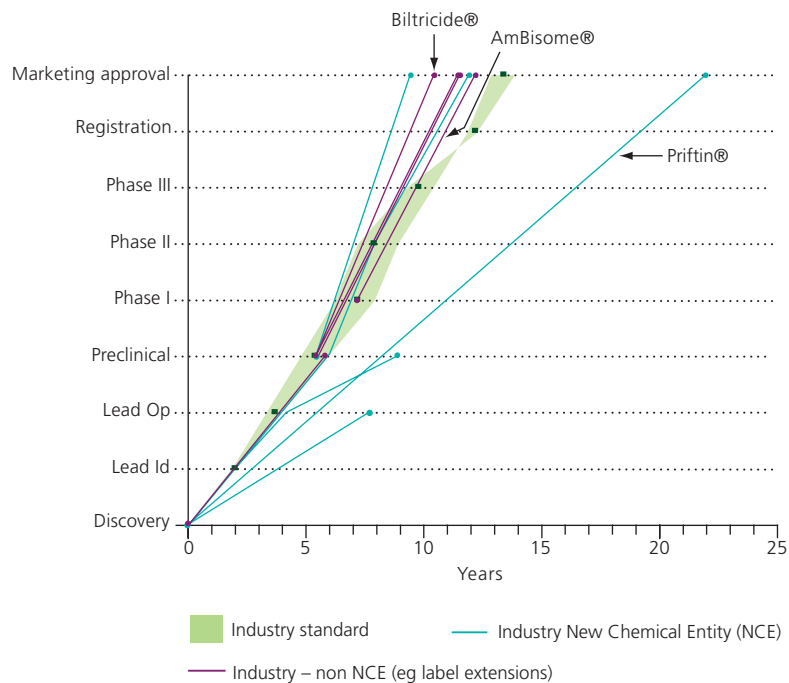
## 2.5 DEVELOPMENT TIMES

Drug development times are influenced by many factors, including the state of science, technical difficulties and the target disease, etc. However, overall they serve as a good proxy for efficiency of the development process, particularly in the preclinical stages. Clinical development times are less indicative since, for instance, TB trials can require up to two year patient follow-up, while malaria trials can take as little as 28 days. The performance of various neglected disease drug development groups – including industry, PPPs and public – has been measured against standard industry benchmarks. They are the Tufts Timeline (based on data on 68 approved new biopharmaceuticals and small molecule New Chemical Entities)<sup>104</sup> and the Parexel/MMV Timeline (based on Parexel's sourcebook).<sup>105</sup> We have excluded projects whose R&D timelines are unclear (several in-house industry projects) and have excluded incomplete stages to avoid over-estimating efficiency – for example, if a drug is currently in Phase II it has only been mapped to the point of completion of Phase I.

## 2.5.1 Industry

Data was available for seven drugs brought to market by industry, and for three drugs developed in house by them up to the point of transfer to a PPP. The small dataset makes generalisations unreliable; however, we note that less cost-intensive label extensions and reformulations were all developed quickly, matching expected industry timelines for this type of R&D (eg Biltricide® and AmBisome®), while development of several New Chemical Entities fell well below average, in one case taking over 20 years (eg Priftin®). Companies themselves offered a possible explanation, noting that – at least in the pre-2000 environment – neglected disease work tended to take lower priority, with staff being ‘preferentially allocated to more commercial programmes’ and R&D being conducted ‘below the parapet’ and ‘when space permitted’. This would be expected to impact more heavily on longer and more resource-intensive projects, such as development of NCEs. As noted in Section 2.3.1, this approach is now changing.

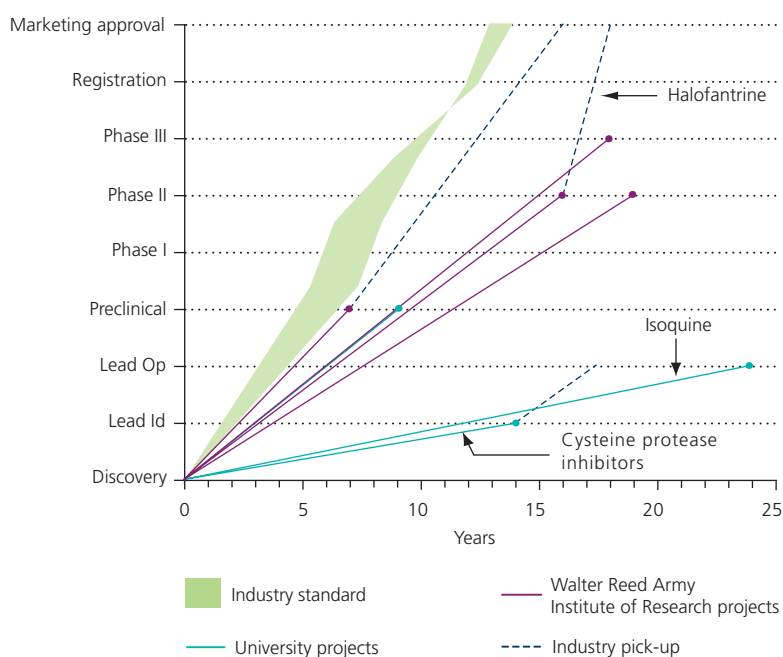
Figure 13. Industry timelines



## 2.5.2 Public

Data was available for seven projects developed in the public sector up to the point of transfer to a PPP or industry partner. These included projects developed by academics, for example, isoquine and cysteine protease inhibitors prior to MMV involvement, and projects conducted by public institutions such as the Walter Reed Army Institute of Research, for example, sitamaquine and halofantrine up to Phase II handover to GSK. The slow development times of these projects appear to reflect lack of funding, lack of drug-making experience, and lack of a primary focus on getting drugs made, with most conducting this work in an interrupted fashion alongside other activities/priorities. We note the increase in project trajectories once an industry partner came on board.

Figure 14. Public timelines

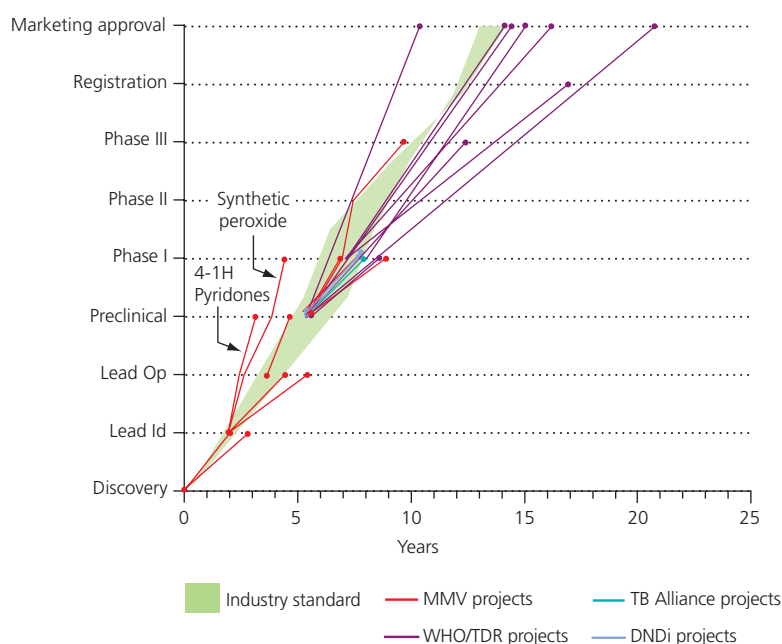


## 2.5.3 Public-Private Partnerships

Data is included for the 20 drug projects conducted by PPPs that met the inclusion criteria outlined above. With the exception of WHO/TDR, PPP projects generally followed or occasionally exceeded standard industry timelines, with MMV being notably efficient. There appeared to be no correlation between speed of drug development and size of partner company, nor with the business model used (partnering or subcontracting), with the two fastest moving projects being synthetic peroxide (a subcontracted project using academics, CROs and a developing country firm) and 4-(1H) pyridones (a partnership involving a multinational company).

Factors associated with higher success were the PPP itself, and the level of resourcing for the individual project. For instance, the two most rapid projects were conducted by MMV, the PPP with the greatest funding and a high level of in-house industry skills, and both received additional funding from the Gates Foundation to allow them to progress without restrictions as part of MMV's 'accelerated projects' mini-portfolio. WHO/TDR's slow performance, on the other hand, appears to reflect lack of funding (with one project on hold for several years) and lack of a primary drug-making focus, as well as structural issues and lack of in-house industry experience (see Section 1.5.1 above).

Figure 15. PPP timelines



## 2.6 COST AND COST-EFFICIENCY

Information on cost and cost-efficiency is inevitably more detailed for PPPs, who have a more open disclosure policy than for industry, for whom R&D costs are commercially sensitive information.

### 2.6.1 Industry

In terms of overall cost-efficiency, drug development carried out by multinational companies is generally the most expensive due to their large overheads and infrastructure costs, and their need to raise R&D investment capital on the share market (cost of capital is estimated at 50 per cent of total R&D cost). A well-known Tufts article estimated the cost of developing a New Chemical Entity (NCE) for Western markets at US \$802 million per drug including cost of failure and cost of capital, and out-of-pocket R&D costs per drug (including cost of failure) at US \$403 million (in 2000 US dollars).<sup>106</sup> Small companies' R&D costs are generally believed to be lower, although they are equally opaque: 'The drug development cost for biotech companies would be much lower than the Tufts estimate [for multinational companies], perhaps by almost an order of magnitude' (John Hodgson, Editor at Large, Nature Biotechnology).<sup>107</sup>

While indicative, these figures do not hold fully for neglected disease drug development, which some companies suggest will be substantially cheaper due to lower developing country trial costs. For instance, as noted in Section 1.2.1, several multinational companies estimated the cost of taking a new neglected disease drug from hit identification stage through to the start of clinical trials at around US \$50 million per successful candidate, and possibly less for subsequent candidates. One firm also suggested neglected disease clinical trial costs could be around US \$100-150 million (for a malaria drug), although this is within a partnered context.

## 2.6.2 Public

Public drug development costs were difficult to ascertain, since this R&D is often subsumed within other activities and budgets, rather than being conducted as a separate project with ring-fenced funding (eg academics may conduct this research as part of their daily work). This is, however, an area we would be interested to explore further.

## 2.6.3 Public-Private Partnerships

Our discussion of costs is necessarily general due to the constraints on publishing hard figures, particularly for projects that involve industry partners – the exception is the handful of projects in the following Section, where full per-project R&D costs could be publicly disclosed.

In terms of overall cost-efficiency, PPPs perform well. Excluding WHO/TDR – for which full figures are not available – the remaining PPPs conducted 46 drug development projects from 2000 to 2004 for a total direct R&D cost of US \$76 million and a total overall cost of US \$112 million. These included 30 early-pipeline projects (from drug discovery to preclinical), ten clinical development projects, one in registration and five terminated discovery projects. (In practice, total R&D costs represent a higher proportion of total PPP budgets than noted here – however, for consistency, we have excluded R&D costs for projects with no formal drug development component, for example protocol trials.) Although the PPP model has proven to be cost-effective, we note that costs would be expected to increase substantially as more projects enter large-scale Phase III trials and that the PPP cost-efficiency profile would therefore also be expected to change, since late-stage failures are more expensive than early-stage failures.

The cost-efficient nature of the PPP approach reflects their ability to optimise resource-use by:

- reducing cost of capital (industry uses a real discount rate of 11 per cent, and substantially higher rates apply to VC-funded companies).<sup>xxxv</sup> Cost of capital for PPPs, if factored in at all, would be at low-risk, long-term US/European treasury rates;
- leveraging in-kind input, including from multinational company partners and public groups (eg trial assistance in DCs, subsidised multinational company R&D, and ad hoc inputs from industry experts);
- avoiding the need to fund a fully loaded pipeline since PPPs can select from a pool of hundreds of public and private domain projects that have already moved some way along the R&D process (without having to purchase these rights retroactively, for a variety of reasons as outlined in Section 1.5.1 above);
- using cheaper developing country sites for clinical trials, and highly competitive developing country partners for formulation and manufacture;
- reducing project risk and cost through portfolio synergy effects (MMV, with 23 projects, has a larger single-disease portfolio than most small companies could sustain);
- ‘piggybacking’ public health work onto commercial work. This includes piggybacking on small companies’ commercial work, as outlined above and ‘scientific’ piggybacking on existing commercial knowledge. For instance, PPPs can build on industry libraries of commercial inhibitors (eg cysteine protease inhibitors for cancer/ malaria) or on industry work on a shared commercial target;
- with a portfolio management approach, projects from multiple sources are compared to each other for their competitive advantage including cost, efficacy, and potential for resistance. Less competitive projects are stopped at an earlier stage, saving significant cost.

<sup>xxxv</sup> These figures are taken from the study carried out by the Tufts Center for the Study of Drug Development published in 2003 (DiMasi J, Hansen R, Grabowski H (2003). The price of innovation: new estimates of drug development costs; *Journal of Health Economics* 22: 151-185), although there is debate as to whether 11 per cent remains the representative rate.

Based on the data made available to us and on PPP interviews, we can also make the following general observations.

*The PPP-multinational company approach* is the least expensive, because of the substantial leveraging of company in-kind input. For example, two PPPs estimated that company in-kind contributions averaged a 1:1 match for PPP cash contributions, with one multinational estimated as contributing more than double as in-kind contributions. Large companies contribute somewhere between half and all direct R&D costs for early drug discovery partnerships, and provide substantial in-kind input in the form of infrastructure, overheads and access to company knowledge and compounds. PPPs are expected to cover most of the direct R&D costs at the clinical development stage, although companies generally continue to offer infrastructural support and/or regulatory services. These partnerships are highly efficient, since they usually require minimal PPP supervision and co-ordination.

*The PPP-small company approach* is more expensive. Small companies focused on Western diseases expect full R&D costs to be covered, although they normally contribute overheads (estimated by two PPPs at around 10-15 per cent additional) and some unpaid management time. Their smaller scale nevertheless means that costs are substantially lower than the full multinational company commercial costs would be. Partnerships with developing country firms were often even cheaper, both because of lower developing country costs and because these firms frequently provided major in-kind services. However, all non-multinational company partners 'tend to be more resource-intensive to manage' and 'much more outsourcing is needed' to fill their skill-gaps, this being particularly the case for small developing country firms (PPP interview 2004).

*PPP-subcontracted projects* were the most expensive option, since CROs normally charge full commercial rates (though these are still well below multinational company commercial costs) and include overheads. CROs were seen as having the highest transaction costs (an inefficiency), since PPPs often needed to devote substantial time and resources to co-ordinating and managing them. Large and experienced CROs can be an exception, for example, by offering volume discounts and substantial experience.

## PPP project costs

Project costs were calculated using full budgets, which were provided by most PPPs.<sup>xxxvi</sup> Costs were estimated by adding up direct project costs and pro-rata project-related costs. Direct project costs are the funds granted to project partners to conduct their drug discovery and development work. Project-related costs include both outsourcing costs directly associated with projects, such as legal costs and costs related to the organisation and travel for project meetings/reviews, and variable staff costs associated with the work of the scientific officers with regard to specific projects. We did not calculate per-project costs for projects that had significant in-kind contributions, because of the difficulty of assigning a reliable value to pro bono services.

The projects in Table 6 are those where full cost disclosure was not bound by confidentiality agreements. These tend to be projects where the relevant IP is held by a public group or the PPP itself (eg PA-824, synthetic peroxide) or the relevant compound is in the public domain (eg artesunate, pyronaridine). Although we could only disclose full costs for these five projects, we note that the figures below are typical of the over 40 PPP project budgets we examined.

MMV's synthetic peroxide project is particularly notable as it has progressed from drug discovery, through lead identification, optimisation and preclinical, to Phase I, using fully paid partners and subcontractors, at a public cost of only US \$11.5 million. While Roche provided expert advice and minor R&D services during the early stages, this would add only a minor increment to the overall total.<sup>xxxvii</sup>

<sup>xxxvi</sup> WHO/TDR was not included, as it could not provide clear budgetary information on individual projects and sometimes shared costs across projects eg oral efloornithine and IV efloornithine.

<sup>xxxvii</sup> Two further Roche staff moved to this project; however, their costs were covered by MMV.

Table 6. R&amp;D costings for selected PPP projects

Project Name	Type of project	R&D costed	Indication	Cost * US \$million	Unquantified pro bono input
<b>ACTUAL COSTS</b>					
FAS II	New chemical entity	<b>Lead identification</b>	Malaria	<b>2.7</b>	Nil
PFT inhibitors	New chemical entity	<b>Lead identification</b>	Malaria	<b>2.2</b>	Some expert advice and data from BMS
Pyronaridine-artesunate	Fixed dose combination	<b>Preclinical (+3 months Phase I)</b>	Malaria	<b>5.3</b>	Shin Poong's input (formulation chemistry)
PA-824	New chemical entity	<b>Preclinical</b>	Tuberculosis	<b>4.5</b>	Expert advice from ex-company employee
Synthetic Peroxide	New chemical entity	<b>Discovery Lead identification Lead optimisation Preclinical (+6 months Phase I)</b>	Malaria	<b>11.5</b>	Expert advice from Roche
<b>PROJECTED COSTS</b>					
Pyronaridine-artesunate	Fixed dose combination	<b>From preclinical up to registration</b>	Malaria	<b>15-20</b>	
PA-824	New chemical entity	<b>From preclinical up to end of phase III</b>	Tuberculosis	<b>86</b>	

\* We have used internal budgets, and added pro-rata'd indirect scientific costs.

## 2.7 CORRELATES OF SUCCESS

An overview of performance across all metrics highlights features common to most successful projects and missing from most unsuccessful projects. These correlates of success are:

- a focus on neglected disease drug development for developing countries over all other considerations**  
 Groups with this tight focus have pipelines that move more rapidly and effectively. Companies with a specific neglected disease focus (overall, or in specialist institutes) perform better, in terms of neglected disease R&D, than companies who conduct this research with half an eye on commercial markets. Likewise, our research suggests that public groups with a sole focus on neglected disease drug development perform better than groups who select projects and/or partners with half an eye on secondary goals such as fostering technology transfer, academic skills, regional integration or capacity-building.
- industry involvement from an early stage**  
 Public groups with limited drug-making experience perform better if assisted by companies with extensive skills and experience in this area, be these small or large companies, contracted pharmaceutical firms or developing country manufacturers. This experience is needed at the earliest stages, since successful drug development relies heavily on selecting the best possible lead compound, as well as at key points throughout the process, including process chemistry, scale-up manufacture and preparation of regulatory dossiers.



- **public involvement from an early stage**  
 Industry groups with limited experience of neglected disease drug development and developing country patients and markets perform better if assisted by public groups who are experienced in these areas. This input should ideally come at the lead identification stage, to ensure the final products will be suitable and affordable for developing country use, and may be informal (eg contracting-in of public skills or consultations with public groups to define optimal drug profiles) or through formal partnerships. Public input is helpful in managing developing country clinical trials and developing country regulatory and implementation processes, and is essential to ensuring optimal product roll-out in developing country settings.
- **appropriate use of the respective skills of the public and industry partners**  
 Each partner should perform tasks in which they have the greatest comparative advantage, as outlined above. Putting together the most effective pipeline (in terms of skills) may require additional contracted or in-kind inputs to supplement the chosen partners. For example, developing country firms and small companies may need CRO trial assistance, and academics may need contracted or in-kind industry medicinal chemistry experience.
- **management and scientific staff with industrial drug-making experience**  
 Public groups with a high level of in-house industry experience are more successful at integrating industry into their drug development projects (a correlate of success) and more likely to secure industry deals on favourable terms for both parties. Staff with industry experience are better at selecting promising projects, keeping these moving efficiently, terminating failing projects, recognising when they need additional help, and moving rapidly to secure this (eg by contracting-in additional project management resources).
- **adequate funding**  
 Inadequate funding slows down drug development and generates inefficient behaviours, for example, the use of cheaper but less experienced partners. The two fastest moving drug projects differ from similar projects conducted by the same PPP in one aspect only – they received accelerated funding.
- **larger portfolios**  
 Larger portfolios are more efficient. They allow skills and services to be shared, reduce the risk that a PPP will continue poorly performing projects in order to ‘have something to show’, and allow projects to be compared with each other for competitive advantage. Large portfolios, for example, MMV’s portfolio of 23 projects (end 2004), are associated with greater ability to do deals, and therefore broader access to industry and academic compounds.

We must emphasise that our insistence on focusing specifically on neglected disease drug-making does not in any way mean that we wish to devalue other goals – such as fostering developing country technology transfer and capacity-building, growing public skills, or encouraging regional integration. Indeed, we strongly support these goals.

However, we remind readers of the old medical adage, ‘See one, do one, teach one’ – in other words, the quickest way to learn new skills is to do so alongside someone who is already experienced in them. PPPs can achieve this not by seeking to start from scratch or by commissioning less experienced groups and companies, but rather by pairing developing country firms with CROs experienced in regulatory submissions, by encouraging academics to work alongside industry experts, and by putting industry drug developers in close contact with public neglected disease scientific experts.

Paradoxically, it is the most focused PPPs who are having the greatest success in fostering many of these parallel goals. By keeping their eyes firmly on their primary goal, they are building larger and more successful portfolios and therefore have greater opportunities to bring in more and different partners, and to give these partners the ‘repeat business’ that will speed them along the steep learning curve of neglected disease drug development.

## RECOMMENDATIONS

### 3.1 Optimal approaches

### 3.2 Policies to support PPPs

- Industry R&D Facilitation Fund
- Other proposals to strengthen the PPP model

### 3.3 Policies to increase small company commercial neglected disease activity

- Reducing barriers to developing country market entry for small firms
- Improving health outcomes from small companies working independently

### 3.4 A new fundraising mechanism: the neglected disease Fast Track Option

### 3.5 Other approaches

### 3.6 Creating a public ‘market’?

## 3.1 OPTIMAL APPROACHES

Good policy-making must include better understanding and use of existing levers, rather than simply providing funds. Policies should match incentives to motivations (financial incentives for those with financial motives, non-financial incentives for those with other drivers) and should tailor these incentives to the skills and needs of stakeholders. Attempting to motivate multinational companies with limited interest or skills in neglected disease R&D is likely to be less effective than motivating companies (large and small) whose interests, business models and/or skills already predispose them to neglected disease activity. Policies should also be carefully tailored to align stakeholder behaviour with desired public outcomes, including incentivising and rewarding best-practice activities. Finally, in some cases, improved outcomes can be more cost-effectively achieved by removing existing obstacles rather than providing additional funds to compensate for them.

The above information on company activity, motivations and needs, when supplemented by analysis of performance metrics and correlates of success, gives us a clearer picture of which approaches work best and helps us to identify unexploited opportunities and potential obstacles to success. This can be used to design more effective and targeted policies to stimulate neglected disease drug development.

Based on this information, we recommend supporting two main approaches:

- **publicly-funded R&D.** If neglected disease R&D is to be supported by public funds, then policy-makers should choose the cheapest and most effective approach. Our findings suggest this is best achieved by combining industry drug development skills with public neglected disease skills through Public-Private Partnerships, including partnerships with interested or potentially interested multinational companies and with small firms who could derive commercial benefit from neglected disease R&D.
- **small company market-driven neglected disease activity.** Since any publicly-funded approach – PPP or otherwise – is subject to the vagaries of political will and public budgets, we additionally recommend examining the scope to complement PPP activity with market-driven activity by small companies. By this, we mean activity driven by consumer demand for neglected disease products, which is a sustainable mechanism, as opposed to ‘markets’ created by public subsidies, since these are no more sustainable than other publicly-funded approaches. We specify small company market-driven activity, since the commercial scale of these firms is more compatible with neglected disease markets than that of multinational pharmaceutical firms.

It is also clear that current and future neglected disease activity, by PPPs or others, inevitably means that we will see more projects entering large-scale clinical trials. This will require not only substantially increased funding but also far greater attention to how clinical trial, registration and implementation processes can be streamlined and facilitated. In many ways this is as important as funding itself, since failure of successful implementation will greatly devalue all previous R&D investments, public or private. This is now a pressing priority for further research and policy attention, although not one that is within the remit of this paper.

## Public-Private Partnerships

If public funds are to be expended to increase neglected disease drug development, then the PPP approach offers the best outcomes for most stakeholders.

PPPs facilitate increased industry involvement by all companies, small and large. They also allow much of this activity to be conducted under a low- or no-profit model for developing country markets, while still meeting companies' broader business needs. For many firms, the PPP role is catalytic – without it, industry activity would in many cases either not commence or would cease.

PPPs are also well placed to meet public needs. They represent a highly cost-efficient use of public funds (in particular, but not only, by excluding the need to cover the cost of capital to industry), and have the highest degree of transparency and public control over R&D choices, expenditures and project progress. PPPs minimise public risk by shifting scientific decisions to experts, by spreading public funds across portfolios, and by requiring lower outlays than other approaches; the PPP-facilitated low- or no-profit model means that outlays under public purchase funds will also be minimised, if such funds are envisioned to supplement buying power in poor settings.

Finally, and importantly, PPPs offer perhaps the best prospect of delivering optimal health outcomes from the patient perspective. They are inherently designed to use industry and public skills to their best advantage, and to allow both industry and public to build up complementary skills without slowing down the process of drug development. The low- or no-profit model is also best placed to maximise sustainable developing country patient access to new neglected disease drug products.

Although it is the best approach overall, the PPP model can nevertheless still be improved by appropriate public policies. For example, it is clear that small companies' potential for partnering is still underexploited. This includes the many Western-focused small firms whose compounds or technologies may have overlapping neglected disease potential, and who may be willing to operate on a no- or minimum-profit basis in the developing country neglected disease market, if their other commercial goals are enhanced. If adequate funding is available, PPPs are also well placed to pick up small company compounds and take them through clinical development (for example, if companies are interested in licensing over such compounds, rather than developing them themselves). We will also face new challenges as more PPP projects enter large-scale clinical trials (experience in this area is still limited). These challenges include a need for improved funding, trial and implementation mechanisms as noted above, as well as donor willingness to accept that late-stage failures are costly but inevitable.

New public policies should build on the strengths of the PPP model as well as addressing its general and specific weaknesses (summarised below in Table 7 for ease of reference). They should also incentivise behaviours that best match the identified correlates of success.

Table 7. PPP strengths and weaknesses

Strengths	Weaknesses
<b>PPPs overall</b>	
<ul style="list-style-type: none"> <li>• The main drivers of industry neglected disease activity</li> <li>• Maximum cost-efficiency</li> <li>• Lower donor risk</li> <li>• Maximum health outcomes for developing country neglected disease patients</li> </ul>	<ul style="list-style-type: none"> <li>• Low sustainability due to heavy reliance on public funding</li> <li>• Modest ability to mobilise industry resources</li> <li>• Constrained access to industry compounds</li> <li>• Requirement for government policy-makers to choose between PPPs</li> <li>• Some PPP projects have insufficient industry input at key stages</li> <li>• Over-reliance on the performance of individual PPPs, since most neglected diseases are catered for by only one group</li> </ul> <p>(Many of these weaknesses are partly due to insufficient public funding)</p>
<b>PPPs with public groups</b>	
<ul style="list-style-type: none"> <li>• Knowledge of neglected diseases</li> <li>• Developing country knowledge and experience</li> <li>• Early-pipeline R&amp;D skills (ie drug discovery)</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of drug-making skills</li> <li>• Lack of regulatory skills (including for clinical trials)</li> </ul>
<b>PPPs with multinational companies</b>	
<ul style="list-style-type: none"> <li>• Critical to multinational neglected disease R&amp;D involvement (a key adjunct to the 'no profit-no loss' model)</li> <li>• Provide a valuable source of innovative drug leads</li> <li>• Provide final drugs to patients at not-for-profit prices</li> </ul>	<ul style="list-style-type: none"> <li>• Low sustainability, since it relies on philanthropic and public funding for PPPs and on company volition</li> </ul>
<b>PPPs with small Western-focused companies</b>	
<ul style="list-style-type: none"> <li>• An under-exploited source of potential new neglected disease compounds</li> <li>• Increased sustainability, as leveraged by commercial motivations</li> <li>• Efficiencies from scientific piggybacking onto existing commercial R&amp;D</li> <li>• Provide final drugs to patients at not-for-profit prices or small mark-ups</li> </ul>	<ul style="list-style-type: none"> <li>• Company participation requires full R&amp;D funding, which resource-constrained PPPs may not be in a position to offer</li> <li>• 'Start-up' funding for new technologies is currently beyond the capacity of most PPPs</li> <li>• R&amp;D agreements can be hampered by lack of understanding on both sides</li> </ul>
<b>PPPs with small companies who have a commercial neglected disease focus (see Table 8)</b>	

### Small company commercial neglected disease activity

Since the PPP approach relies heavily on philanthropic and public funding, we further recommend that policy-makers examine the possibility of complementing PPP activity with support for small company market-driven activity, which is more sustainable.

Existing neglected disease markets (developing country and Western) appear to offer unexploited opportunities, particularly for small firms, who can be motivated by lesser returns than multinational pharmaceutical companies. The combination of small companies' inventiveness with developing country manufacturing and distribution capacity promises to offer a cheaper alternative pipeline for neglected disease drugs. In other words, instead of creating larger neglected disease 'markets' using public funds, we may be able to leverage existing commercial markets for small companies.

Several global neglected disease markets (including TB, malaria and possibly leishmaniasis) offer comparable returns to average orphan markets that small companies routinely pursue. However, many firms we spoke to highlighted that these were less attractive than they could be because of their developing country component. In particular, they were deterred by the substantial additional barriers to entry that are characteristic of these large, disseminated and unfamiliar markets. Identified barriers included:

- poorly quantified market value;
- lack of in-house neglected disease knowledge;
- the need for companies to be able to access large-scale clinical trial, manufacturing and distribution capacity;
- difficulty finding suitable developing country partners;
- lack of familiarity with developing country markets (eg public tender markets) and developing country health and regulatory systems;
- difficulty accessing developing country public markets or centralised markets (such as international purchasers).

Since the difficult nature of developing country markets, rather their overall value, is a primary barrier, public policy-makers may be able to make these more attractive to small firms by instituting measures that reduce barriers to entry. In most cases, *these facilitating measures require little or no investment* – and may therefore be attractive to governments who do not wish to finance neglected disease R&D directly. In the final event, additional purchase funds may still be needed to complement the market – but these ‘top-up’ funds may be likely to be smaller than would otherwise be needed (eg if barriers to entry remained high or if ‘top-ups’ were needed to match large company expectations).

A further important point to consider, when developing new policies aimed at increasing small company market-driven activity, is that the overall health outcomes of the small company model can differ markedly depending on whether the company targets these markets on its own or by working within a PPP. The partnered approach offers significant advantages from a public health perspective, since it guarantees public health input from the earliest stages and allows the public partner to have some input over company R&D choices and some influence over the marketing, distribution and price of the final products. This is particularly true if the PPP has provided the company with early and/or substantial assistance (as noted above). This public input protects and improves public health outcomes for developing country patients.

When small companies work independently, however, the balance sheet of advantages and disadvantages changes, with these differences highlighted in the bold text in Table 8 below. Independent small company R&D activity occurs largely without public funding or effort, but the trade-off is a loss of public control over outcomes. In particular, firms seeking to maximise their returns may be tempted to focus development on Western needs (eg resulting in inappropriate formulations), to exclude high-liability patient groups (eg children and pregnant women), and may price the final products at levels that poor patients cannot afford, requiring the implementation of public purchase funds to increase patient access. In developing new policies to increase small company commercial neglected disease activity, it would be prudent to learn from the experience and problems of the past 30 years, in particular by linking any new incentives to measures that protect public health outcomes in developing countries (or by encouraging firms to take a partnering approach).

Finally, most small companies are inexperienced in large-scale clinical development and commercialisation and would be expected to require substantial assistance to overcome these skills gaps. While subcontracting in the relevant skills is likely to go some way towards addressing this issue (for example, using CROs experienced in developing country trials), we cannot automatically assume that this will be enough if a small company is working in unfamiliar territory from the disease, market and technical perspectives. These issues will need close attention in order to determine whether independent small company activity does indeed represent a useful back-up to PPP activity.

Table 8. Small companies with a commercial neglected disease focus

Strengths	Weaknesses
<b>PPPs with small companies who have a commercial neglected disease focus</b>	
<ul style="list-style-type: none"> <li>• Automatic – company activity occurs even without public intervention</li> <li>• Maximum sustainability since market-driven</li> <li>• R&amp;D is more closely targeted to developing country needs and capacity to pay</li> <li>• Require less public support</li> </ul>	<ul style="list-style-type: none"> <li>• Limited company interest, partly on account of unfamiliarity and higher barriers to market entry</li> <li>• For-profit prices in developing countries (partially mitigated by the need to capture developing country public and private markets)</li> <li>• Limited public influence over R&amp;D choices, marketing, distribution and price</li> <li>• May require supplementary public purchase funds for the poorest patients</li> </ul>
<b>Small companies with a commercial neglected disease focus working independently</b>	
<ul style="list-style-type: none"> <li>• Automatic – company R&amp;D activity occurs even without public intervention</li> <li>• Maximum sustainability since market-driven</li> <li>• Requires little or no public support</li> </ul>	<ul style="list-style-type: none"> <li>• Limited company interest, partly on account of unfamiliarity and higher barriers to market entry</li> <li>• For-profit prices in developing countries (possibly mitigated by the need to capture developing country public and private markets)</li> <li>• <b>No public influence over R&amp;D choices, marketing, distribution and price</b></li> <li>• <b>R&amp;D is likely to target both Western and developing country needs, with potential drawbacks for developing country patients</b></li> <li>• <b>More likely to require supplementary public purchase funds for poor patients</b></li> </ul>

## Overall

We have used this information to develop a broad range of policy recommendations, as below, with a focus on supporting the two approaches discussed above, including building on their strengths and addressing their weaknesses. In some cases, these policies require a commitment of additional public funds. In many other cases, improvements can be generated through more efficient public policies, without the need for additional funding. Whichever the case, it is clear that there is already much useful R&D activity that could be supported, and many existing opportunities that have not yet been fully exploited.

## 3.2 POLICIES TO SUPPORT PPPs

### 3.2.1 Industry R&D Facilitation Fund (IRFF)

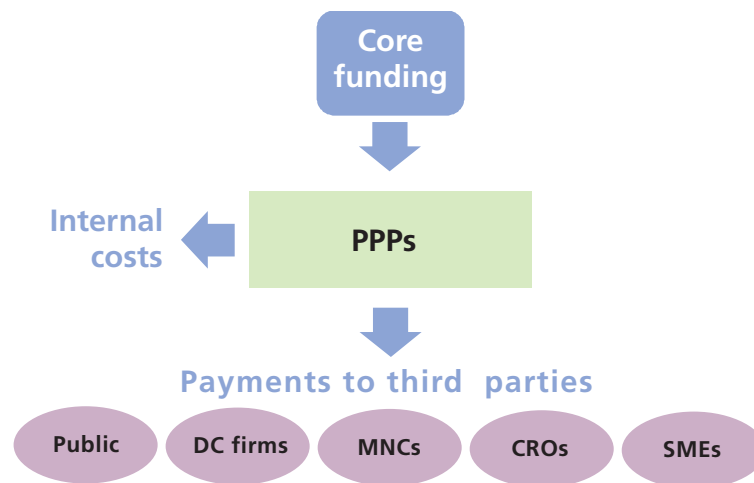
The IRFF has been developed with a view to easy implementation by public policy-makers. Implementing the IRFF would allow G8 countries to rapidly fulfil their July 2005 pledge of ‘increasing direct investment ... through such mechanisms as Public Private Partnerships ... to encourage the development of ... drugs for AIDS, malaria, tuberculosis and other neglected diseases’.<sup>108</sup> It would also be highly suitable for implementation by EC member states.

#### The proposal

The Industry R&D Facilitation Fund (IRFF) is a proposed long-term grant fund of between US \$130 million and US \$190 million per year to underwrite industry participation in Public-Private Partnerships, with the dual aims of increasing industry neglected disease R&D and improving PPP outcomes.

PPPs currently receive core funding from philanthropic and public groups, and use this core funding to finance their R&D projects and cover internal costs (see Figure 16). Two-thirds of external R&D expenditure goes directly to industry and one-third to public and academic groups.

Figure 16. PPP cash flows under current model



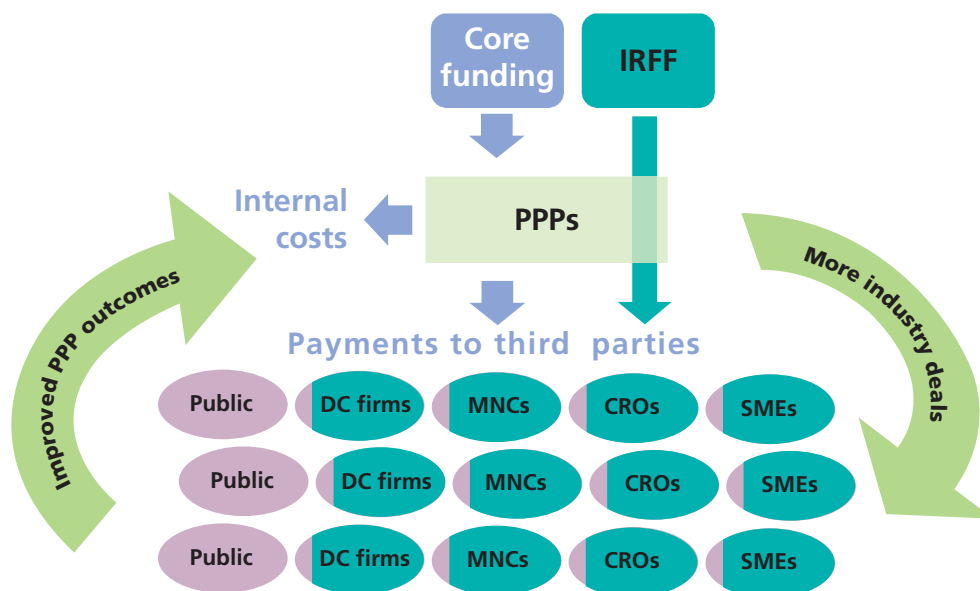
\*MNCs: Multinational Pharmaceutical Companies, SMEs: Small and Medium-sized Enterprises, CROs: Contract Research Organisations, DC: Developing Country

We propose the formation of a new public fund – the IRFF – that will finance PPPs for their payments to industry, as follows:

- as they currently do, PPPs will continue to pay industry for neglected disease R&D, including commercial contracts with small company partners, competitive subcontracts with CROs, and co-payments to multinational company partners;
- PPPs will receive a long-term commitment from the IRFF to partially finance their industry payments (eg perhaps 80 per cent of total industry payments – see Cost Section on page 71), since partial rather than full financing limits risks of potential overuse by PPPs;
- The replenished PPPs will now be able to sign up additional neglected disease projects, including further industry contracts.

The IRFF funds are additional to the core funding PPPs currently receive from public and philanthropic groups and flow through to industry partners, rather than financing PPPs as organisations (see Figure 17).

Figure 17. PPP cash flows under IRFF model



## Benefits for neglected disease R&D: a virtuous cycle

The IRFF has been specifically designed to address current PPP strengths and weaknesses, and to align the incentives of all players with the correlates of success.

### Increased industry involvement (large and small firms)

The IRFF will attract more companies into neglected disease R&D as fully-funded PPPs will be able to offer terms that are more attractive and more closely matched to company needs:

- longer-term and more sustainable commitments;
- financial support for the 'no profit-no loss' model, allowing multinationals to continue operating in the neglected disease area;
- increased small company participation, since PPPs can offer commercial rates rather than pressuring small companies for in-kind and discounted business; and can structure deals that match small companies' financial needs (thousands to millions of dollars, not billions). In particular, increased partnered activity by companies focused on Western diseases, now a largely untapped area.

As a positive flow-on, the IRFF may also allow increased R&D contracts with public institutions, since it liberates core funding previously spent on industry payments.

### Improved PPP outcomes

The IRFF incentivises behaviours associated with the correlates of success:

- it promotes increased industry input to PPP projects, leading to improved PPP project performance, as noted above. PPPs that choose not to use industry assistance in areas where it is shown to improve performance, for example, in optimising academic leads or preparing regulatory submissions, are free to do so but this choice would not be subsidised by public funds via the IRFF;



- it promotes the expanding of PPP portfolios because of their increased ability to sign industry deals (and academic deals using freed-up core funding);
- adequate funding allows PPPs to accelerate promising projects, and diminishes the counter-productive cost-saving measures outlined earlier (see Section 1.5.3 above).

## Benefits for donors

### Improved efficiency of public R&D funding

The IRFF supports and enhances the PPP drug development approach, which our analysis shows is the most cost-efficient and the most effective from the public health point of view. It also favours optimal performers within this approach, since PPPs who have the most projects moving the most quickly will draw most frequently on the fund.

Through the IRFF, public funders can allocate resources across all PPP projects in the exact amounts needed *exactly when* they are needed, allowing all R&D projects to move forward simultaneously without delay. This is far more efficient than the current intermittent grant-based funding system for PPPs. The IRFF also centralises information for donors, for instance, on what projects are being carried out, on potentially duplicative R&D, and on how public funds are being spent.

### Minimised public risk

The IRFF is a global consolidator: it removes the need for donors to choose which PPP or which project to fund since governments now invest in a multi-PPP portfolio, encompassing all PPP neglected disease drug projects. The bigger the portfolio, the bigger the benefits, for example, higher efficiencies and lower risks (as these benefits have been widely documented elsewhere they will not be further discussed here). In many ways, the IRFF optimises neglected disease drug development portfolios in a fashion similar to mergers and acquisitions within the pharmaceutical and biotechnology industry.

### Rapid deliverables

The current PPP global portfolio will deliver a rapid and high yield for public donors. The PPP approach has already been thoroughly piloted (largely using private philanthropic funds) and is expected to deliver six to seven drugs within five years, with the first two by end of 2006. This is excellent value for the average US \$130 to 190 million/year public funding that the IRFF would require (see cost Section overleaf).

## The mechanism

The suggested operational framework below provides a starting point for discussion. All details would, of course, need to be decided and finalised in conjunction with stakeholders.

### Access to the IRFF

IRFF access criteria could include requirements that a PPP must fulfil to be eligible. For instance, it must:

- be a registered not-for-profit public health entity;
- have an overriding focus on drug development for neglected diseases;
- have a charter that includes access to final products for developing country patients (for example, affordability and appropriateness);
- have a solid portfolio, which is non-redundant with that of other PPPs;
- have scientific and management teams with drug-making experience;
- have a detailed forward budget;
- have been funded and in operation for two years or more;
- be able to produce yearly audited accounts.

### Funding mechanism

The IRFF must be a *long-term funding mechanism* so that PPPs can make commitments that match the long-term nature of the pharmaceutical R&D process. Therefore we propose that once a PPP is given access to the IRFF, a multi-year planning exercise (perhaps five years) should be prepared by the PPP in conjunction with the IRFF management team in order to anticipate long-term financial needs. This process would also provide better projections as a basis for estimating future public funding needs.

A funding ceiling could then be conditionally committed over this period, with periodic reviews to ensure satisfactory portfolio management and to adjust forward projections. The funding ceiling should be on a portfolio basis, rather than a project-per-project-basis, in order to allow PPPs to retain responsibility for selecting, progressing and terminating projects. Funds could be disbursed to PPPs in arrears, for instance, on the basis of invoices, although policy-makers could also consider providing up-front funding over set periods. The latter option is, however, potentially less transparent and more difficult to manage from the public perspective, and may be less flexible for PPPs.

### Management structure

Based on the above, the role of the IRFF management structure would be likely to include:

- accrediting PPPs;
- reviewing R&D portfolios of funded PPPs and managing the *global cross-PPP portfolio* (eg ensuring non-duplication of efforts, identifying gaps);
- reviewing and advising on yearly budgets;
- ensuring streamlined disbursement of funds;
- providing PPPs with financial/portfolio planning advice and support where needed;
- reporting to donors;
- managing any unspent donor-committed funds.

A potentially efficient structure to manage the IRFF would be a small management team with a focus on pharmaceutical portfolio and fund management, supported and directed by an advisory board with a mix of neglected disease experience and financial knowledge (for accountability purposes).

Our discussions to date show that biotechnology-focused VC firms are interested in playing this role, and could provide many of the skills needed if supported by an appropriately public health-focused panel. The European Investment Fund has also expressed keen interest in being part of the Advisory Panel, although not in the management structure directly. Whoever is chosen, we recommend that the hosting structure be as lean as possible and sit outside government or international bureaucracies.

### Cost

We recommend partial rather than full reimbursement of PPP payments to industry in order to avoid moral hazard, ie in the absence of an internal cost constraint, PPPs may be encouraged to overuse the fund. A possible formula would be 80 per cent reimbursement from the fund, with PPPs covering the remaining 20 per cent from their core funding. Ultimately, the most appropriate ratio will need to be determined through further analysis and consultation with stakeholders.

Our current forecast uses an 80 per cent reimbursement ratio, and on this basis the estimated funding requirement for the IRFF to support the four existing PPPs<sup>xxxviii</sup> for the next five years would be between US \$575 and US \$690 million (at a yearly average of US \$115 to US \$138 million). Over the next ten years, US \$1.3 to US \$1.9 billion may be needed, although these longer-term forecasts will become clearer over time. *We note that these numbers do not cover any additional needs stemming from independent activity by small and developing country companies, or non-PPP public groups.*

<sup>xxxviii</sup> WHO/TDR is currently excluded as we could not obtain budgets.

The projection above should be seen as indicative only, as our forecasting model includes several caveats (the underlying assumptions are summarised in Figure 18 below):

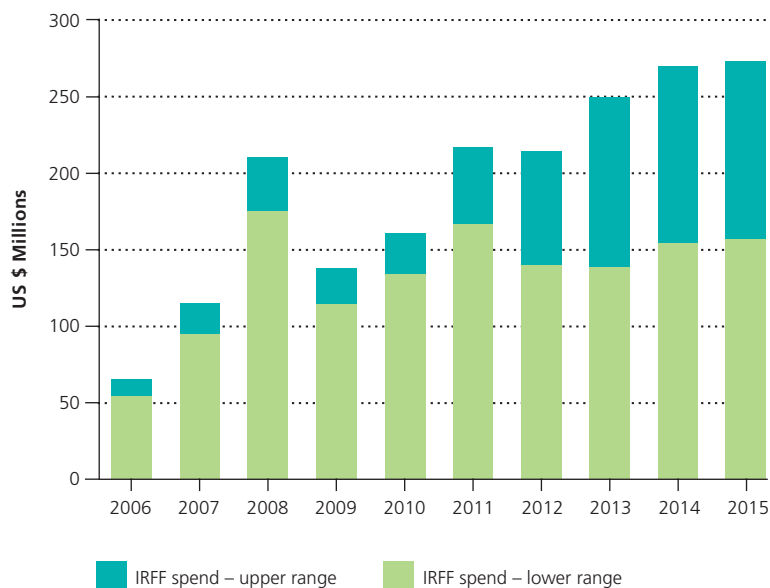
Firstly, the PPP projections on which it is based are not precise. MMV's and the TB Alliance's projected expenditures until 2010 assume that all drugs in their current portfolio will succeed (ie no attrition has been applied). On the other hand, neither includes provision for funding new projects, which they assume will be covered by the funding unspent on failed projects. In the long run this may even out for MMV, which has reached its target size (20+ projects) and has a maturing portfolio. But the formula may be less likely to be representative for the TB Alliance, which aims to more than double its portfolio in the coming years. DNDi figures are based on the projections of their 2003 business plan using a two year time lag (as suggested by them), as this young organisation is still in the process of building a long-term financial plan based on their developing project experience. iOWH projections have been modelled on the basis of MMV's trajectory (with iOWH agreement) since we were unable to obtain projections from the PPP itself. We note that the IRFF could play a key role in providing management support to PPPs and help them forecast their future funding needs with more accuracy, benefiting both PPPs and donors.

The second set of limitations stems from uncertainties inherent in the process of drug development itself. For instance, the TB Alliance is currently unable to predict the cost of Phase III TB trials, which will vary widely depending on whether regulatory authorities will agree to approve a TB drug based on combination trials (cheaper) or will insist on substitution trials (much more expensive). Discussions on this issue are in progress. The evolving state of science and the ability of PPPs to keep feeding their pipeline to maintain their target portfolio size and mix are other unknowns that will affect the size of the IRFF.

Lastly, new PPPs could be set up in the coming years to focus on other neglected diseases, such as dengue fever, which would increase the burden on the IRFF. However, this eventuality has not been included in our estimates as guessing the number, start-up year and portfolio trajectory of these PPPs would be too speculative.

Overall, to cover some of these eventualities, our projections over the next five years to 2010 include a 20 per cent upward margin. Post-2010, PPPs were unable to provide projections, given the uncertainties above. However, a funding range was agreed with MMV and the TB Alliance, and a 30 per cent security margin was applied to both DNDi and iOWH projections.

**Figure 18. Projected IRFF spend to 2015 for DNDi, iOWH, MMV and the TB Alliance\***



\* Estimates based on MMV's and the TB Alliance's own projections to 2010, DNDi's business plan projections to 2015 taking account of a two-year lag (as suggested by DNDi), and assumptions about iOWH's forward trajectory. Assumes IRFF spurs 10 per cent increase in PPP activity. Assumes a 15 per cent increase in value of commercial deals with small companies (no more overhead discount). Assumes no change in CRO's terms of payments (already fully commercial) or multinational payments (unchanged in-kind/paid ratio).

To the end of 2004, PPPs combined spent 45 per cent of their total budgets on industry payments (two-thirds of their direct R&D expenditures). In the future, the share of PPP expenditures going to industry, and hence the cost burden on the IRFF, will increase significantly as PPPs expand their portfolios and move successful candidates into clinical trials (see Figure 18). For instance, the TB Alliance anticipates their budget will quintuple between 2005 and 2010, as PA-824 and moxifloxacin<sup>xxxix</sup> enter clinical trials, with over 90 per cent of external payments going to private sector partners. Overall, based on 2005-2010 PPP projections, the share of industry payments of all PPPs is expected to rise to around 70 per cent of their combined total budget. With the IRFF financing 80 per cent of these payments, *our projections cover only about half of PPP financial needs for that period, and should therefore not be used directly as an indication of PPP future funding requirement.*

### Building on the IRFF

The fund could also be linked to, or serve as a hub for, shared or centralised services across all PPPs (as per the policy recommendations below). For instance it could:

- provide platform services to PPPs, for example, shared legal or human resources services, regulatory support services, assistance in negotiating industry deals or intellectual property advice;
- act as an information clearing-house for industry and PPPs, for example, providing information on R&D funding sources or advising companies on targets or compounds of potential interest to PPPs;
- provide a structured platform to co-ordinate industry in-kind inputs to PPPs.

### 3.2.2 Other proposals to strengthen the PPP model

Below are several further ideas to capitalise on opportunities identified by PPPs and companies who work with them. These are conceptual only and would need to be fleshed out before implementation:

- sufficient funding to allow PPPs to offer 'start-up' funding for new small companies with compounds of neglected disease interest and funding to license preclinical compounds from small companies who are uninterested in pursuing them or do not wish to do so alone. These approaches would require larger amounts, in the order of US \$1 to 5 million for licensing and several million/year over several years for 'start-ups', but would be expected to give a substantial boost to small company interest and activity (see FTO proposal below for a new source of funds to support this recommendation);
- consideration of a shared services platform across PPPs to reduce duplication and provide volume discounts. For example, PPPs could consider sharing legal services, human resources services, CRO services etc. (perhaps attached to the IRFF, as noted above);
- substantial reductions on patent filing and maintenance fees relating to neglected disease drugs for developing country use;
- upgrading DC clinical trial sites to meet regulatory standards, including training local trial staff and monitors;
- offer PPPs support in negotiating industry deals, particularly with small companies (for example, support from industry and/or public groups with a successful history of technology transfer negotiations). This could include support on intellectual property issues, including advice on ways to move forward on neglected disease compounds while still protecting core commercial IP.

<sup>xxxix</sup> We note that agreement between the TB Alliance and Bayer HealthCare to develop Moxifloxacin for TB in collaboration has not been signed yet.

## 3.3 POLICIES TO INCREASE SMALL COMPANY COMMERCIAL NEGLECTED DISEASE ACTIVITY

### 3.3.1 Reducing barriers to developing country market entry for small firms

Possible measures include:

- providing small companies with a better quantification of neglected disease markets, including better differentiated information on developing country markets (eg high-, middle- and low-income developing country markets) and their respective public and private sectors (eg by researching and collating existing private sector sales figures, public procurement data etc);
- providing structured assistance in locating suitable developing country manufacturing and distribution partners, thereby reducing the costs of discovery and due-diligence for small firms, for example, through small business assistance schemes/ trade bureaus etc;
- providing centralised information on developing country clinical trial sites, for example, sites that have been or are being upgraded by groups such as the ECDTP (European and Developing Country Clinical Trials Partnership);
- increasing assistance from Western regulatory authorities, including regulatory reliefs, technical regulatory assistance, automatic access to fast track review for neglected disease drugs, and assistance in linking with developing country regulatory authorities;
- providing impetus and public support to the set-up of a double bottom-line equity fund to finance small start-up companies working in the neglected disease area, or with neglected disease-relevant technologies. Double bottom-line funds seek both financial and social returns on their investment (hence 'double' bottom line), accepting sub-market private returns in exchange for achieving desired public good outcomes. In our proposal, the fund would seek public health returns in the form of new drugs being developed for neglected diseases as well as private returns;
- providing a clear implementing mechanism to roll out new neglected disease products in developing countries. The lack of such a mechanism has been repeatedly identified as a major problem. A useful starting point would be to facilitate small company contact and co-ordination with WHO, although more needs to be done. This is an area that needs urgent attention;
- consolidating disseminated developing country markets by providing easier company access to centralised purchasing mechanisms (eg UNICEF, GFATM), and considering expansion of existing central purchase mechanisms where these are insufficient (eg along the lines of IFPMA's proposed Tropical Disease Purchase Fund to supplement the GFATM);
- assisting with developing country market entry, for instance, by facilitating contacts with developing country governments, regulatory/health authorities or central procurement agencies.

One final approach that deserves highlighting is a low-cost initiative to provide a formal neglected disease assistance 'package' for small companies developing neglected disease drugs. This 'package' would overcome many of the problems small companies face in knowing what assistance is available and how to access it. For instance, the package could include and link up many of the above proposals, and should ideally at a minimum include:

- fast track regulatory review for neglected disease drugs;
- automatic regulatory fee reliefs;
- WHO pre-qualification of newly registered neglected disease drugs;
- expedited listing on the WHO Essential Drugs List, which guides developing country treatment choices;
- approval for purchase by international procurement bodies.

This approach has three further advantages, beyond the efficiencies it offers. First, by specifically linking these benefits to developing country relevant compounds, companies would be encouraged to focus on developing country needs (which would trigger these benefits) rather than prioritising Western neglected disease usages. Second, it would bring new drugs to patients in need far more quickly, without the long delays that are currently the norm. And third, it would provide these gains for a very limited public investment of funds. For example, expedited WHO pre-qualification could be achieved by funding a handful of additional staff; while funding a scoping study for a more linked-up system could cost even less.

Finally, the benefits of streamlined market access will flow on to *all* groups developing neglected disease drugs, including PPPs and large companies, and will improve the cost-benefit equation for all incentives aimed at bringing these drugs to patients.

### 3.3.2 Improving health outcomes from small companies working independently

If public donors seek to support and increase unpartnered small company activity in neglected disease drug development – particularly, but not only, if these measures involve provision of public funding – they should strongly consider linking these measures to complementary policies that protect public health outcomes in developing countries. Our work in this area is at too early a stage for us to make formal recommendations, but we note some early ideas as a starting point for further discussion.

The public sector could provide a formal neglected disease scientific network to assist small companies, mirroring the use of industry networks to support publicly-driven R&D activity (eg the use of PPP Scientific Advisory Committees). For instance, this network could provide:

- expert guidance on the suitability of drug leads to DC needs;
- neglected disease expertise;
- expertise in the design of developing country trials (including trials in higher-risk patient groups, such as children and pregnant women);
- expertise in developing country regulatory and implementation issues that could affect the R&D process (eg consideration of WHO treatment protocols).

International purchase funds (new or existing), working in conjunction with WHO, could also provide broad drug ‘specifications’ to guide industry activity (Target Product Profiles), for instance by stipulating that antimalarials need to be oral, have treatment courses of less than three days and fall within certain price guidelines, in order to be considered for purchase. This would provide at least some direction and certainty for small companies hoping for large-scale developing country implementation of their products.

### 3.4 A NEW FUNDRAISING MECHANISM: THE NEGLECTED DISEASE FAST TRACK OPTION<sup>xI</sup>

We propose selling off the right to 'fast track' regulatory review of a commercial drug, with the resulting funds (expected to raise well over US \$100 million/sale) being used to finance neglected disease R&D. For instance, funds could be used to finance the IRFF or, indeed, any of the policy recommendations listed.

#### What is Fast Track?

Fast track is a formal package of regulatory measures that allows drugs to be developed and registered more quickly and therefore reach patients sooner.

Fast track registration is already used by the US to expedite registration of drugs for serious and life-threatening diseases, and for a limited number of commercial diseases, including diabetes and obesity. However, most commercial drugs, including priority drugs (defined by the FDA as drugs offering a clear benefit to US patients over existing therapies),<sup>109</sup> are currently ineligible for fast track. The components of fast track are also available in Europe under new EMEA regulations although, unlike the FDA, the EMEA does not have a formal co-ordinated 'fast track' package.

Fast track uses two main measures to expedite development of new drugs. We emphasise that only the first of these is included in our proposal. They are:

- **regulatory efficiencies:** drug development is expedited by the provision of scientific advice to improve trial design and data collection, by early and continuous interactions with the regulatory agency during drug development, by cutting out time-lags in the regulatory process, and by priority regulatory assessment of the fast tracked drug.
- **shortcuts in the R&D process:** fast track can allow companies to use unproven surrogate endpoints or smaller trials when developing drugs for serious and life-threatening diseases. Such measures are **categorically excluded** from our proposal.

Analysis of data from 1998 to 2003 by the Tufts Center for Drug Development<sup>110</sup> shows that the FDA's fast track programme delivered an average overall reduction in drug development time of three years, including a cut in clinical development time of two to two and a half years, and a one year cut in approval time. These time gains represent very substantial financial benefits for industry.

#### Neglected disease Fast Track Option (FTO)

We propose selling off the right to partially fast track (ie without R&D shortcuts) one additional *commercial* drug per year (including priority drugs) using the resulting funds to finance neglected disease R&D.

Firms would purchase the right to fast track a commercial drug of their choice, for instance, an anti-hypertensive, which would give them the benefit of reaching the market (and profits) before their competitors. A company who acquired an FTO would have access to regulatory fast track during development of the commercial drug of its choice – with the important proviso that this would NOT include access to R&D 'shortcuts', but only to regulatory efficiencies. Nevertheless, even without R&D shortcuts, fast track offers potential time gains to companies of six months to two and a half years, depending on how early in the development process the company applies the FTO to the chosen drug. A two year fast track time gain on a successfully registered blockbuster would deliver additional after-tax returns to the company in the order of US \$0.5 billion to US \$0.75 billion<sup>xLI</sup> (see costings below).

<sup>xI</sup> For full details on this policy proposal, please refer to our detailed paper previously published on the topic: Fast Track Options as a fundraising mechanism to support R&D into Neglected Diseases, Pharmaceutical R&D Policy Project, Wellcome Trust-LSE, Jan 2005.

<sup>xLI</sup> Estimated as present value of future returns at time of purchasing the FTO, assuming the drug is five years away from registration. The use of the FTO for that drug is assumed to lead to a launch two years early.

A proportion of these gains are shared with the public sector through the purchase price paid by the company, which would then be allocated to finance neglected disease R&D. If desired, funds raised by FTOs could be matched one-to-one by governments, thereby doubling funding for neglected disease drug development. The relatively small expenditures associated with FTO (eg cost of any additional regulatory staff needed and cost of managing the sale of FTOs) could also be recouped from the funds raised in order to prevent the FTO drug from displacing resources within the regulatory agency at the expense of other products.

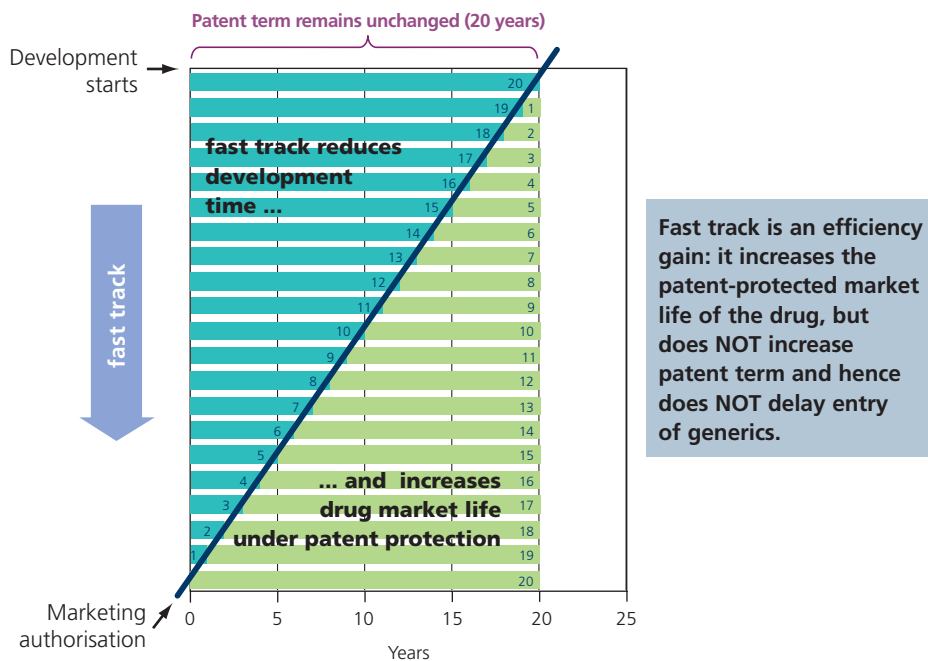
A potentially promising mechanism to optimise the price of FTOs may be the use of a yearly auction of one FTO, although the periodicity could be chosen to ensure enough companies are competing at each auction. This would reduce the risk of government setting the 'wrong' price, since industry – who have the best knowledge of their cost structures and likely market – will bid competitively up to the appropriate level. Auctions have also the benefit of being an accepted mechanism for industry (eg auction of pollution rights) and do not require disclosure of commercial/confidential information on R&D costs. However, auctions can also lead to sub-optimal outcomes, in particular when too few companies compete or collude to drive the price down. Ultimately, what the optimal sale mechanism should be, and who should administer the sale of the FTO to avoid any risk of regulatory capture, should be issues for further exploration at time of implementation.

## Benefits to the public sector

### FTOs raise new funds by harnessing efficiency gains

Fast track delivers more efficient drug development and regulatory review. As a result, drugs spend more of their patent life on the market – and this *without* extending the length of the patent period (see Figure 19 below). The sale of an FTO allows industry and the public sector to harness these efficiency gains and share the resulting value of the FTO between them. This occurs without requiring new public funding, ie the financial benefit stems from harnessing efficiencies.

Figure 19. The fast track mechanism





### Benefits to Western patients

Beyond raising new money for neglected disease R&D, FTOs offer a number of other public health benefits:

- fast track allows greater scrutiny of clinical trials and trial results by the regulatory authorities. (We note that NO fast tracked drugs have been involved in safety recalls);
- intensive scientific advice from regulatory authorities during development should improve the quality of clinical trials from the public perspective;
- there is less risk of 'regulatory capture' since the agency conducting the fast track review does not receive the funds (unlike what happens with the normal regulatory process);
- FTOs do not delay, and in many cases expedite, generic entry (see Figure 20 below);
- FTOs bring new drugs to patients more quickly.

Since the fast tracked drug is available to patients 1 to 2 years earlier, health systems will be required to purchase it earlier. This represents an additional cost to the health system. We note, however, that this additional outlay is for purchase of the *additional health benefit* derived from earlier access to the therapy. While from a theoretical point of view, health budget expenditures would be lower if the fast tracked drug – and indeed all drugs – could be delayed in the regulatory process, this works against the ultimate aim of improving patient access to new treatments.

If desired, FTOs could be restricted to 'priority' drugs (most of which are currently ineligible for fast track), since all would agree that earlier access to these products is beneficial. However, restricting FTOs to these may also restrict their value, thereby reducing the funding available for developing country drug development. This is a trade-off for policy-makers to weigh up.

### FTOs allow more efficient neglected disease funding

FTOs provide a neglected disease cash fund that can be used with maximum flexibility, rather than linking a single large reward to a single product (as would be the case, for example, if the FTO were offered in return for *developing* a new neglected disease drug). For instance, policy-makers could use the funds to finance the proposed IRFF, thereby distributing the funds across the current 40-plus PPP neglected disease drug projects.

### Benefits to industry

An FTO offers numerous benefits to the purchasing company:

- a fast track time gain of two years on a top decile drug represents increased returns of *up to US \$0.75 billion* (see quantification below);
- reductions in R&D costs due to shorter duration and increased efficiency of the drug development process;
- first mover advantage over competitor products;
- increased certainty of outcome (EMEA data shows that provision of scientific advice is strongly correlated with a positive outcome);<sup>111</sup>
- possible public relations benefits for companies, who will be seen as *funding* neglected disease R&D, rather than being seen as 'rich drug companies asking for money'.

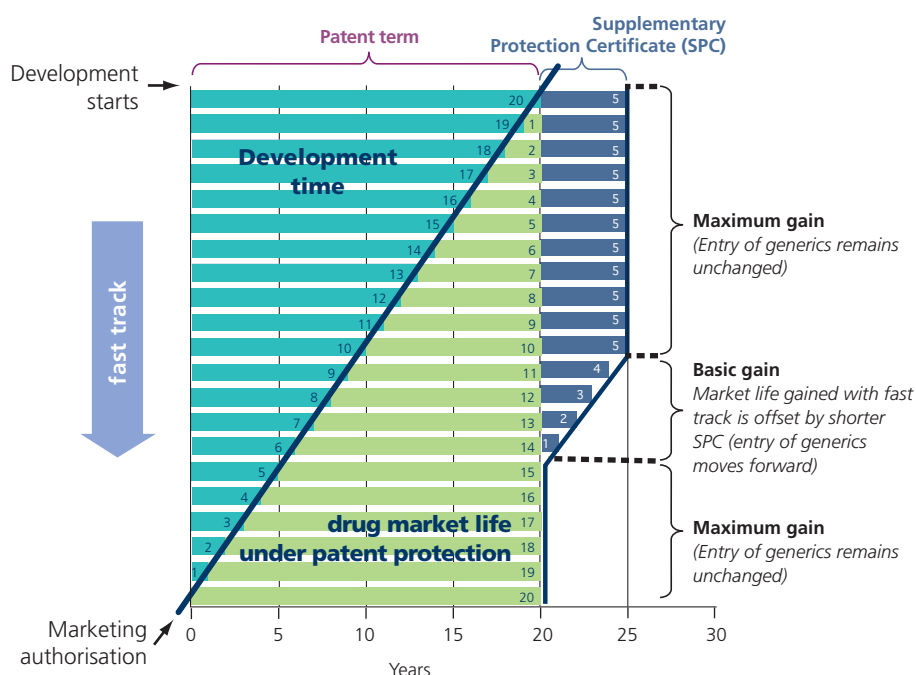
### Quantifying FTOs

The value of an FTO to a company depends on which drug is chosen for fast tracking. In particular, it depends on how long the drug development process is, and whether the drug is already eligible for additional market protections such as Supplementary Protection Certificates (SPCs) in Europe (see Figure 20). SPCs are, in effect, patent extensions of up to five years granted to drugs with a new active ingredient, to compensate for regulatory delays throughout development and approval time.

In some cases, fast track will move the monopoly sales period forward in time but *without* extending market-life; this is when the time gains obtained with fast track are offset by a shorter SPC. In this case, the gains to the company come largely from earlier access to sales revenues ('basic gain').

In other cases, when a drug is not eligible for an SPC or when there is no SPC offset, fast track moves the monopoly sales period forward but the end-date of market protection remains unchanged, thereby giving an *effective* extension of market-life in addition to earlier access to revenues ('maximum gain').

**Figure 20. Effect of Supplementary Protection Certificates on fast track gains and entry of generics (European context)**



Prozac® offers a useful example of the financial benefits of a Fast Track Option (see Table 9), if applied to a blockbuster drug. If Prozac® had been fast tracked during the last half of its development, the company would have reaped US \$761 million in additional after-tax returns (estimated at time of purchase, five years before launch). Even if fast track had been sought only for the last two years of development, the company would still have gained nearly US \$500 million in additional returns.

**Table 9. The impact of an FTO using Prozac® as an example**

	Launch one year early		Launch two years early	
	NPV gain estimated at time of purchase (two years before launch)		NPV gain estimated at time of purchase (five years before launch)	
	On a successful drug	Discounting for risk	On a successful drug	Discounting for risk
<b>Basic gain</b>	+US \$290m	+US \$275m	+US \$447m	+US \$306m
<b>Maximum gain</b>	<b>+US \$495m</b>	+US \$470m	<b>+US \$761m</b>	+US \$521m

- Net Present Value of after-tax returns in 2004 US \$, based on 18 years of Prozac® sales data.
- Includes real cost of capital at 11 per cent, risk discounting based on Tufts phase attrition figures (DiMasi J, Hansen R, Grabowski H (2003). The price of innovation: new estimates of drug development costs; Journal of Health Economics 22: 151-185).
- Model does not include increased sales from first-mover advantage and R&D savings.

Of course, industry is unlikely to pay up to anywhere near this value, since it will have to factor in the risk that, after purchasing and applying the FTO, the chosen drug fails during the R&D process. The estimated risk-discounted value of the FTO is lower, although still substantial, being between US \$0.27 and US \$0.52 billion on a typical first decile drug such as Prozac® (without including the benefits of R&D savings and the first-to-market effect).

As rational actors, industry would be expected to be willing to pay towards this lower target. If the drug failed, they would lose the value of the price paid for the FTO (minus R&D savings from earlier termination). It has been suggested that the fast track right could be transferred from a failed drug to another drug since this would decrease company risk and therefore increase the potential value of a Fast Track Option; however, this would need to be further discussed. On the other hand, if the drug was successful, the company which had developed it could gain up to US \$0.75 billion. On the basis of the lower risk-adjusted value, a yearly sale of one FTO could be expected to raise well over US \$100 million per year for neglected disease R&D.

## 3.5 OTHER APPROACHES

Our research has highlighted a number of other interesting opportunities that we have not had the resources to pursue. These are briefly listed here as areas worthy of further exploration.

### 3.5.1 General

Significant efficiencies would be reaped by providing a formal communication mechanism so that all groups with potentially shared neglected disease interests are aware of relevant opportunities and can link to these without needing to reinvent the wheel each time.

For example, by providing a central clearing-house for information on:

- targets or compounds relevant to neglected disease drug development. Provision of this information would alert companies and PPPs to potential avenues for co-operation or in-kind input (see Section 3.5.3). This could be particularly helpful in the case of shelved large-company compounds and for small Western-focused companies who may have in-house compounds with overlapping neglected disease potential that could be licensed to, or developed with, public/PPP groups;
- neglected disease funding sources, such as PPPs, philanthropic organisations, government grants;
- services/skills offered by different public partners, for example, whether they provide R&D funding, neglected disease expertise, assistance with clinical trials, purchase funds etc.

### 3.5.2 Multinational companies who conduct R&D

A significant reputational prize could be awarded to the multinational that has contributed the most to neglected disease drug development each year. (At least four major companies would now be in the running for this).

### 3.5.3 Multinational companies who are R&D-inactive

A central opportunity is to provide efficient alternatives for multinational companies who do not want to conduct neglected disease R&D themselves but are seeking other ways of contributing. This need could be met through the creation of a structured platform that correlates company inputs with the identified needs of public groups, academics and PPPs who are conducting neglected disease R&D. Ideally, this would include, or be linked to, the communications platform outlined above and/or to the proposed IRFF. For example, large companies could use this platform to offer:

- expertise in medicinal chemistry;
- 'generic' expertise in:
  - regulatory dossier preparation
  - trial data management

- project management
- financial and portfolio planning
- legal advice
- high throughput screening of relevant company compound libraries;
- an avenue for industry staff on sabbatical or retired who are interested in contributing to neglected disease research, for example as Scientific Advisory Committee members to PPPs.

### 3.5.4 Public drug development

As noted, our research does not cover public activity in the pre-drug development stage (ie basic research activity). However, in the course of this work it has also become apparent that this area offers many unexploited opportunities. A few informal thoughts include:

- ensuring that public basic research funding includes minimum funding targets for translational research;
- offering industry medicinal chemistry assistance to academics or public groups working on drug discovery. For instance, academics could be linked to the structured platform for industry inputs noted above and academics seeking drug discovery grants could be encouraged to factor industry input into their proposals (for example, by including contracted medicinal chemistry input or industry link-ups);
- open-source research has been discussed at length by others (for example, Maurer, Rai and Sali).<sup>112</sup> Therefore, we note only briefly that open-source research – particularly research in the early stages, such as X-ray crystallography or the study of structure-activity relationships – deserves urgent attention as a potential route to more rapid and efficient development of neglected disease drug leads.

## 3.6 CREATING A PUBLIC ‘MARKET’?

A further approach under discussion is to stimulate new company activity by creating public ‘markets’, for example, by committing public funds to an advance purchase commitment (APC) for specified future products.

We have not focused on APCs since our research suggests that neglected disease R&D is best conducted through joint public-private collaboration, rather than by industry alone (or public agencies alone), and that APCs are a less cost-effective way to spend public R&D funding than alternative public-private approaches (eg under an APC approach, the public must cover industry’s cost of capital, which the Tufts Institute suggests *doubles* the cost of R&D).

A further consideration was that APCs may not be best suited to multinational pharmaceutical companies who already conduct neglected disease R&D. For firms who are already active, incentives lose their main function of stimulating new activity, and seem likely to change company behaviour in ways that have not been fully examined. For example, APCs may change company neglected disease R&D priorities or, as suggested by BIAG/IFPMA,<sup>113</sup> may primarily incentivise ‘adaptive’ research, as noted previously. Large companies are also encouraged to move from a not-for-profit approach – which is designed to provide drugs to patients at affordable prices – to a for-profit approach requiring substantial public subsidies that may not always be forthcoming in the future. (This design appears to reflect a belief that large companies can only be motivated by profits on neglected disease drugs, a tenet we believe no longer holds true). If companies are seeking APCs as insurance that their products will be used in developing countries, then a simple purchase fund for not-for-profit drugs seems more likely to sustainably deliver this goal, rather than the much larger fund needed to cover for-profit purchase of the same goods.

We also considered the possibility of APCs to stimulate R&D-inactive multinational companies to enter the field; however, these companies were very clear that even large public purchase funds were unlikely to incentivise them to return to neglected disease R&D.

That said, APCs may offer opportunities to increase the activity of small companies, for whom these lower-value public markets can still be attractive. However, before such an approach is pursued, we would want to see more detailed exploration of several points.

One issue would be to amend or adapt the purchase fund to encourage small companies to seek early and regular public input – particularly important in the neglected disease field, where most small Western-based companies have little or no experience. A second issue would be to scale down the size of the reward to match small company needs and expectations – do we need billions, or hundreds of millions? And are we seeking to motivate the least interested or the most interested players? Finally, most small companies are ill suited to conduct large-scale clinical trials, manufacture and distribution in developing countries. In these situations they often need to seek assistance from multinational companies (in commercial areas), or from public groups or developing country partners (in low-profit areas). Small companies could contract-in these skills and pass the subsequent costs on in the final price; however, this would be a difficult learning curve for most. In outlining these issues we do not wish to imply that a purchase fund aimed at small companies should be discarded – it is certainly likely to stimulate significant new small company activity – however, we would like to see more detail before recommending this approach.

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## ANNEXES

### Annexe 1. List of active neglected disease drug R&D projects as of end 2004 (grouped as PPPs and industry projects)

#### Annexe 1A. Neglected disease drug R&D landscape – PPPs (December 2004)

	Compound	PPP	Partners	Indication	Current stage
1	Artemisone	MMV	Bayer HealthCare, Hong Kong Uni	Malaria	Clinical (Phase II)
2	DHF reductase	MMV	BIOTEC (Thailand), LSHTM, Monash Uni	Malaria	Lead identification
3	Peptide deformylase-PDF	MMV	GSK	Malaria	Discovery
4	4(1H)-pyridones	MMV	GSK	Malaria	Preclinical
5	4(1H)-pyridones back-ups	MMV	GSK	Malaria	Lead optimisation
6	Isoquine	MMV	GSK, Liverpool Uni	Malaria	Preclinical
7	FAB 1	MMV	GSK	Malaria	Discovery
8	Falcipains	MMV	GSK, UCSF	Malaria	Lead identification
9	Chlorproguanil dapsone/artesunate (CDA)	MMV	GSK, WHO/TDR, Liverpool Uni	Malaria	Clinical (Phase II)
10	DB-289 Malaria	MMV	Immtech, North Carolina Uni	Malaria	Clinical (Phase I – II)
11	New dicationic molecules	MMV	North Carolina Uni, STI	Malaria	Lead optimisation
12	FAS II	MMV	Texas A&M Uni, Albert Einstein College of Med, Jacobus	Malaria	Lead identification
13	Artemether-lumefantrine (Paediatric Coartem®)	MMV	Novartis	Malaria	Clinical (Phase I)
14	Novel tetracycline	MMV	Paratek	Malaria	Lead identification
15	Synthetic peroxide (Oz)	MMV	Ranbaxy, Nebraska Uni, Monash Uni, STI, Roche	Malaria	Clinical (Phase I)
16	Synthetic peroxide (Oz) Next Generation	MMV	Nebraska Uni, Monash Uni, STI	Malaria	Lead identification
17	Pyronaridine/artesunate	MMV	Uni Iowa, Shin Poong, WHO/TDR	Malaria	Clinical (Phase I)
18	Dihydroartemisinin-piperaquine (Artekin®)	MMV	Sigma Tau, Chongqing Holley, Holleykin Pharma, Oxford Uni	Malaria	Clinical (Phase I-III)
19	GAPDH	MMV	STI	Malaria	Discovery
20	Manzamine A	MMV	Mississippi Uni	Malaria	Lead optimisation
21	8-aminoquinolone	MMV	Mississippi Uni	Malaria	Preclinical
22	Pf-PFT inhibitors	MMV	Washington Uni, Yale Uni	Malaria	Lead optimisation
23	IV Artesunate	MMV	WRAIR	Malaria	Preclinical
24	Gatifloxacin	WHO/TDR	Lupin, EC Consortium, Thammasat University, TBRC (India)	Tuberculosis	Clinical (Phase III)
25	Eflornithine – oral	WHO/TDR	MSF	HAT*	Clinical (Phase III)

Continued

	Compound	PPP	Partners	Indication	Current stage
26	Berenil	WHO/TDR	Unknown	HAT*	Preclinical
27	Posaconazole for Chagas	WHO/TDR	Unknown	Chagas disease	Preclinical
28	Rectal artesunate	WHO/TDR	Unknown	Malaria	Registration/ Phase IV
29	Moxidectin	WHO/TDR	Wyeth	Onchocerciasis	Clinical (Phase II)
30	Isocitrate lyase inhibitors	TB Alliance	GSK	Tuberculosis	Lead identification
31	Enoyl-ACP-reductase inhibitors	TB Alliance	GSK	Tuberculosis	Lead identification
32	Pleuromutilins	TB Alliance	GSK	Tuberculosis	Lead optimisation
33	Focused screening	TB Alliance	GSK	Tuberculosis	Discovery
34	Quinolones	TB Alliance	KRICT, Yonsei Uni	Tuberculosis	Lead identification
35	Macrolides	TB Alliance	Illinois Uni	Tuberculosis	Lead identification
36	Nitroimidazole analogs	TB Alliance	Novartis, NIAID	Tuberculosis	Lead optimisation
37	Nitroimidazole PA-824	TB Alliance	Fully subcontracted to CROs, RTI	Tuberculosis	Preclinical
38	Carboxylates	TB Alliance	Wellesley College	Tuberculosis	Lead identification
39	HTS on whole cell trypanosomes	DNDi	Harvard Uni (ICCB)	HAT*	Discovery
40	Trypanothione reductase inhibitors	DNDi	Harvard Uni (ICCB), Dundee Uni	HAT*	Discovery
41	Protein farnesyl- transferase inhibitors	DNDi	Washington Uni	HAT*	Discovery
42	Paromomycin for VL for Africa	DNDi	Leishmania East Africa Platform (LEAP), WHO/TDR	Visceral leishmaniasis	Clinical (Phase III)
43	Artesunate- mefloquine FDC	DNDi	Far Manguinhos, Mahidol Uni, Universiti Sains (Malaysia), Oxford Uni, MSF, WHO/TDR	Malaria	Clinical (Phase III)
44	Artesunate- amodiaquine FDC	DNDi	Sanofi-Aventis, Centre Nationale de Recherche et de Formation sur le Paludisme (Burkina Faso) Tropival/ Bordeaux 2 Uni (France), Universiti Sains (Malaysia), Oxford Uni, MSF, WHO/TDR	Malaria	Clinical (Phase III)
45	New technology for artemisinin production	iOWH	Amyris Biotechnologies, UCSF Keasling lab	Malaria	Discovery
46	CRA 3316/K777	iOWH	NIH, Celera Genomics, UCSF	Chagas disease	Preclinical
47	Paromomycin for VL for India	iOWH	WHO/TDR, IDA, Indian pharmaceutical manufacturer	Visceral leishmaniasis	Registration

\* Human African Trypanosomiasis

## Annexe 1B. Neglected disease drug R&amp;D landscape – MNCs working alone (December 2004)

	MNC	Compound	Indication	Current Stage
1	Sanofi-Aventis	Thiazolium	Malaria	Lead optimisation
2	Sanofi-Aventis	Choline uptake inhibitors	Malaria	Lead optimisation
3	Sanofi-Aventis	Ferroquine (SSR 97193)	Malaria	Phase I
4	Sanofi-Aventis	Trioxaquine	Malaria	Lead optimisation
5	Sanofi-Aventis	Intrarectal quinine	Malaria	Phase III
6	Novartis	PDF inhibitors	Tuberculosis	Lead optimisation
7	Novartis	NS3 helicase	Dengue**	Discovery
8	Novartis	NS5 polymerase	Dengue**	Discovery
9	Novartis	NS3 protease	Dengue**	Discovery
10	AstraZeneca	DNA synthesis inhibitors	Tuberculosis	Lead identification
11	AstraZeneca	Methyl erythritol pathway inhibitors	Tuberculosis	Lead identification
12	AstraZeneca	Unspecified development project	Tuberculosis	Lead optimisation
13	Pfizer	U 100480	Tuberculosis	Preclinical?
14	Pfizer	Zythromicin+chloroquine	Malaria	Phase III
15	J&J	R207910 (diarylquinolone)	Tuberculosis	Phase I
16	GSK	Sitamaquine (WR6026) oral	Visceral Leishmaniasis	Phase III

\*\* There is no PPP for Dengue

## Annexe 1C. Neglected disease drug R&amp;D landscape – MNCs partnering with PPPs (December 2004)

	MNC	Compound	PPP	Indication	Current Stage
1	GSK	4 (1H) Pyridones	MMV	Malaria	Preclinical
2	GSK	CDA	MMV	Malaria	Clinical (Phase II)
3	GSK	Falcipains	MMV	Malaria	Lead identification
4	GSK	FAB 1	MMV	Malaria	Discovery
5	GSK	Isoquine	MMV	Malaria	Preclinical
6	GSK	Peptide deformylase-PDF	MMV	Malaria	Discovery
7	GSK	Pyridone back-up (GW844520)	MMV	Malaria	Lead identification
8	GSK	Enoyl-ACP-reductase (inh A) inhibitors	TB Alliance	Tuberculosis	Lead identification
9	GSK	Pleuromutilins	TB Alliance	Tuberculosis	Lead optimisation
10	GSK	Isocitrate lyase	TB Alliance	Tuberculosis	Lead identification
11	GSK	Focused screening	TB Alliance	Tuberculosis	Discovery
12	Novartis	Artemether-lumefantrine (paediatric Coartem®)	MMV	Malaria	Clinical (Phase I)
13	Novartis	Back up compounds for PA 824	TB Alliance	Tuberculosis	Lead optimisation
14	Bayer HealthCare	Artemisone	MMV	Malaria	Clinical (Phase II)
15	Sanofi-Aventis	Artesunate-amodiaquine FDC	DNDi	Malaria	Clinical (Phase III)
16	Wyeth	Moxidectin	WHO/TDR	Onchocerciasis	Clinical (Phase II)



**Annexe 1D. List of projects that were not included in our assessment and reasons for exclusion (December 2004)**

Institution and Project name	Reason for exclusion
<b>TB Alliance</b>	
Rifalazil Analogs	Agreement not reached between the parties by end 2004
KRQ-100018	Folded into the Quinolozinones project in 2004. Thus, counted under this project
<b>DNDi</b>	
Nifurtimox-eflornithine for HAT	Protocol study (not an R&D project)
Combination therapy for VL	Protocol study (not an R&D project)
Target validation of kinetoplastid DHRF-thymidylate synthase	Pre-drug development (target validation)
<b>iOWH</b>	
SP303	Still under negotiation (Dec 2004)
<b>GSK</b>	
Tafenoquine	In development for prophylaxis (not treatment) of malaria in non-immune adults

For reasons already stated in the report, we did not include in our analysis work by small companies or developing country firms working independently from PPPs. We recognise however that these players also make a significant contribution to the global R&D effort for neglected diseases, and more research needs to be done on quantifying their input. For instance, examples in the TB area include:

- Sequella (small firm, US) – Diamine SQ-109
- FASgen (small firm, US) – Synthase inhibitor FAS20013
- TaiGen (China/Taiwan) with Procter and Gamble – Non fluorinated quinolone
- Lupin (India) – Pyrrole LL-3858

## Annexe 2. List of health experts contacted

Health expert	Area of expertise	Institution
Professor Mike Barrett	Trypanosomiasis/ Leishmaniasis	University of Glasgow (UK)
Dr Bernard Bouteille	Trypanosomiasis	Institut d'Epidémiologie Neurologique et de Neurologie Tropicale (France)
Professor Paulo Marcos Coehlo	Schistosomiasis	Oswaldo Cruz Foundation (Brazil)
Dr Jose Rodrigues Coura	Trypanosomiasis	Instituto Oswaldo Cruz-Fiocruz (Brazil)
Dr Simon Croft	Leishmaniasis	London School of Hygiene and Tropical Medicine (UK)
Professor Win Gutteridge	Malaria	London School of Hygiene and Tropical Medicine (UK)
Dr Amina Jindani	Tuberculosis	St George's Hospital Medical School (UK)
Dr Charles Peloquin	Tuberculosis	National Jewish Medical and Research Center (US)
Professor David Molyneux	Filariasis	Liverpool School of Tropical Medicine (UK)
Dr Koert Ritmeijer	Leishmaniasis	Médecins Sans Frontières (Holland)
Dr Bertie Squire	Tuberculosis	Liverpool School of Tropical Medicine (UK)
Dr Shyam Sundar	Leishmaniasis	Institute of Medical Sciences, Banaras Hindu University, Varanasi (India)
Professor Steve Ward	Malaria	Liverpool School of Tropical Medicine (UK)
Dr Christopher Whitty	Schistosomiasis, Onchocerciasis	London School of Hygiene and Tropical Medicine (UK)
Professor Peter Winstanley	Malaria	The University of Liverpool (UK)

### Annexe 3. Sample template for assessment of neglected disease drugs\*

MALARIA				
	0	1	2	Score
<b>Efficacy</b>				<b>/8</b>
<b>Cure rates</b> <b>Double score</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/4</b>
	<60% cure rate	60-90% cure rate	>90% cure rate	
Calculated as parasitological cure at end of 28 day follow-up				
<b>Susceptibility to resistance</b> <b>Double score</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/4</b>
	High	Medium	Low	
As perceived from preclinical experimental data from in vivo and in vitro studies, characteristics of the drug including mechanism of action				
<b>Safety</b>				<b>/4</b>
<b>Side effects</b> <b>Double score</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/4</b>
	Severe adverse events have been commonly described	Severe side effects seen only rarely	Mild side effects	
<b>Appropriateness to Developing Country (DC) use/Disease: Malaria</b>				<b>/12</b>
<b>Formulation</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/2</b>
	Intravenous	Intramuscular	Oral	
<b>Formulation suitable for the treatment of the most relevant group (children)</b> <b>Double score</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/4</b>
	Not for children	Children 1-10 years	Children <1 year	
<b>Suitable for routine use in pregnant and nursing women</b>	<input type="checkbox"/>	–	<input type="checkbox"/>	<b>/2</b>
	No		Yes	
<b>Treatment course</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>/2</b>
	Length of treatment longer than three days	Length of treatment is three days	Length of treatment shorter than three days	
<b>Technical storage issues (eg cold chain)</b>	<input type="checkbox"/>	–	<input type="checkbox"/>	<b>/2</b>
	Present		Absent	
<b>Access</b>	<b>0</b>	<b>3</b>	<b>6</b>	<b>/6</b>
<b>Price</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	DC price more than US \$5 per treatment	DC price between US \$2 and US \$5 per treatment	DC price less than US \$2 per treatment	
<b>Total</b>				<b>/30</b>

\* Templates used to assess drugs developed for the other neglected diseases were tailored to each disease (leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis and tuberculosis).

#### Annexe 4. PRPP list of drugs developed for the treatment of neglected diseases (1975 to December 2004)

Drug name trade®	Drug name – generic	Marketing approval	Developed by
1 Vansil	Oxamniquine	1975	Pfizer
2 Rochagan	Benznidazole	1981	Roche
3 Zentel, Albenza	Albendazole	1981	GSK
4 Praziquantel	Praziquantel	1982	Bayer HealthCare- WHO/TDR
5 Lariam	Mefloquine	1984	Roche
6 Mectizan	Ivermectin	1987	Merck-WHO/TDR
7 Halfan	Halofantrine	1988	GSK
8 Rifadin	Rifampin IV	1989	Sanofi-Aventis
9 Ornidyl	Eflornithine IV	1990	Sanofi-Aventis- WHO/TDR
10 Mycobutin	Rifabutin	1992	Pfizer
11 Paser	Aminosalicylic acid	1994	Jacobus
12 Malarone	Atovaquone/proguanil	1996	GSK
13 Arsumax	Artesunate	1996	Sanofi-Aventis
14 Paluther	Artemether IM formulation	1996	Sanofi-Aventis- WHO/TDR
15 AmBisome	Amphotericin B liposomal	1997	Gilead/Fujisawa US
16 Priftin	Rifapentine	1998	Sanofi-Aventis
17 Coartem	Artemether/lumefantrine	1999	Novartis
18 Artemotil	B- Arteether	2000	Artecef-WHO/TDR
19 Impavido	Miltefosine	2002	Zentaris-WHO/TDR
20 Lapdap	Chlorproguanil/dapsone	2003	GSK-WHO/TDR
21 Coartem (paediatric label extension)	Artemether/lumefantrine	2004	Novartis-WHO/TDR

Discrepancies with other published lists	Reason for excluding the drug
<b>Pecoul et al (1999)*</b>	
Pentamidine isethionate	Used and/or registered for the ND indication before 1975: – First used in the 1950s for the treatment of HAT, – Approved in 1984 only for P carinii infection in the US
Nifurtimox	Used and/or registered for the ND indication before 1975: – First registered in Latin America in 1974
<b>Trouiller et al (2002)**</b>	
Pentamidine isethionate	See above
Pyrazinamide	Used and/or registered for the ND indication before 1975: – First registered in the United States in 1971
Nifurtimox	See above

Other neglected disease orphan drugs registered since 1975, and reasons for exclusion	
Discrepancies with other published lists	Reason for excluding the drug
Clofazimine (Lamprene®)	Used and/or registered for the ND indication before 1975: – First registered in Europe for the treatment of leprosy in 1969 – Re-registered in the US in 1986
Thalidomide	Used and/or registered for the ND indication before 1975: – Although approved in 1998 for erythema nodosum leprosum or type II lepra reactions (related to leprosy) by the FDA, the use of thalidomide for this indication had been established since the mid-1960s. Also, the drug had been recommended by the World Health Organization as effective in this disorder since the mid 1980s
Aminosidine (paromomycin)	Marketing approval for visceral leishmaniasis not granted yet: – First marketed in 1959 for cutaneous leishmaniasis, then received orphan designation in the US in 1994 for the treatment of visceral leishmaniasis
Allopurinol	Marketing approval not granted yet: – Orphan designation in 1985 for the treatment of leishmaniasis and Chagas disease

\* Pecoul B, Chirac P, Trouiller P, Pinel J (1999) Access to essential drugs in poor countries: a lost battle? JAMA 281: 361-67.

\*\* Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R and Ford N (2002) Drug development for neglected diseases: a deficient market and a public health policy failure. The Lancet. 359(9324):2188-94.

## Annexe 5: Pharmaceutical R&D Policy Project team members and contributors



### Dr Mary Moran, Director

MBBS (Bachelor of Medicine, Bachelor of Surgery); Grad Dip FAT (Foreign Affairs and Trade)

Dr Mary Moran is a medical doctor with 13 years experience in Emergency Medicine. A degree in international relations and politics then led her into a diplomatic career with the Australian Department of Foreign Affairs & Trade, including a posting to London where she focused on international trade and climate change negotiations. Before setting up the Pharmaceutical R&D Policy Project, Mary worked for three years with Médecins Sans Frontières, initially as Director of the Access to Essential Medicines Campaign in Australia, and subsequently as a Europe-based advocate on a range of issues relating to access to medicines for neglected patients.



### Anne-Laure Ropars

BSc, MSc (Mech Eng); MA in Political Economy and International Relations

Anne-Laure Ropars trained as a mechanical engineer and worked with John Crane (US) for three years. After completing a Masters degree in Political Economy and International Relations at the University of Chicago in 2000, she worked for a number of years as a consultant, specialising in European and developing country health systems and policies. Her clients included the EU-based pharmaceutical industry, philanthropic organisations (Rockefeller Foundation, Gates Foundation) and government bodies (DFID, USAID). Anne-Laure's project experience spans drug procurement policy in sub-Saharan Africa, competitive strategies to ensure affordability of essential medicines in Ghana, to drug reimbursement policies in European countries.



### Dr Javier Guzman

MBBS (Bachelor of Medicine, Bachelor of Surgery); MSc in Health Policy, Planning and Financing (LSHTM – LSE)

Dr Javier Guzman trained as a medical doctor and worked in the planning and implementation of primary health care projects in the Colombian countryside for several years. Javier moved to the UK in 2002, where he worked as a Post Graduate Clinical Fellow in Paediatrics at the Royal London Hospital. In 2004, he obtained his MSc in Health Policy, Planning and Financing from the LSE and the London School of Hygiene and Tropical Medicine. Previous work also includes early detection and treatment programmes of endemic infectious diseases such as Tuberculosis and Chagas disease.



### Dr Jose Diaz

MBBS (Bachelor of Medicine, Bachelor of Surgery); MSc in Social Policy and Planning in Developing Countries (LSE)

Dr Jose Diaz is a medical doctor with two years experience in the planning, implementation and on-site monitoring of malaria programmes and other parasitic diseases in areas of armed conflict. After coming to the UK, Jose worked as a Post Graduate Clinical Fellow in Internal Medicine at the Mayday Hospital in Croydon before being selected as a Chevening scholar to pursue his MSc in Social Policy and Planning in Developing Countries at the LSE. Jose wrote his dissertation on the importance of the role of government in the fight against the HIV/AIDS epidemic for which he obtained a merit degree in December 2004.



**Christopher Garrison**

MA, LL.M

Christopher Garrison is an independent legal advisor focusing principally on the area of international intellectual property law. Christopher took his first degree in Physics at the University of Oxford, followed by a Masters degree in International and Comparative Law at the University of London. Following consultancy in biophysics for Amersham International plc, he qualified in private practice as a European Patent Attorney in 1995 and subsequently practised in-house with British Telecommunications plc from 1995 to 2001. Since 2001 he has been consulting on the intellectual property dimensions of access to, and R&D for, new medicines, vaccines and diagnostics for a number of organisations including Médecins Sans Frontières, the World Health Organisation and latterly the PRPP.

**Contributors**



**Dr Barrie Rooney**

BSc, PhD (Microbiology)

Dr Barrie Rooney trained as a microbiologist. After working for a number of years in the pharmaceutical industry, Barrie set up the Biotechnology company ExCyte specialising in characterising new drug targets emerging from the human genome project. Since the merger of ExCyte with another Contract Research Organisation, Barrie has worked on a range of projects including a drug trial for Sleeping Sickness in Congo-Brazzaville with Médecins Sans Frontières. Barrie is also known for the extensive research she carried out on the efficacy of recombinant biomolecules used as therapeutics while a lecturer at the University of Kent in Canterbury.



**Premal Pajwani**

BCom, MBA

Premal Pajwani has an MBA from the University of Cincinnati and a BCom from the University of Bombay. Premal is an independent research analyst focused on the pharmaceutical sector – a field he has been covering for 14 years. From 1991-2000, Premal worked as an analyst for various financial institutions in New York including Schroder, Dresdner, JPMorgan, Sanford Bernstein, and Value Line. Following his posting from 2000-2004 as the head of JPMorgan's European pharmaceuticals team in London, Premal consulted with the PRPP, focusing on analysing the changes in the pharmaceutical sector. He currently works as a research analyst in the Pharmaceutical and Healthcare team at Eden Financial Ltd in London.

**Ratna Singh**

BSc (Microbiology), MBA

Ratna Singh has over 15 years of US and UK experience as a Management Consultant and entrepreneur. Having served a variety of blue chip clients in all aspects of business strategy, she formed a 'start-up' technology company in Silicon Valley and worked with Fortune 50 retailers. She was also one of five founding executives in the US of an e-venture formed by HP, Safeway (US) and AT&T. Following this, Ratna was Entrepreneur/Executive-in-Residence at McKinsey & Company, San Francisco. Ratna is currently working with a large private equity fund investigating healthcare buy-out targets in continental Europe. Ratna consulted with the PRPP, focusing on interviewing small pharmaceutical and biotechnology firms and analysing trends in this sector.

## REFERENCES

- 1 Pecoul B, Chirac P, Trouiller P, Pinel J (1999). Access to essential drugs in poor countries: a lost battle? *JAMA*. 281: 361-67.
- 2 Commission for Africa (2005). Final report: 'Our common interest'. March 2005. Available at [www.commissionforafrica.org/english/report/thereport/english/11-03-05\\_cr\\_report.pdf](http://www.commissionforafrica.org/english/report/thereport/english/11-03-05_cr_report.pdf)
- 3 CMR (2002). International Pharmaceutical R&D Expenditure and Sales 2001: Pharmaceutical Investment and Output Survey 2001: Data Report I.
- 4 Milne C et al (2004). Meeting the Challenge of the Evolving R&D Paradigm: What Role for CROs? *The Journal of Pharma and Biopharma Contract Services*. March/April 2004.
- 5 Garnier J P (2005). Chairman of GSK, Contribution at Conference of the British Chancellor of the Exchequer, February 4, 2005.
- 6 Pharmaceutical Shareholders Group (2004). The Public Health Crisis in Emerging Markets. September 2004. Available at [www.cis.co.uk/images/pdf/P56\\_REPORT\\_SEPT04.pdf](http://www.cis.co.uk/images/pdf/P56_REPORT_SEPT04.pdf)
- 7 Tufts CSDD (Center for the Study of Drug Development) (2002). Impact Report, Vol 4, Number 3, May/June 2002.
- 8 Milne C, Kaitin K, Ronchi E (2001). Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty. CMH Working paper series. Paper No WG2:9. Dec 2001.
- 9 Torrent-Farnell J (2005). Five years with the orphan drug directive in the EU, achievements by the COMP. Presented at the International conference on rare diseases and orphan drugs. Stockholm, Feb 2005.
- 10 IFPMA (2001). Working paper on Priority Infectious diseases requiring additional R&D, WHO-IFPMA Working Group, July 2001.
- 11 IFPMA (2005). Submissions by BIAG and IFPMA to the WHO Commission on Intellectual Property Rights and Innovation in Health, May 2005.
- 12 IFPMA (2005). Industry proposals to increase research and development for 'neglected diseases', IFPMA, May 2005.
- 13 IFPMA (2005). Industry proposals to increase research and development for 'neglected diseases', Submissions by BIAG and IFPMA to the WHO, May 2005.
- 14 Guerin P et al (2002). Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *The Lancet Infectious Diseases*. Vol 2 August 2002.
- 15 Sundar S, Rai M (2002). Advances in the treatment of leishmaniasis. *Curr Opin Infect Dis* 15:593-598.
- 16 Amyris (2005). Mission statement. Available at [www.amyrisbiotech.com/mission.htm](http://www.amyrisbiotech.com/mission.htm). Accessed on the 14 May 2005.
- 17 Cambridge Major Laboratories (2005). Available at [www.c-mlabs.com](http://www.c-mlabs.com). Accessed on the 14 May 2005.
- 18 El Feki S (2005). Prescription for change. *The Economist*. 18 June 2005.
- 19 OECD (2005). Main economic indicators. June 2005.
- 20 Maurer S (2005). The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research. Presented at the WHO meeting of The Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) June 2005.



- 21 FDA (1998). Rifapentine Anti-Viral Advisory Committee Hearing. Center for Drug Evaluation and Research. Gaithersburg, Maryland, Food and Drug Administration (FDA – US).
- 22 NGC (2005). Prevention and treatment of tuberculosis among patients with infected human immunodeficiency virus: Principles of therapy and revised recommendations. National Guidelines Clearinghouse – U.S. Department of Health and Human Services.
- 23 FDA (1998). Rifapentine Anti-Viral Advisory Committee Hearing. 5 May 1998.
- 24 WHO (2005). Report: Global tuberculosis control – surveillance, planning, financing.
- 25 Pearson R, Jeronimo S, Lareau S (1999). US food and drug administration approval of liposomal amphotericin B for the treatment of visceral leishmaniasis: a model for orphan Drug development. *Curr Infect Dis Reports* 1:415-416.
- 26 Meyerhoff A (1999). U.S food and drug administration approval of Ambisome (Liposomal Amphotericin B) for treatment of visceral Leishmaniasis. *Curr Opin Infect Dis* 28:42-48.
- 27 Sundar S, Afrawal G, Rai M, et al (2001). Treatment of Indian visceral leishmaniasis with single or daily infusion of low dose Liposomal amphotericin B: randomized trial. *BMJ*. 323:419-422.
- 28 WHO (2002). Review of application for inclusion of a drug in the WHO essential list. Fixed Combination of Artemether and Lumefantrine. Coartem® CDS/RBM, 18 March 2002.
- 29 Sanofi-Aventis (2004). Drug prices obtained from pharmaceutical company.
- 30 GSK (2004). Drug prices obtained from pharmaceutical company.
- 31 WHO (2001). The use of antimalarial drugs, Report of an informal consultation. Geneva, 13-17 November 2000, WHO/CDS/RBM/2001.33.
- 32 WHO (2001). The use of antimalarial drugs, Report of an informal consultation. Geneva, 13-17 November 2000, WHO/CDS/RBM/2001.33.
- 33 Schuster BG, Canfield CJ (1989). Preclinical studies with halofantrine. In: Halofantrine in the treatment of multidrug resistant malaria. *Parasitology Today*. Suppl:65-79.
- 34 Basco LK, Le Bras J (1992). In vitro activity of halofantrine and its relationship to other standard antimalarial drugs against African isolates and clones of *Plasmodium falciparum*. *American Journal of Tropical Medicine and Hygiene*. 47(4):521-527.
- 35 Peters W et al (1987). The chemotherapy of rodent malaria. XLII. Halofantrine and halofantrine resistance. *Annals of Tropical Medicine and Parasitology*. 81(5):639-646.
- 36 Monlun E et al (1995). Cardiac complications of halofantrine: a prospective study of 20 patients. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 89(4):430-433.
- 37 Nosten F et al (1993). Cardiac effects of antimalarial treatment with halofantrine. *The Lancet*. 341:1054-1056.
- 38 Castot A, Rapoport P, Le Coz P (1993). Prolonged QT interval with halofantrine [letter; comment]. *The Lancet*. 341:1541.
- 39 Baird J K (2005). Effectiveness of Antimalarial drugs. *New England Journal of Medicine*. 352: 1565-77.
- 40 Phillips-Howard P A, ter Kuile FO (1995). CNS adverse events associated with antimalarial agents. Fact or fiction? *Drug Safety*. 12(6):370-383.
- 41 Weinke T et al (1991). Neuropsychiatric side effects after the use of mefloquine. *American Journal of Tropical Medicine and Hygiene*. 45(1):86-91.
- 42 Fontanet A L et al (1993). High prevalence of mefloquine-resistant *falciparum* malaria in eastern Thailand. *Bulletin of the World Health Organization*. 71:377-383.
- 43 Thaithong S, Beale G H, Chutmongkonkul M (1988). Variability in drug susceptibility amongst clones and isolates of *Plasmodium falciparum*. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 82(1):33-36.

- 44 CDC (2003). Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America June 20, 2003 / 52(RR11);1-77.
- 45 CDC (2003). Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America June 20, 2003 / 52(RR11);1-77.
- 46 IMS (2004). Lifecycle database September 2004.
- 47 Squire, Bertie (2005). Liverpool School of Tropical Medicine. Personal Communication. January 2005.
- 48 O'Donnell M M, Souza Carvalho S, Gadelha A J, Morgado M G, Galhardo M C, Lourenco M C, Rolla V C (2002). Poor response to tuberculosis treatment with regimens without rifampicin in immunosuppressed AIDS patients. *Braz J Infect Dis.* Dec;6(6):272-5. Epub 2003 Nov 3.
- 49 Squire, Bertie (2005). Liverpool School of Tropical Medicine. Personal Communication. January 2005.
- 50 Jindani, Amina (2005). St George's Hospital Medical School. Personal Communication. December 2004.
- 51 WHO (2004). Procurement manual for the DOTS-plus projects approved by the green light committee. Available at [www.who.int/gtb/policyrd/DOTSplus.com](http://www.who.int/gtb/policyrd/DOTSplus.com)
- 52 WHO (1997). Guidelines for the management of drug-resistant tuberculosis. Available at [www.who.int/docstore/gtb/publications/gmdrt/PDF/tb96\\_210.pdf](http://www.who.int/docstore/gtb/publications/gmdrt/PDF/tb96_210.pdf)
- 53 WHO-IDA (2003). Procurement manual for the DOTS-plus projects approved by the Green Light Committee.
- 54 Peloquin, Charles (2005). Infectious Disease. National Jewish Medical and Research Center Personal communication. February 2005.
- 55 FDA (2000). Priftin®. Approved Labeling. October 2000.
- 56 Mitchison D A (1998). Development of rifapentine: the way ahead. *Int.J.Tuberc.Lung Dis.* 2:612-615.
- 57 FDA (1998). Rifapentine Anti-Viral Advisory Committee Hearing. May 5, 1998.
- 58 NGC (2005). Prevention and treatment of tuberculosis among patients with infected human immunodeficiency virus: Principles of therapy and revised recommendations. National Guidelines Clearinghouse.2005.
- 59 Center for Drug Evaluation and Research (1998). Approval package for Priftin®.
- 60 WHO (2002). Strategic Framework to to decrease the burden of HIV/TB.
- 61 IMS (2004). Lifecycle database September 2004.
- 62 Pham P and Bartlett J G ( 2005). John Hopkins Antibiotic Guide.
- 63 INCOSUR (2003). Xlla. Reunion Intergubernamental INCOSUR/Chagas, Santiago, Chile. Marzo 2003.
- 64 Pinto J C (2003). Tratamiento etiológico de la enfermedad de Chagas: una síntesis. Xlla Reunion Intergubernamental INCOSUR/Chagas. Santiago, Chile, March 2003.
- 65 Andrade A L, Zicker F, de Oliveira R M, Almeida Silva S, Luquetti A, Travassos L R, Almeida I C, De Andrade S S, de Andrade J G, Martelli C M (1996). Randomized trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *The Lancet* 348: 1407-1413.
- 66 Rodriguez Coura J (2005). Brazilian experience on the treatment of Chagas diseases with benznidazole. (unpublished).
- 67 Rodriguez Coura J, Castro S L (2002). A critical review on chagas disease chemotherapy. *Mem Inst Oswaldo Cruz, Rio de Janeiro.* Vol 97 (1): 3-24.

- 68 Kilpatrick M E, Farid Z, Bassily S, El-Masry N A, Trabolsi B, Watten R H (1981). Treatment of schistosomiasis mansoni with oxamniquine-five years' experience. *Am J Trop Med Hyg* 30 (6):1219-1222.
- 69 Cioli D, Pica-Mattocchia L, Archer S (1995). Antischistosomal drugs: past, present ... and future? *Pharmacol Ther.*68(1):35-85.
- 70 Katz N (1980). Current results in the clinical therapy of Schistosomiasis mansoni. *Rev. Inst.Med Trop. Sao Paulo* 22 (Suppl. 4): 8-17.
- 71 Médecins Sans Frontières (2004). Access News. July 2004 No.10.
- 72 Seaman J, Boer C, Wilkinson R, et al (1995). Liposomal amphotericin B (AmBisome) in the treatment of complicated kala-azar under field conditions. *Clin Infect Dis* 21: 188-193.
- 73 Laguna F, Lopez-Velez R, Pulido, et al (1999). Treatment of visceral leishmaniasis in HIV-infected patients: treatment with high dose Liposomal amphotericin B. *AIDS*; 12:1063-69.
- 74 Molyneux D (2004). Liverpool School of Tropical Medicine. Personal communication. November 2004.
- 75 Shibuya K, Bernard C et al (2005). Global burden of onchocerciasis in the year (2000) Summary of methods and data sources. *Epidemiology and Burden for Disease (EBD)*, Global Programme on Evidence for Health Policy (GPE), World Health Organization. Draft 17 June 2005.
- 76 Chitsulo L, Loverde P, Engels D (2004). Schistosomiasis. *Nat Rev Microbiol.* Jan; 2(1):12-3
- 77 WHO (2005). Useful information on Schistosomiasis and STH. Page 2. Available at [www.who.int/wormcontrol/statistics/useful\\_info/en/index1.html](http://www.who.int/wormcontrol/statistics/useful_info/en/index1.html). Accessed on the 14 June 2005.
- 78 WHO (2005). Letter from WHO Department of Control, Prevention and Eradication to Zentaris, 5 January 2005.
- 79 Barrett M, Croft S (2004). Personal communication. November 2004
- 80 WHO/TDR (2003). Lapdap: a new antimalarial for Africa. *TDR news.* No 70. Sep 2003.
- 81 WHO (2002). Review of application for inclusion of a drug in the WHO Essential Drugs List: Artemotil and alpha/beta arteether. *CDS/RBM*, 18 March 2002, p2.
- 82 WHO (2002). Review of application for inclusion of a drug in the WHO Essential Drugs List. *CDS/RBM*, 18 March 2002.
- 83 WHO (2002). 12th Expert Committee on the Selection and Use of Essential Medicines Meeting, 15-19 April 2002.
- 84 WHO (2002). Review of application for inclusion of a drug in the WHO Essential Drugs List. *CDS/RBM*, 18 March 2002.
- 85 Sanofi-Aventis (2004). Drug prices in Kenya and Nigeria obtained from pharmaceutical company.
- 86 WHO (2001). WHO and Novartis join forces to combat drug resistant malaria. Press release. Geneva.
- 87 Pinock S (2003). Drug company to offer new malaria drug cheaply in Africa. *BMJ.* 327(7411):360.
- 88 Winstanley P (2001). Chlorproguanil-dapsone (LAPDAP) for uncomplicated falciparum malaria. *Tropical Medicine and International Health.* Vol 6 No II. PP 952-954.
- 89 WHO/TDR (2003). Lapdap: a new antimalarial for Africa. *TDR news.* No 70. Sep 2003.
- 90 Comentary to Allouche A et al (2004). Chlorproguanil-dapsone for malaria in Africa. *The Lancet.* Vol 363: 1838-9.
- 91 Winstanley P (2001). Chlorproguanil-dapsone (LAPDAP) for uncomplicated falciparum malaria. *Tropical Medicine and International Health.* Vol 6 No II. PP 952-954.

- 92 WHO (2005). Useful information on Schistosomiasis. Statistics & Facts. Available at [www.who.int/wormcontrol/statistics/useful\\_info/en/index1.html](http://www.who.int/wormcontrol/statistics/useful_info/en/index1.html)
- 93 Sundar S (2002). Oral Miltefosine for Indian Visceral Leishmaniasis. *N Engl J M ed*, Vol. 347, No. 22.
- 94 Sundar S (2005). Availability of Miltefosine for the treatment of kala-azar in India. *Bulletin of the World Health Organization*. 83 (5): 394-395.
- 95 Guerin P J, Oliaro P, Sundar S, Boelaert M, Croft S L, Desjeux P, Wasunna M K and Bryceson ADM (2002). Visceral Leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *The Lancet of Infectious Diseases* 2: 494-501.
- 96 Croft S.L (2004). London School of Hygiene and Tropical medicine. Personal Communication.
- 97 Sundar (2001). Drug resistance in Indian visceral leishmaniasis. *Tropical Medicine and International Health*. Vol 6 No II: 849-854.
- 98 WHO (2005). Letter to Prof Jurgen Engel signed by Dr Jorge Alvar. Department of Control, Prevention and Eradication (CPE).
- 99 Burchmore R, Barret M et al (2002). Chemotherapy of HAT. *Current Pharmaceutical Design*. 2002. 8, 257.
- 100 Burri C, Brun R (2002). Eflornithine for the treatment of HAT. *Parasitol Res*. 2003 Jun. p 49-52.
- 101 Burnham G (1998). Onchocerciasis. *The Lancet*. 351:1341-46.
- 102 Taylor H R, Greene B M (1989). The status of ivermectin in the treatment of human onchocerciasis. *Am J Trop Med Hyg*. Oct; 41(4):460-6.
- 103 FIIM-IFPMA (2004). 'Research and development for neglected diseases, lessons learned and remaining challenges'.
- 104 DiMasi J, Hansen R, Grabowski H (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics*. 22 p.160.
- 105 MMV (2003). MMV Business Plan 2003-2007, Appendix 9.2 'Estimated phase durations'.
- 106 Di Masi J A, Hansen R W, Grabowski H G (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics* 22: 151-185.
- 107 Hodgson J (2004). The \$ 802 million fallacy, *Nat Biotechnol*. Sep;22(9):1076.
- 108 DFID (2005). Highlights of the G8 communiqué on Africa. Available at [www.number-10.gov.uk/output/Page7880.asp](http://www.number-10.gov.uk/output/Page7880.asp). Accessed on the 13 July 2005.
- 109 FDA (2005). Priority Review Policy, MAPP 6020.3, Center For Drug Evaluation And Research, Food and Drug Administration.
- 110 Tufts CSDD (Center for the Study of Drug Development) (2003). Volume 5, Number 6, FDA's Fast Track Initiative Cut Total Drug Development Time by 3 Years, November/December 2003.
- 111 EMEA (2003). Annual Report, p.22.
- 112 Maurer S M, Rai A, Sali A (2004). Finding cures for tropical diseases: is open source an answer? *PLoS Medicine*. Dec;1 (3):e56.
- 113 BIAG (2005), Article 9: Proposals to increase R&D for Neglected Diseases. Biomedical Industry Advisory Group submission to the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH).



