

**PUBLIC PRIVATE
PARTNERSHIPS FOR
RESEARCH AND
DEVELOPMENT:
MEDICINES AND
VACCINES FOR
DISEASES OF POVERTY**

Hannah Kettler and Adrian Towse



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KETTLER/TOWSE



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Hannah Kettler and Adrian Towse



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CONTENTS

4	Glossary	6
	Executive Summary	7
	1 Introduction	12
	2 Defining the R&D Problem and the Potential Role for PPPs	16
	2.1 R&D and neglected diseases	16
	2.2 Product development public private partnerships defined	20
	2.3 Linking R&D and access	23
	2.4 The commercial model versus the PPP model versus the public-only model	24
	3 Understanding Pharmaceutical R&D Processes	29
	3.1 Changing boundaries in the conduct of R&D	29
	3.2 Changing relationship between the public and private sectors	31
	3.2.1 The move to greater private sector collaboration with universities	34
	3.2.2 University patenting	36
	3.2.3 Implications of changing public/private relationships for PPPs	37
	3.3 The impact of the rise of biotech/genomics companies on the R&D market	38
	3.4 The trend to subcontracting	42
	3.5 How important are the competences of large pharmaceutical companies?	43
	3.6 What will the R&D market place look like?	45
	3.7 What are the implications for R&D costs and time to market?	46
	3.8 What are the implications for PPPs?	47
	4 Public Private Partnerships Assessed	49
	4.1 Five key aspects of performance	49
	4.2 The management arrangements	49
	4.2.1 Management team	50
	4.2.2 Board of directors	51
	4.2.3 Scientific advisory committee	52
	4.2.4 Stakeholder board	52
	4.3 The effectiveness of the governance arrangements	53

CONTENTS

4.3.1	The debate about PPPs and governance	53
4.3.2	The governance challenge for PPPs	55
4.4	The organisation of the PPP R&D process	57
4.4.1	Opportunities and obstacles to virtual R&D development	58
4.4.2	'Social' venture capitalists	59
4.4.3	Managing the portfolio	62
4.4.4	Moving through the R&D process	63
4.5	Funding and cost savings	64
4.5.1	Funding	64
4.5.2	Cost saving by using the 'global health' and 'industry' networks	65
4.6	Deals and intellectual property	67
4.7	An assessment of performance to date	69
5	Conclusions	76
	References	84
	List of interviewees	89
	Appendices	
Appendix 1	Medicines for Malaria Venture (MMV)	90
Appendix 2	International AIDS Vaccine Initiative (IAVI)	94
Appendix 3	Global Alliance for TB Drug Development (GATB)	101
Appendix 4	Malaria Vaccine Initiative (MVI)	106
Appendix 5	The Medicine R&D Process from the Lab to the Patient	111
Appendix 6	PPP boards of directors	116
Appendix 7	PPP stakeholders and donors	120
Appendix 8	MMV's pipeline	124
Appendix 9	IAVI's pipeline	126
Appendix 10	MVI's pipeline	130
Appendix 11	GATB's pipeline	133

GLOSSARY OF ABBREVIATIONS

6	DALY	Disability Adjusted Life Year
	GAVI	Global Alliance for Vaccine and Immunisation
	GAT8	Global Alliance for TB Drug Development
	IAVI	International AIDS Vaccine Initiative
	IFPMA	International Federation of Pharmaceutical Manufacturers Associations
	IP	Intellectual Property
	IPPPH	Institute on Public Private Partnerships for Health
	IPR	Intellectual Property Rights
	LDC	Less Developed Country
	MMV	Medicines for Malaria
	MSF	Médecins Sans Frontières
	MVI	Malaria Vaccine Initiative
	NGO	Non Governmental Organisation
	PATH	Programme for Appropriate Technology in Health
	PPP	Public Private Partnerships
	RBM	Roll Back Malaria
	R&D	Research and Development
	TB	Tuberculosis
	TDR	Tropical Diseases Research
	WHO	World Health Organisation

EXECUTIVE SUMMARY

Objectives

Improving the health and life expectancy of the populations of the less developed countries of the world requires both better access to medicines and research and development (R&D) of new drugs, vaccines and diagnostics. Achieving the latter is a critical part of a package of steps needed to treat and ultimately eradicate the infectious diseases prevalent predominately in the poorest regions of the developing world.

This book focuses on the role of public-private partnerships (PPPs) as an innovative approach to the discovery, development and provision of drugs and vaccines for less developed countries. It considers the challenges such PPPs will face if they are to be successful, using four case studies. These are:

- the Medicines for Malaria Venture (MMV);
- the International AIDS Vaccine Initiative (IAVI);
- the Malaria Vaccine Initiative (MVI); and
- the Global Alliance for TB Drug Development (GATB).

All four focus on the top three infectious disease killers in the developing world: malaria, TB, and HIV/AIDS.

The problem that PPPs are intended to address

Studies have been conducted to identify the reasons for the lack of new private R&D into these infectious diseases. Assuming similar cost and scientific hurdles for neglected diseases as for researched diseases, a key factor that discourages private investment is the poor expected return. Despite high need – a large number of patients – these patients are unable to pay for medicines and thus effective demand is very low.

The public policy challenge is to construct incentives to engage public and private researchers so that they invest in R&D to develop products for the neglected diseases of the poor. Three alternative models for generating this R&D have been put forward:

- the first model – the commercial approach – strives to make neglected diseases more attractive for private companies making investments through policies aimed at reducing costs ('push') and enhancing the value of markets ('pull');
- the second model, public-private partnerships (PPPs), seeks to address R&D gaps in specific diseases. A not-for-profit PPP entity

- 8** manages a budget and supports a pipeline of projects undertaken in academic and industry settings. The PPP organisation is responsible for ensuring that products meeting quality, safety, efficacy, and effectiveness standards move through the R&D process and ultimately reach the patients in need;
- a third model is for a public-only needs-based model to channel essential new R&D into the most neglected diseases. Médecins Sans Frontières (MSF) has conducted exploratory work into the establishment of a not-for-profit research facility to address the most neglected of the neglected diseases such as leishmaniasis, Chagas disease and schistosomiasis.

The subject of this book is the second model, PPPs. With PPPs, the unit overseeing the partnerships would direct and control the projects but private industry, often in partnership with public researchers, especially in the early discovery phases, would conduct the R&D. The public objective motivates the process, though the goal is to establish win-win contracts and arrangements whereby companies can expect some return on their investments while at the same time contributing to a vital public health process. PPPs put money into the system, jump-start projects, and get others to join. The PPPs' success will depend on their ability to raise funds, to manage public and private R&D collaborators to discover and develop effective medicines, and to attract commercial partners at key points in the process.

Understanding pharmaceutical R&D processes

The traditional model of the pharmaceutical R&D process assumes a rigid separation between 'basic research' carried out in universities and 'applied research' carried out in vertically integrated major pharmaceutical companies. However, this has been changed fundamentally by three major trends:

- greater collaboration between the public and private sectors in 'basic research' to understand disease mechanisms;
- the rise in the 1980s of specialist private sector 'biotech' companies, often spun off from universities, followed in the 1990s by the rise of companies specialising in 'genomic' technologies;

- a trend to subcontracting of some R&D, sales and manufacturing activities by the major pharmaceutical companies.

As a result, pharmaceutical R&D now has the characteristics of a dynamic network. Major pharmaceutical companies typically play a central, though not exclusive, role in coordinating discovery activities and in bringing products through development to market. There may be short term, project specific, contracting between biotech suppliers and large pharmaceutical company customers. In some cases this dynamic model may be more 'virtual'. Biotech companies may develop products on their own, perhaps through collaborations or alliances with each other; sometimes using major pharmaceutical companies, sometimes not; and relying on research organisations and contract sales organisations to do work that major pharmaceutical companies have done in the past.

The implications for the PPPs are that a virtual approach to undertaking R&D is contractually feasible and gives each PPP maximum flexibility in identifying public and private partners. However, large pharmaceutical companies continue to dominate commercialisation activities. Whilst there is evidence from the US 'orphan drug' sector that smaller biotech companies are able to bring products to market, there are particular characteristics of these orphan drug markets that are not applicable to PPP target markets in less developed countries. This means that PPPs have to contract with large companies at some point, or else develop substantial in-house co-ordination competencies if they are to manage all stages from discovery to market on a virtual basis.

Assessing the PPP model

The four PPPs considered in this book face challenges in five key areas:

- organising their R&D collaborations to take advantage of the dynamic R&D market place;
- managing their activities effectively to deliver products to patients;
- 'governance', i.e. being accountable to stakeholders, including those less developed countries (LDCs) where the diseases they are seeking to tackle are prevalent. An important aspect of this is performance measurement – setting realistic targets and tracking progress;

- putting in place an intellectual property strategy that will help achieve the social purposes of the PPP;
- developing a viable financial model both for the PPP and for achieving access in LDC markets to new drugs and vaccines.

Our overall assessment of the four PPPs is that substantial progress has been made on the first four of the five challenges. However, the ability of PPPs to solve the fifth challenge – creating a viable financial model that addresses the R&D funding gap – is less clear.

The key challenge – funding PPP discovery, development, and commercialisation

The four PPPs have successfully raised about a half a billion dollars as of mid 2002, about half of their targeted R&D funds for 2005. The Gates Foundation and the governments of northern Europe have made the largest contributions so far. All have successfully initiated research programmes. MMV is working to balance its portfolio with the selection of some development projects. IAVI's support has helped vaccine products to move into Phase I trials. MVI has successfully done a deal with GlaxoSmithKline to jointly complete Phase III trials on that company's malaria vaccine.

All four PPPs depend on major pharmaceutical company and/or biotech company involvement in both R&D and commercialisation activities to succeed. MMV assumes that the malaria market is large enough to make investments from Phase III onwards profitable. The other PPPs assume that additional incentives, such as a global purchase fund, are needed. Though companies' total R&D costs will be significantly reduced by their operating with a PPP (because the PPP is making up-front investment in discovery and because other costs, such as clinical trial costs, may be lower), these investments will still not be profitable in the late development and commercialisation stages without a market for the final product. So a combination of PPPs with push and pull incentives is needed for success.

The amount of money that PPPs need to bring products to market will depend on two factors. The first is the extent to which there are push and pull incentives. These could be of three sorts:

- the pull incentive provided by the existence of markets in richer

countries, or in the richer parts of middle or low income countries, where commercial prices (i.e. including a mark up to recover R&D costs) can be charged. Segmenting markets in poorer countries to identify the size of any payer market is work that the PPPs can assist with;

- the use of a global purchasing fund as a pull incentive, to purchase products for the target LDC populations, either at manufacturing plus distribution cost or including some mark-up to recover R&D cost;
- push incentives, such as R&D tax credits for companies undertaking work on products for LDC diseases.

The second factor affecting PPPs' funding requirements is the extent to which the PPPs are able to reduce the estimated average cost of \$800m needed to bring a new product to market. In principle this could be done by co-ordinating research efforts, reducing attrition rates and time taken during the R&D process, reducing the cost of clinical trials and the cost of capital, and by obtaining fast track regulatory approval.

Conclusion

In conclusion, PPPs are a valuable part of a total solution to the challenge of getting new drugs, vaccines and diagnostics to meet the health needs of the populations of less developed countries. But Governments must not become complacent by assuming that the problem has been solved with the allocation of relatively small amounts of money to the PPPs. The international aid organisations and non-governmental organisations, likewise, must not only support PPPs but also continue to lobby for other push/pull incentives, particularly for a global purchase fund, such as the Global Fund for Aids, TB, and Malaria, to operate in these disease areas. PPPs are a viable model to tackle the killer diseases of poverty, but they cannot succeed in isolation.

1 INTRODUCTION

12

Developing new drugs, vaccines and diagnostics is a critical part of a package of steps needed to treat and ultimately eradicate the diseases of poverty – malaria, tuberculosis, HIV, and other infectious diseases prevalent predominately in the poorest regions of the developing world. The inability of the majority of patients to pay for new products in diseases of poverty, combined with the fact that the private for-profit pharmaceutical industry possess the majority of skills, know-how, and resources required to turn research ideas into marketable products means that the need for new products continues to significantly outpace the supply.

An on-going debate exists around the question of how best to reduce this gap between supply and need. Three solutions have been offered:

- the commercial model where a package of incentives is introduced to reward private companies for taking the risk and investing in diseases of poverty;
- the public-private partnership (PPP) model where a new entity is created to identify, fund, and manage partnerships between the best of public and private resources to advance new product development); and
- the public-only model where a new entity is established to conduct publicly funded basic and applied research.

All three can draw on examples and experiments from elsewhere but are relatively untested as solutions to the R&D gap in diseases of poverty. The Report of the Commission on Macroeconomics and Health (2001) ‘Macroeconomics and Health: Investing in Health for Economic Development’ for the World Health Organisation argues that more money should be invested in PPPs, as well as in publicly funded basic research, and measures to make diseases of poverty more commercially attractive to the mainstream pharmaceutical industry. This report, originally written as a commissioned paper for Working Group 2 of the Commission on Macroeconomics and Health¹,

¹ The Commission on Macroeconomics and Health, in consultation with partners, established six Working Groups to assess critically and, where appropriate, to extend the evidence base pertaining to issues it addressed. Working Group 2 addressed public policies to stimulate development of vaccines and drugs for neglected diseases of major

provides an analysis of the PPP model. Relying on information from four different cases, it seeks to identify the key issues product development PPPs in general must address as well as the indicators upon which their performance should and will be evaluated.

It is too early to use the PPPs' accomplishments to date as a means to evaluate the prospects for the PPPs model to succeed in its primary goal of bringing new, effective and affordable products to patients. Of the four cases, the oldest entity is six years old and the newest less than two. From the standpoint of new product development, a process that takes 12-15 years on average, the work has only just begun. None the less, details about the make up of the management teams, their success to date of raising funds, their perceived credibility with pharmaceutical companies, and their ability to negotiate deals, do provide important raw data upon which to identify areas of strength and weakness, anticipate problems and propose possible solutions.

The four cases are: Medicines for Malaria Venture (MMV), International Aids Vaccine Initiative (IAVI), Malaria Vaccine Initiative (MVI), and the Global Alliance for TB Drug Development (GATB). All four focus on the top three infectious disease killers in the developing world – malaria, TB, and HIV/AIDs. A comparison gives us an opportunity to consider three different organisational strategies to use public money to harness the contributions of private industry. MMV provides grants and brokers partnerships to boost existing projects, based either in academic laboratories or companies. GATB licenses in compounds and seeks to manage their development by way of a 'virtual' network of companies and organisations. MVI and IAVI make investments in new technologies, often in small companies, to advance that technology's application for malaria and HIV vaccines respectively.

We draw on different sources of literature to evaluate and analyse these new product development PPPs. Certainly the idea of pooling private and public resources to pursue 'public services' is not new – and others have commented on examples from health care and

importance in low- and middle-income countries. The work also dealt with how the resulting products could be brought into widespread use. For a complete list of the commissioned papers see <http://www.cmhealth.org/wg2.htm>.

elsewhere looking at strengths, weaknesses, successes and failures. The Global Health Forum's Initiative on Public Private Partnerships for Health (IPPPH) (www.ippph.org) has established a PPP database and seeks to find models of best practice and facilitate learning between existing and new PPPs. The IPPPH has two primary aims: to monitor, analyse and facilitate the exchange of information on PPPs; and to foster the development of effective new partnerships.

In this report we approach the subject from a different angle, analysing how PPPs work as alternative models of R&D focussing in particular on:

- what composition of actors are needed to further the R&D agenda in neglected diseases;
- what their respective roles should be;
- what can be done to engage the pharmaceutical industry in this effort;
- how the intellectual property system can be used to advance the research agenda; and
- how much money is needed and where this money come from.

Chapter 2 provides context for our discussions. We first review the R&D problem – why private industry tends to neglect investments in diseases of poverty. Second we present and briefly compare the three solution models, including PPPs, under consideration by interested parties.

We address the organisation of public and private actors to address R&D in 'non-neglected' diseases in Chapter 3 and draw out the implications for PPPs. As a point of departure for this analysis, the piece focuses on the private sector's recent experience with the R&D process and its increasing reliance on a complex network of collaborations among major pharmaceutical companies, biotech firms, and service providers. We use 'private' models of R&D as a starting point and consider how these PPPs compare, what can be learned from private to PPP (and, potentially, the other way round).

Each PPP is organised slightly differently. In Chapter 4 we present details of each case – how is it organised and managed, what the accountability and governance structures are, who the funders are, what kind of collaborations they seek to establish, and how they plan

1 INTRODUCTION

to move the products through to market. We consider how intellectual property contracts are being used as a strategic tool to try and incentivise private industry to participate while at the same time to ensure that the goals of affordability and access are also met.

We present a preliminary assessment of how well the four cases are doing to date in Chapter 5 concluding by examining the overall financial viability of the PPP model.

2 DEFINING THE R&D PROBLEM AND THE POTENTIAL ROLE FOR PPPS

2.1 R&D and neglected diseases

Developing new drugs, vaccines and diagnostics is a critical part of a package of steps needed to treat and ultimately eradicate the infectious diseases prevalent predominately among the poorest segments of the peoples of the developing world.

The primary actors involved in the research and development (R&D) of pharmaceuticals and vaccines are public research institutions in developed countries and private pharmaceutical companies in developed countries (49% and 44% of the total R&D expenditure in 1992 respectively). The public researchers contribute primarily to the early discovery stages; private companies invest in all stages but dominate the processes of development, production and commercialisation. As we discuss in greater detail in Chapter 3, that division of labour has changed somewhat over the past 20 years though the relative comparative advantages have probably stayed the same².

There is much evidence that diseases such as malaria, TB, leishmaniasis and others are a low priority. Surveys of company pipelines and alliance databases support the much cited figures of only 5-10 per cent of health R&D going to less developed country diseases, with 1 per cent of new products between 1975-1997 developed specifically for tropical diseases (summarised in Kettler, 2000). For example, according to the PhRMA website (PhRMA, 2001), there are two products in its member company's pipelines for malaria, one for leishmaniasis, one for African Trypanosomiasis and three for TB. According to the ReCap.com alliance website there are currently 12 alliances in research that might relate to malaria, 17 to TB and 6 to HIV vaccines.

2 This in part reflects the 'public good' characteristics of basic R&D. By this we mean that, once acquired through basic research effort, knowledge about a disease process can be used by scientists and other researchers at the same time at no additional cost. It cannot be patented and will not therefore normally be undertaken by the private sector unless it is integral to the discovery of a product that is patentable.

Private companies are not the only group neglecting these diseases. It is difficult to assign some of the National Institute of Health (NIH) research investments to specific diseases. We set out an analysis in Table 2.1. It shows that in 2001 only 0.21 per cent of the total \$41,887 million going to Research Initiatives and Programs of Interest went to TB and 0.52 per cent to AIDS vaccines compared with 10 per cent to cancer, the disease with the largest NIH budget. The findings of a joint WHO/IFPMA group's thorough investigation of the public and private sectors' involvement in neglected diseases correspond with this other empirical evidence (WHO/IFPMA, 2001).

Studies have been conducted to identify the reasons for the lack of new private R&D into these diseases (Kettler, 2000, Kremer, 2001, PIU, 2001). Assuming, at least to start with, similar cost structures and scientific hurdles for neglected diseases as for the developed country diseases, a key factor that discourages private investment is the poor expected return. Despite high need – a large number of patients – these patients are unable to pay for medicines and thus expected demand is very low.

In 1998, for example, the peoples of Africa made up 10 per cent of the world's population but suffered 25 per cent of the disease burden, measured in terms of disease adjusted life years (DALYs). Sixty eight per cent of those DALYs lost were linked to communicable diseases (World Bank, 1999 and WHO, 1999).

Taking the case of malaria, MMV has estimated that 'a new drug that sold well in endemic countries, with a low margin, and achieved an aggressive 30 per cent market share in the travellers market, at a 50 per cent margin, would result at most in \$50m annual returns, not enough for pharmaceutical companies seeking annual sales potential of \$250m-\$300m for a new drug' (MMV Draft Business Plan, 2000).

The public policy challenge is to construct incentives to engage public and private researchers to invest more aggressively in R&D for new products in the neglected diseases of the poor. The policy discussions focus primarily on three alternative solutions.

- (i) The first model – the commercial approach – strives to make neglected diseases more attractive relative to other, non-neglected, diseases for private companies making investments. Cost reducing

Table 2.1 **National Institutes of Health**
Research initiatives and programmes of interest

Research/ Disease Areas	Amount invested		
	FY 1999 (\$m) Actual	FY 2000 (\$m) Estimate	FY 2001 (\$m) Estimate
Aging	\$1,215.0	\$1,382.5	\$1,454.5
AIDS(Budget Authority)	1,792.70	2,006.20	2,111.20
Vaccines AIDS	182.3	238.7	267.5
Behavioral R and SSR	1,569.00	1,776.70	1,866.90
Cancer Research	3,377.30	3,856.60	4,076.80
Cardiovascular Research	1,327.10	1,500.30	1,588.20
Clinical Research	4,920.50	5,560.40	5,808.60
Decade of the Brain (Brain Disorders)	3,122.20	3,567.40	3,760.40
Mental Health	1,089.30	1,244.80	1,313.40
Pediatric Research	1,902.80	2,154.50	2,264.00
Prevention	3,876.90	4,420.00	4,664.30
Tuberculosis Research	72.8	81.7	86.8
Vaccine Development	364.1	434.7	474.8
Vaccine Related	405.8	483.2	526.1
Women's Health Research	2,320.10	2,610.70	2,759.00
Other	7477.0	8599.70	9132.10
Total	34,832.60	39,679.40	41,887.10
Share of Total			
Cancer % of Total	9.70	9.72	9.73
TB % of Total	0.21	0.21	0.21
All Vaccine Development % of Total	1.05	1.10	1.13
AIDS % of Total	5.15	5.06	5.04
AIDS vaccine % of AIDS total	10.17	11.90	12.67
AIDS vaccine % of Total	0.52	0.60	0.64

Source: <http://grants.nih.gov/grants/oe.htm>

(‘push’) and market enhancing (‘pull’) policies would improve the expected profitability of investments in neglected diseases so attracting more private sector R&D into these diseases. R&D tax

credits and grants, fast track approval, and social venture funds are examples of push incentives. Examples of pull incentives include guaranteed purchase funds, a tax credit on sales of neglected disease products and roaming patent exclusivity, where a company can extend the patent of another product in exchange for delivering a product in a neglected disease to patients at affordable prices.

- (ii) In the second model, public-private partnerships (PPPs) are set up to address R&D gaps in specific diseases. A not-for-profit entity manages a budget and supports a pipeline of projects underway in academic and industry settings. The organisation is responsible for ensuring that products meeting quality, safety, efficacy, and effectiveness standards move through the R&D process and ultimately reach the patients in need.
- (iii) A third model proposed is of a public-only needs based (as opposed to market driven) model³. Its advocates see it as the only way to channel essential new R&D into the very neglected diseases⁴. Médecins Sans Frontière (MSF) has conducted exploratory work into the establishment of a not-for-profit research facility to address the neglected of the neglected diseases such as leishmaniasis, Chagas disease, and schistosomiasis. In their view, 'with a shift to needs-driven research and development, the needs of millions in the developing world will continue to be ignored. Such an initiative would remove the process of researching and developing life-saving drugs from a market-drive logic' (Trouiller et al., 2002, p2193).

We consider the relative merits of these three models in section 2.4.

3 The purely public model has, until now received less attention, in part because of the lack of resources and expertise within the public sector to conduct specific stages in the R&D process. The expectation is that it would be at a minimum very costly to duplicate the resource and know-how that sits in industry for a narrow set of diseases within a public research group. A recent audit of the US' investments in public vaccine manufacturing facilities also point to insufficient incentives, at least in these cases, to complete the applied work (compared with a favourable environment for exploratory research) (DOD, 2000).

4 These can be defined as diseases for which there is no high or middle income country incidence and which it may therefore be much more difficult to attract private sector input via either the commercial push/pull model or the PPP model.

2.2 Product development Public Private Partnerships defined

Work by Buse and Walt (2000a,b,c) and the research group the Initiative for Public Private Partnerships for Health (IPPPH) have both identified a more general trend towards the greater use of PPPs to address global health issues. These PPPs bring together members of civil society, (a category which includes academia, non governmental organisations (NGOs), philanthropists and other not-for-profits), the public sector (government agencies and inter-government agencies) and the for-profit sector (pharmaceutical companies, biotech companies and other commercial companies from relevant industries). IPPPH's database thus far includes almost 80 'collaborative relationships' covering a broad range of goals, arrangements, legal status, management structures and strategies. We focus on PPPs conducting product development. Those identified by the IPPPH as product development PPPs are listed in Table 2.2.

As noted, we focus on four product development PPPs; the Medicines for Malaria Venture (MMV), the International Aids Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI) and The Global Alliance for TB Drug Development (GATB). All four are disease specific. MMV and GATB focus on drugs and MVI and IAVI on vaccine development. They have a common aim to use public funds to engage private and public researchers in the development of new drugs and vaccines in the specific diseases. The ultimate goal is to ensure that these products reach the patients who need them, particularly poor patients in the developing world. They are first and foremost involved with the R&D problem, that is, with the task of funding and supporting a set of research projects. Table 2.3 provides some comparative statistics on our four cases. Descriptive details about our four cases are presented in Appendices 1 – 4.

Except for MVI (which is a programme within the non-profit organisation PATH (Programme for Appropriate Technology in Health)), our cases are newly established not-for-profit legal entities, distinct from project management teams that sit within an inter-government agency such as Stop TB and Roll Back Malaria (RBM) at

Table 2.2 **Partnerships for control of disease – product development**

Alliance for Microbicide Development
CICCCR – Consortium for Industrial Collaboration in Contraceptive Research
Concept Foundation
Cooperative Research Center for Vaccine Technology (Brisbane, Australia)
Development of Autodestruct Syringes
Development of Vaccine Vial Monitors
Development of Dengue Vaccines (Aventis Pasteur/Mahidol University)
Epidemic Meningitis Vaccines for Africa (EVA) (Proposed)
European Malaria Vaccine Initiative
Global Alliance for TB Drug Development
Hookworm Vaccine Initiative (at Sabin Foundation)
Institute for One World Health
International AIDS Vaccine Initiative
Japanese Pharmaceutical, Ministry of Health, WHO Malaria Drug Partnership (JPMW)
LAPDAP antimalarial drug combination (DFID/WHO/SKB)
Leishmaniasis Vaccine Initiative [at Infectious Diseases Research Institute (IDRI), Seattle]
Malaria Vaccine Initiative
Medicines for Malaria Venture
MSF Access to Essential Medicines Project
Norplant
Sequella Global Tuberculosis Foundation
Sexually Transmitted Infections Diagnostic Group
TB Diagnostics Initiative (WHO)
Trypanosomiasis/Leishmaniasis Consortium (UNC)
Various national mechanisms to promote industry involvement in ‘neglected’ product development (e.g., Challenge/Partnership Awards, CREADAs, Small Business Awards in USA)

Source: Widdus, et al, 2001, IPPPH Website (www.ippph.org)

Table 2.3 Summary of Public Private Partnerships

	Disease/tool focus	Year founded	Location	Key founders	CEO	Staff size	Projects in pipeline
MMV	malaria drugs	Nov-99	Geneva	WHO, IFPMA	Chris Henschel	10	12 (2*)
MVI	malaria vaccines	Jun-99	Rockville, MD (Washington DC area)	PATH, Gates Foundation	Regina** Rabinovich	10	9
IAVI	HIV vaccines	1996	New York	Rockefeller Foundation	Seth Berkley	75 ++	7
GATB	TB drugs	Oct-00	New York, Brussels, Cape Town	Rockefeller Foundation, WHO	Maria Freite	3 +	1

* under negotiation, 7/02

** moving to the Gates Foundation, November 2002

+ only senior staff listed

++ including consultants

Sources: www.mmv.org, www.iavi.org, www.tballiance.org, www.maliavaccines.org

the WHO. The legal status of the PPP has important implications for the governance and accountability structures as well as the sources of funding and the strategic flexibility and boundaries. 'A legal identity separate from those of collaborating (inter) governmental agencies or for-profit organisations is useful to these ventures to enable them – under their own rules – to accept and disburse funds, to hire staff, and to determine policies and initiate activities focused exclusively on their chosen missions' (Widdus et al., 2001, p6).

In general, these PPPs face a common challenge of motivating groups with widely diverse values, mandates and cultures to focus on a shared global public health goal. Their ultimate success will, at least in part, depend on whether common goals can override uncommon values. 'The effectiveness of HealthPPPs depends on clearly specified, realistic and shared goals; clearly delineated and agreed roles and responsibilities; distinct benefits for all parties; the perception of transparency; active maintenance of the partnership; equality of participation; and the meeting of agreed obligations' (Buse and Walt, 2000b, p704).

We can identify several key elements in a definition of a product development PPP:

- a 'not for profit' organisation using public, NGO, and (in some cases) private funds;
- legal and operational independence from the collaborating bodies;
- inclusion in its governance structures of representatives of the not-for-profit elements of civil society and of the public sector and the for-profit sector;
- a method of working (in both contractual and non-contractual relationships) that seeks to combine the skills of the three groups to achieve the public health goal of developing new products for LDCs.

2.3 Linking R&D and access

With the health systems of the targeted population in mind, manufacturing complexity and costs, dose regimes, and storage requirements are among the factors that PPPs consider in the project selection process and follow-on funding decisions. The funding contracts all involve an exchange of money to support R&D projects

24

for a pledge by participating companies to make any final products stemming from their collaboration available to patients in the developing world. This might be achieved by the company delivering the product itself or through the transfer of the product to other companies or organisations for delivery and distribution.

Above and beyond the activities conducted within the PPP organisations, all the PPPs are essential contributors and players in a wider network of partner organisations that are involved directly in tackling the access problem. MVI, for example, is a programme within the Gates Foundation established PATH. PATH and other Gates funded and managed programmes such as Global Alliance for Vaccine and Immunisation (GAVI) have teams who focus on vaccine purchase, distribution and delivery. MVI will work with these organisations to explore commercialisation, procurement and delivery strategies that will maximise availability in the countries most affected by malaria. IAVI has a specific department, 'Policy and Public Sector Support' that is responsible for working with partner organisations to design and build up distribution and delivery infrastructure for AIDS vaccines as well as actively lobby governments and inter-governmental organisations to establish vaccine purchase funds. In addition, IAVI, seeks to advance the development of AIDS vaccine research above and beyond its own R&D pipeline.

By contrast, MMV has a relatively narrow mandate and plans to use its funding, selection, and contracting decisions to develop products that should be integrated into other, outside efforts of organisations such as WHO Roll Back Malaria to improve the access problem. An estimated 10-15% of funds are dedicated explicitly to access problems (Interview, Robert Ridley). GATB sees itself as working within a developed network of tuberculosis organisations and initiatives to which it will contribute new drugs. Table 2.4 summarizes the four organisations' mission statements.

2.4 The commercial model versus the PPP model versus the public-only model

It is not the purpose of this paper to provide a detailed comparison of the

Table 2.4 PPP Mission statements

<p>MMV – The mission of MMV is to bring public, private and philanthropic partners together to fund and manage the discovery, development and registration of new medicines for the treatment and prevention of malaria in disease-endemic countries.</p>
<p>IAVI – IAVI’s mission is: ‘to ensure the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world’.</p>
<p>GATB – The organisation’s mission is to accelerate the discovery and/or development of cost-effective, affordable new TB drugs that will:</p> <ul style="list-style-type: none"> ● shorten or simplify TB treatment. Shortening the current 6 month treatment to 2 to 3 months and/or significantly reducing the total number of doses to be taken under the supervision of a health care worker could improve patient compliance (and hence treatment efficacy) as well as potentially reducing the total cost per treatment episode; ● provide a more effective treatment of multi-drug-resistant TB; and ● improve the treatment of latent TB infection.
<p>MVI – The mission of the MVI at PATH (Programme for Appropriate Technology in Health) is: ‘to accelerate the development of promising malaria vaccine candidates and ensure their availability and accessibility for the developing world.’ Within this, MVI’s prime focus is on children.</p>

three models (commercial, PPP, public-only) set out in section 2.1. However, some observations are helpful before we discuss in Chapter 3 the changing nature of the R&D process.

All three models rely on upfront public investment. This is a departure from the conventional way in which the public sector has traditionally bought medicines and vaccines. In the traditional model, the public sector has bought in a ‘spot market’ or used short term contracts. It only buys the drugs it wants, i.e. where the R&D has been successful in producing a product of medical benefit available at an acceptable price. The risk, in this case, is carried entirely by the private company. By contrast, in all three models, this risk is shared. The amount and form of upfront public investment does differ between the three models:

- in the commercial approach public investment is required to

incentivise the private sector through ‘push’ measures such as R&D tax credits. However, the bulk of funding will only begin when purchasing the drugs for LDCs if the R&D is successful;

- in the PPP model a more substantial upfront public investment is required to get R&D projects to the stage at which an agreement can be made with a company to take on the product and commercialise it on terms that include access for LDCs;
- in the public-only model the public sector must find all upfront investment. However, supporters of this approach have argued that this approach will be lower cost in the long run as it avoids paying market rates for the use of private sector organisations.

The models also differ as to who directs and conducts the R&D projects and what the key objectives are driving the projects forward. In the first (incentives) case, private industry orchestrates and controls the projects, seeking out partners in the same way they do for other diseases, driven, as in other cases, primarily by the expectation of return on investment. There is no guarantee however that many (or any) companies will initiate research in these areas. It may be that only those with competencies in-house already are likely to respond, or companies with products sitting on the shelf, or when discovery research identifies potential uses for these specific diseases.

In the second (PPP) case, the unit overseeing the partnerships would direct and control the projects but private industry, often in partnership with public researchers, especially in the early discovery phases, would conduct the R&D. The public objective motivates the process, though the goal is to establish win-win contracts and arrangements whereby companies can expect some return on their investments while at the same contributing to a vital public health process. PPPs put money into the system, jump-start projects, and potentially incentivise others to join. However, the PPPs success will depend in part on their ability to manage public and private R&D collaborators. This is not easy⁵.

⁵ Buying or commissioning research gives rise to many problems, mostly related to the differences in knowledge between the parties. For example, the researchers have a better understanding than the buyer of how much effort they are putting in and what the chances of success are given the external state of knowledge. This is a problem that the private sector appears to have developed expertise in managing – as we discuss in Chapter 3.

In the third, public-only, model the public sector is not only the funder but also the provider of all R&D services. For success this model requires not only significant upfront public funding, but public sector skills in all aspects of R&D.

The first two models are not mutually exclusive. An important conclusion of this study is that PPPs' success depends on there being credible pull mechanisms in place that enhance the expected size of the market and thereby incentivise major pharmaceutical companies to participate in the late stage clinical trial and commercialisation stages of the process for products in the pipelines of the PPPs. Without this a PPP will not be able to draw on the key private sector skills it requires unless it is able to subcontract activity to them.

We are sceptical about the logic of the public-only model. The PPP model is designed to work with private industry in part because many of the background patents that researchers would need to gain access to in order to conduct their work are in the hands of companies. In addition, the private sector possesses skills and resources that no one else has experience of or access to. For the public sector to seek to replicate all of these skills would be highly inefficient and time consuming⁶. Clearly for very neglected diseases more substantial public funding will be required than for those neglected diseases where there is a market in high and middle income countries. However, such

6 We can put the development PPPs we are discussing in the context of the wider debate about the use of PPPs in the provision of services paid for by the public sector. There has been a world wide shift from 'pure' public provision of public services to greater involvement of the private sector – often by creating some combination of public and private involvement in service provision through a PPP based on a long term contract. In most cases the service continues to be paid for by the public sector and is effectively free at the point of use. The shift is in provision. One purpose of these complex PPP arrangements is to better align risks and benefits with the bodies most suited to deal with them, which, if achieved, should in theory improve the efficiency of service provision. Given that development PPPs are established to bring public funding upfront to R&D activities that have predominantly been undertaken in the private sector the context differs. However, the principle – of seeking to best align public and private efforts to achieve a public goal – is the same, and, not surprisingly therefore, concerns with the wider use of PPPs have been echoed in the context of development PPPs by those supporting the public-only model, including:

- will the level of private profit exceed that appropriate for the risks being borne?
- will there be a high enough commitment to the values of public service, in terms of the effort put in to meet the primary purpose of meeting the needs of the public?

2 DEFINING THE R&D PROBLEM AND THE POTENTIAL ROLE FOR PPPS

28 funding could be directed through a PPP working with both the public and private sectors, or via a pull mechanism such as a guaranteed purchase fund, or a combination of both.

3 UNDERSTANDING PHARMACEUTICAL R&D PROCESSES

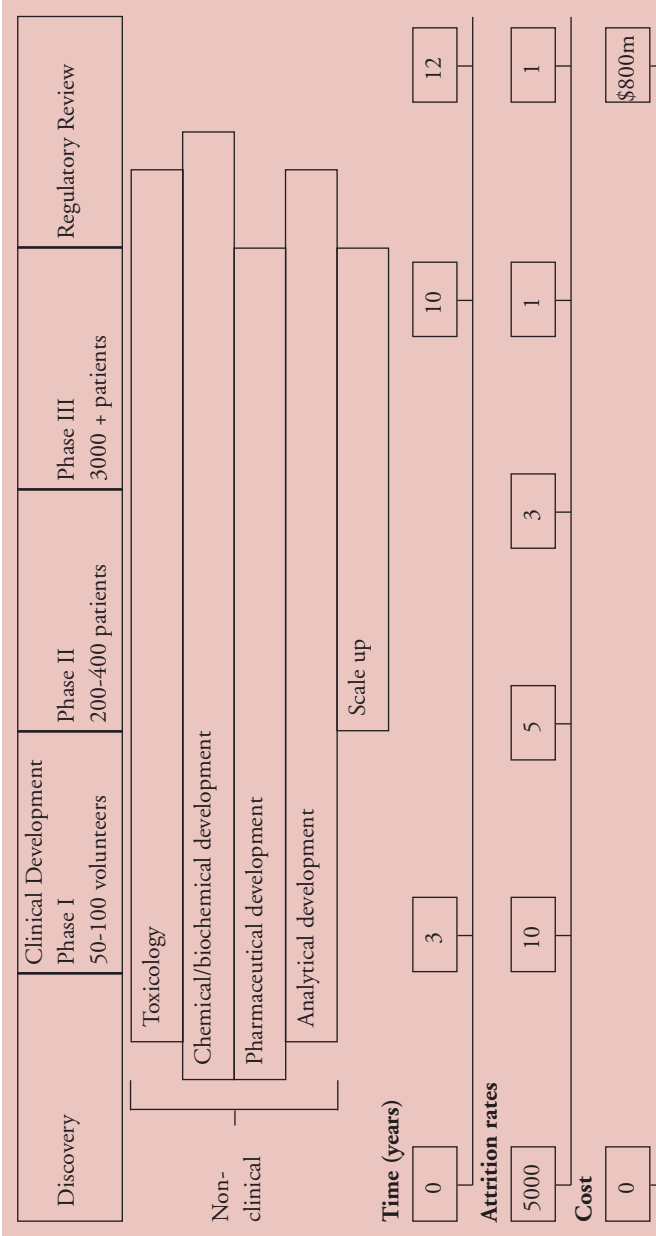
3.1 Changing boundaries in the conduct of R&D

The post-war model of pharmaceutical R&D was one of 'in house' research, development and manufacture by vertically integrated major pharmaceutical companies (Galambos and Sturchio, 1998). Basic research into disease mechanisms had largely taken place in universities. Indeed Cockburn et al (1999a) have argued that 'random' screening did not necessarily require a company to understand disease mechanisms, for example, injecting hundreds of randomly selected compounds into hypertensive rats in the hopes of finding something that would lower their blood pressure. This model of the R&D process, with a rigid separation between 'basic research' carried out in universities and 'applied research' carried out in vertically integrated major pharmaceutical companies, has been changed fundamentally by three major trends. First, there has been a private sector move towards 'open science' with greater collaboration between the public and private sectors in understanding disease mechanisms. This dates from the 1970s, although there are earlier examples. Second there has been a rise of specialist private sector 'biotech' companies in the 1980s, often spun off from universities, followed in the 1990s by the rise of companies specialising in 'genomic' technologies. And third, we see a trend by major pharmaceutical companies towards subcontracting R&D, sales and manufacturing activities.

We discuss each of these trends, highlighting the impact on the role of large pharmaceutical companies' competences in R&D, the future shape of R&D markets and the cost of R&D and time to market. All of this is important for our central concern, namely whether PPPs are likely to be able to operate in the R&D market place given their focus on virtual and contract based R&D.

By way of context, a detailed description of the R&D process is set out in Appendix 5. Figure 3.1 summaries the key activities.

Figure 3.1 Sequence of R&D activities



3.2 Changing relationship between the public and private sectors

We observe two trends in public and private sector participation in the R&D process. First there was a move towards greater private sector collaboration with universities in the 1970s. Second, there is an increased tendency of universities to patent the outputs of their research.

Both aspects relate to the same underlying issue and have implications for PPPs' access to knowledge and the respective roles of the public and private sectors in drug discovery and development. They reflect a further blurring of the traditional view of basic research as a university activity and applied research as a commercial company activity.

To put this changing relationship in context we take as our starting point evidence on where new drugs have come from.

Cockburn and Henderson (1997) looked at 21 drugs identified by two experts as 'having had the most impact upon therapeutic practice' between 1965 and 1992. They found that only 24 per cent (six) were developed with no public sector input into the basic or applied research that was necessary to bring the product to the market place – a lower share than was found in an earlier study by Maxwell and Eckhardt (1990) – suggesting not only that public sector research input was usually essential to private sector drug discovery but that it had become more important over time. They note that the public sector can also be important in providing insight into new uses for existing drugs. Conversely the discovery of an effective compound by the private sector can provide evidence as to how the body works, providing new avenues for basic research in universities into human physiology and molecular biology.

However, in a review of the 21 examples, Reichert and Milne (2000) concluded that only seven of the drugs were directly assisted by basic research done in the US public sector, with three of these seven and another four of the 21 drugs receiving US public sector support in funding or conducting clinical trials⁷. Our purpose here is not to

⁷ We should also note that three of the 21 drugs – acyclovir, propranolol and cimetidine – won their industry inventors Nobel Prizes.

enter a debate as to the validity of the Cockburn and Henderson analysis but to use these examples to understand the nature of the interaction between the public and private sectors and the links between the basic and applied research carried out in each sector. Table 3.1 sets out six of the examples given by Reichert and Milne and the Joint Economic Committee (JEC) of the US Senate (2000), which also looked at these drugs, focusing on ties to the NIH.

The view of the JEC is straightforward:

‘Once knowledge discovered by basic research has been disseminated, any one can use it without charge. Therefore investment in basic research can be unprofitable for private industry except insofar as it has well-defined links with applied research. However, this implies that the economy wide rate of return on basic research is higher than the private rate of return that industry can capture – a situation that creates a case for government support of basic research, such as medical research. Federal research and private research are complimentary. Private research in the United States has produced a cornucopia of medicines, medical devices, and techniques. Private research has built on a foundation funded by federal research. Many of the ideas underlying private research and commercialisation were developed by federally funded research. Together, federal funding and private funding have produced networks of innovative research that have served the American public well.’ (p.9)⁸

8 It has been argued that the essential role of the public sector in much drug R&D is not adequately rewarded as the private sector obtains the patent. The JEC makes the point that the social returns to drugs far exceed their private returns – hence there is a return to public sector basic research if it is efficiently exploited by the private sector. Where the public sector is producing patentable research then it is increasingly itself patenting the work in order to directly obtain a return – as we discuss in the next section. It is also possible, in principle, for the public sector to obtain a return on investments it makes in applied research, such as clinical trials for drug development, by seeking to obtain royalties or a financial payback of some kind if a commercially successful product is eventually produced by the private sector. This, of course, depends on the commercial viability of any product and if the transaction costs associated with negotiating a deal are low relative to any expected pay-off. If they are not, then the applied research should still be undertaken by the public sector if the expected social payoff exceeds the cost of the investment. We discuss the use of intellectual property by PPPs in section 4.6.

Table 3.1 Examples of public private linkages in drug development

Cisplatin, which was first prepared in 1845. Biological activity was not reported until 1965 at Michigan State University, by researchers on a US Public Health Service Grant. Synthesis and identification of cisplatin's anti-cancer role was done at Michigan which patented the compound. It was licensed to Bristol-Myers Squibb for commercialisation. The National Cancer Institute (NCI) funded post-licensing trials to explore combination uses and continues to explore its use in other cancers.

AZT was synthesized in 1963 at the Detroit Institute of Cancer Research, with part funding from the NCI. Burroughs Wellcome resynthesised the compound and tested it for antiviral activity in 1984 following work reported by European scientists. The NCI screened the compound for antiviral activity, and collaborated with the company on a Phase I study. Burroughs Wellcome funded a Phase II study on the basis of which AZT was licensed in 1987. After a legal dispute the courts established that Burroughs Wellcome were entitled to hold the patent.

Captopril was synthesized at Squibb in 1974. Prior work in the public sector, funded by the NIH, had shown that peptides derived from snake venom had anti-hypertensive properties, but were unlikely to be able to be turned into drugs that could be taken orally, as peptides are generally degraded in the stomach. After further collaboration with an NIH funded laboratory, Squibb synthesised compounds that resembled peptides but were not degraded in the stomach.

Tamoxifen was synthesized in 1962 by ICI (now AstraZeneca). The primary purpose of the programme was to develop an oral contraceptive but other possible uses including hormone-dependent tumours were investigated in the initial clinical studies. Funding for the initial pre-clinical testing on laboratory animals was part publicly funded. The NCI also participated in pre-clinical work. It has funded more than 100 clinical trials of tamoxifen.

Recombinant erythropoietin was first reported in 1985 by Amgen and by the University of Chicago. The product was then jointly developed by Amgen and three other companies. Public sector research had established the role of erythropoietin in the 1950s and early 1960s. The University of Chicago had worked on various aspects of its isolation and characterisation

from sheep and humans over 25 years with grants from one of the NIH Institutes. The technology required to develop recombinant erythropoietin was developed in the late 1970s;

Fluoxetine was synthesized in 1970 by Eli Lilly as part of an anti-depressant drug discovery programme set up in the 1960s. Work funded by two NIH Institutes since 1954 (when an NIH funded researcher first found that the chemical reserpine could produce depression in humans) had also discovered that depression is caused by a lack of specific chemicals in the brain, notably serotonin.

The main point is that the typical product coming to market in the 1970s and 1980s involved either direct collaboration between the public and private sectors or indirect collaboration via the scientific literature, and that this collaboration was crucial to the eventual launch of a successful product. The key public science input is in basic research, but the public sector also funds and undertakes applied research. Conversely, the private sector also undertakes basic research where it sees opportunities to capitalise upon it.

3.2.1 The move to greater private sector collaboration with universities

Cockburn et al (1999a) note the move in the 1970s to 'science-based drug discovery' or 'rational' drug design aimed at taking advantage of increased scientific understanding about the biological basis of disease. Success in applied research became more dependent on an understanding of basic research. To access such information, companies had to encourage their researchers to interact more closely with the scientific community external to the firm. This was a two-way process. For example, the experiments which identify potentially valuable commercial drugs will also tend to be empirical tests of specific (and most likely previously unproven) biological or biochemical theories. Successful participation involved publishing in the scientific literature. They became participants in 'science', in a wider sense, rather than just users of scientific knowledge. Cockburn et al concluded that a positive publication strategy and the pursuit of basic research in-house were key for companies seeking to build links

with publicly funded scientists and so gain access to leading edge understanding of disease mechanisms.

In an earlier study, Cockburn and Henderson (1997) sought to explore in more detail the relationship between the ‘public good’ aspects of basic science and the private returns to innovation. They hypothesised that collaboration in preparation of research papers was an important opportunity for the exchange of tacit knowledge between the public and private sectors and looked at patterns of co-authorship of scientific papers between 1980 and 1994 where one author was a researcher in a company. Their key findings include:

- extensive company publications totalling 68,186 papers – an average of just over 227 papers per firm per year with a strong upward trend;
- that universities account for 34 per cent of co-authorships, with hospitals accounting for 10 per cent and other private, non-profit and public accounting for 11 per cent in total. Other company employees accounted for the balance of co-authorships;
- that company co-authorship of papers with universities had a positive and significant effect on research productivity as measured by significant patents (i.e. those taken out in the US, Europe and Japan); and
- having ‘star’ scientists (measured by the fraction of publications attributable to the top 10 per cent of a company’s scientists) also correlates positively and significantly with research productivity.

These results offer support for the hypothesis that ability to access and interact with the public sector is an important determinant of the productivity of downstream private sector research. The implications for PPPs are clear. There are significant gains from ensuring that company scientists invest effort in publishing i.e. in an ‘open science’ approach, as well as putting effort into applied research leading to patents. The reward structures should encourage scientists to make appropriate trade-offs between the two activities. This does not exclude enabling the PPP to appropriate the benefits of the research it funds – the Henderson and Cockburn work and that of Cockburn, Henderson and Stern (1999b) suggests that patenting and publication strategies are complementary.

Further evidence of the complementary relationship of publication and patenting comes from another Cockburn and Henderson paper (1994a) which explored the importance of externalities between mainstream pharmaceutical companies. Using detailed data on R&D investments and outcomes for 10 pharmaceutical companies over the period 1975 – 1990 the authors found that output (as measured by important patents, i.e. those filed in two or more of the USA, Europe and Japan) shows a strong positive correlation between own output and the success of rival firm's efforts (after controlling for shifts in technological opportunity). The mechanism for achieving the spillover benefit is via the scientific literature and scientific meetings. Far from there being a 'mining out' of opportunities which are appropriated by patenting, competitors' research appears to be a complementary activity to in-house R&D. Patenting does not enable a company to appropriate all of the benefits of the applied research they have undertaken. This is because to be successful companies have to publish as well as patent and this brings benefits to the research efforts of others working in the field.

3.2.2 University patenting

Cockburn and Henderson raise a concern that efforts to realise a direct return on public investments in research by increasing the appropriability of public sector research, particularly through university patenting, may lead to a weakening of the culture and incentives of 'open science' such that the productivity of the whole system of biomedical research may suffer. Orsenigo (2001) raises a similar concern.

However, work by Owen Smith (2001) on the patenting activities of the 89 most research intensive US universities since the passage of the Bayh Dole Act in 1980 suggests that public science (i.e. the output is published) and private science (i.e. the output is patented) are not necessarily in conflict within universities. The top patenting universities are also the top scientific publishing universities. His econometric modelling found an increasing overlap between public and private science. By the 1990s, scientific reputation (in terms of publication) was having a positive impact on patenting and patenting

was in turn leading to increased citation and enhanced academic prestige. Those universities that are successful are the ones that manage the tensions between the two realms of activity in a way that supports both. Perhaps not surprisingly, these results are similar to those of Henderson and Cockburn discussed above in relation to large pharmaceutical companies. There is no longer a choice between patenting and publishing. Success in patenting requires both. The move of universities in the US to patent does not appear to have threatened the ability of the private sector to gain access to basic research. What it has done is encourage the universities to apply the basic science themselves, as well as to publish, to produce applications that are of value to the private sector and will give the public sector a return.

3.2.3 Implications of changing public/private relationships for PPPs

In the context of the debate about the relative contributions of the public and private sector this suggests that there has been some further blurring of the basic science in the public sector/applied science in the private sector separation. However, most basic research occurs in the public sector and most applied research in the private sector. This has implications for where the PPPs seek to build relationships⁹. It also shows that the public sector can obtain Intellectual Property Rights (IPR) where it is financing or undertaking applied research – and the PPPs can learn from the patenting approach of universities as well as of companies. It also means that collaboration is increasingly the way forward. The PPPs need to ensure there is a collaborative culture in those organisations they contract to work with, and that they, as PPPs, are able to successfully harness the various R&D activities going on that are relevant to their missions. This integrator role is one that appears currently to be performed well by the major pharmaceutical companies – as we discuss later.

⁹ It also reinforces our view that the ‘public only’ model discussed in Chapter 2 is unlikely to be a particularly efficient way of seeking new drugs for LDC diseases.

3.3 The impact of the rise of biotech/genomics companies on the R&D market

Henderson et al (1997) analyse the impact of the revolution in molecular biology on the structure of the pharmaceutical industry and hence on the structure of R&D markets. They note that only one company – Syntex – the developer of the oral contraceptive – succeeded in entering the industry prior to the mid 1970s. By contrast, the revolution in biomedical science and genetics has posed greater threats to the mainstream pharmaceutical industry because of its potential to make some of the key competences that the industry has irrelevant.

It has led to the use of biotechnology as a production technique, initially on ‘large molecule’ proteins whose therapeutic qualities were well understood. Of the three biotech products that have been major commercial successes (insulin – Genetech and Eli Lilly, erythropoietin – Amgen and Ortho, tPA – Genetech) the first two were recombinant versions of established products. As a production technique (the ability to manufacture proteins) biotechnology enabled new market entry. This reflected the difficulty of the processes and the lack of relevance of the existing manufacturing competences of pharmaceutical companies.

Genetics and molecular biotechnology can be used to enhance the productivity of the discovery of conventional ‘small molecule’ synthetic chemical drugs. In this area, new competencies have reinforced the dominance of the more scientifically sophisticated large firms (particularly some of the US, British and Swiss companies) and not destroyed it.

There has been the advancement of discovery and development of biotechnology based large molecule drugs. This combines the previous two techniques and does require some new competences to identify large molecules. An examination of patenting activity shows that new biotech companies accounted for 41 per cent of US origin patents at the European Patent Office in 1987-1993 (38 per cent were from established companies and 21 per cent from universities). New biotech companies were initially also more successful in bringing new

biological entities to market (although most of these were orphan drugs – Kettler (2000)). The three drugs referred to above put Genentech and Amgen into the top 10 pharmaceutical industry innovators. Of 21 New Biological Entities approved for the US market by 1994 only two came from established pharmaceutical companies operating in their own right. Although some large pharmaceutical companies have sophisticated biotechnology capabilities in-house they have yet to emerge as major players in the large molecule drug market in their own right. However, the number of large molecule drugs that are approved for marketing each year is still small relative to the number of small molecule drugs.

Incumbents still have the advantage of competence in clinical trials and commercialisation. Genentech and Amgen have been the exceptions of new biotech companies becoming fully integrated major pharmaceutical companies¹⁰. The trend since the 1970s has been for a market for knowhow to develop with start-up firms positioned as upstream suppliers of technology and R&D to established firms.

Henderson et al see biotech companies as 'an institutional response to the technical opportunities created by the new scientific know how'. They do not specifically comment on the long term impact on the R&D market, but the implication is that biotech companies will be a permanent feature of the R&D process although large pharmaceutical companies will retain a major, if not a dominant, role. This is because of their continued role in discovery combined with their competences in the management of large-scale clinical trials, in the process of gaining regulatory approval, and in marketing and distribution. The latter in particular appear to continue to act as powerful barriers to entry.

Pammolli and Riccaboni (2000) reach similar conclusions from their research which examined 859 agreements between 355 firms (83 established pharmaceutical companies and 272 dedicated biotech companies). They conclude that:

- the molecular biology revolution and the appearance of dedicated new firms based on general purpose technologies (such as combinatorial chemistry, genomics, bio-informatics, and high

¹⁰ Genentech was bought by Roche, but not until it had already become a major player. It continues to be run on an arms length basis as a separate company.

40

throughput screening) has led to a new division of innovative labour between established large companies and new small companies;

- the network of R&D collaborative agreements is based on this division of innovative labour, with vertical differentiation and specialisation across firms. The biotech companies are active in the early stages of R&D as ‘originators’ (those selling a technology). The established pharmaceutical companies are specialised mainly in downstream development and commercialisation activities as ‘developers’ (those buying a technology);
- biotech companies succeed when they specialise on a cluster of related biological targets or research technologies. However, the key to success for established pharmaceutical companies is the breadth of their absorptive and integrative capabilities, as reflected in the measures of the extent of their technological diversification. The division of labour within the industry is thus sustained by the co-existence of vertical specialisation for ‘originators’ and horizontal diversification for ‘developers’. For the established pharmaceutical companies technological diversification is matched with integrative and evaluative capabilities. These enable the exploitation of economies of scale and of internal spillovers of knowledge between programmes, plus the achievement of technological coherence in R&D across disease areas.

Gambardella et al (2000) noted that large firms had adapted and ‘continue to represent the inner core of innovators in the industry’ (p38). Increases in the costs of R&D have increased barriers to entry and ‘large innovative corporations play a crucial integrative role across different bodies of knowledge as well as providing complementary assets in clinical development, regulatory affairs and distribution channels’ (p38). Gambardella et al are also clear, however, that they expect the market for technology to be a permanent one and the relative success of large pharmaceutical companies will depend on their in-house integrative capabilities and their ability to access the market for technology.

One of us (Kettler, 2001) has previously examined trends in the R&D market place using, inter alia, survey evidence of 26 large

pharmaceutical companies and 20 biotech companies (Ashton et al, 2001). The large companies surveyed by Ashton et al were spending 15 per cent of their discovery budgets on alliances. Although alliance activity had flattened in the late 1990s, 75 per cent were expecting to spend more in the next five years. Companies were pursuing different strategies, both in terms of the numbers of deals they were doing and whether they sought acquisitions or alliances. Confirming the analysis of Henderson et al (1997), Kettler found that large pharmaceutical companies and biotech companies each accounted for 45 per cent of the discoveries of biotech products so far brought to market (with universities accounting for the other 10 per cent), but biotech companies had only brought 20 per cent to market themselves. Conversely, biotech companies contributed in some way to 30 per cent of the new molecular entities (both new chemical entities and new biological entities) brought to market in 1998 and 1999. There was evidence of a division of labour between pharmaceutical and biotech companies and evidence that the major pharmaceutical companies expected to continue trading in the R&D market place with the biotech companies.

We should note, by way of contrast, the view of Galambos and Sturchio (1998) that the rise of biotech companies is a one-off and therefore potentially time limited consequence of the slow response by the major pharmaceutical companies to the opportunities presented by the new science. They state that by the 1990s 'it was also evident that the division of labour was less significant than it had appeared to be a decade before.' Large pharmaceutical companies had pursued one of two strategies – building alliances or 'in house' capabilities related to specific products they were marketing or had targeted for R&D, or seeking more general biotech capability, usually through acquisition. By the 1990s the major pharmaceutical companies had internalised significant capabilities in molecular genetics and rDNA. However, Galambos and Sturchio acknowledge that networks of biotech – pharmaceutical collaboration 'will remain important for many years to come'. Their point is that the large manufacturers have adapted their in-house R&D capabilities and will therefore continue to be the dominant players in global R&D markets.

Arora and Gambardella (1990) take a similar perspective to Galambos and Sturchio when drawing conclusions from a study of large pharmaceutical company linkages with other entities. They note that ‘the network-like structure of the organisations responsible for innovation in biotechnology may well be a temporary phenomenon arising from the relative immaturity of the technological paradigm’. In their research they find that agreements by large companies with other large companies, research agreements with universities, minority participations in new biotech companies and acquisitions of new biotech companies are all positively correlated. They conclude that these strategies target distinct sets of resources and are therefore complementary to one another. They also point to an alternative conclusion to that of Galambos and Sturchio stating that ‘our findings raise the question whether in modern capitalist economies the innovation process requires new and different organisational arrangements in order to allow specialised complementary assets, controlled by different types of agents, to be combined.’ In other words, the new R&D market place is here to stay.

3.4 The trend to subcontracting

Kay (2001) comments that it is logical for the pharmaceutical industry to follow the publishing and film industries in separating those responsible for origination, for publishing (co-ordination, project selection, finance and marketing) and for distribution. He notes that in pharmaceuticals origination and publishing may not be as separable as in other sectors but also points out that the traditional arguments for vertical integration – asset and competence specificity – can be achieved by contract within a market place of independent players.

Independently of the rise of biotech and genomic companies there has been a substantial growth in subcontracting by major pharmaceutical companies at many stages of the R&D process. This subcontracting has occurred in each of the stages of clinical development (Phases I, II, III and IV), in toxicology, and, to a lesser extent, in other aspects of non-clinical development. Companies are also increasingly using co-marketing deals and contract field force organisations to ‘rent a sales force’.

The rise of these contract organisations has made it easier for new entrants (a category in which we can include PPPs) to construct a virtual organisation. However, it raises again the issue as to how important the role of ‘integrator’ is and whether it can be replicated by organisations other than the major pharmaceutical companies.

3.5 How important are the competences of large pharmaceutical companies?

Will the established major pharmaceutical companies remain an essential part of the R&D process? Our literature review suggests that large pharmaceutical companies have two distinct areas of competence: in their role as a discovery integrator and in their competences in clinical trials and commercialisation.

We consider these in turn.

In Henderson and Cockburn (1996) the authors seek to explore the relationship between R&D and scale, scope, spillovers and research productivity for large pharmaceutical companies, drawing on a dataset covering 38 research programmes in 10 major R&D pharmaceutical companies over a period of up to 30 years. They conclude that large firms do have an advantage in the conduct of research in terms of productivity (measured by patents granted in major markets for the years 1961-1988) but that this comes from economies of scope rather than of scale. There are spillover effects between programmes within the company.

In another study Henderson and Cockburn (1994) tested for two broad classes of capability that might act as sources of firm advantage (measured in terms of significant patents i.e. one granted in two out of three of the USA, Europe and Japan). Using quantitative and qualitative pharmaceutical research data from 10 major US and European pharmaceutical companies for the period 1975-88 they found that locally embedded knowledge and skills enabled a large firm to acquire one or both of a unique disciplinary expertise or a proprietary knowledge of a particular disease area. They call these ‘competences’. Second, integrative capability was significantly positively correlated with research productivity. By integrative

capability they meant a company's ability to make use of its competences by maintaining an extensive flow of information *within* the firm and *across* the firm.

Both of these studies suggest that large pharmaceutical companies retain 'integrator' or 'co-ordination' skills in discovery that are key to getting products to the market place. However, as we noted in section 3.4, externalities arising from spillovers from the public good aspects of knowledge generated by competitors are also important. Economies of scope – whether arising from the use of specialised assets or specialised competences across a number of activities or from internal spillover effects from related programmes – can in principle be achieved by specialist suppliers in the R&D market place who could achieve these economies whilst supplying a number of different companies. If the market is competitive they will pass on the benefits to their customers. If not the gains will still be realised but will accrue to the specialist supplier. However, if a large organisation can benefit more because of the potential breadth of scope economies or because it can internalize spillover benefits whilst smaller companies can only exploit public domain material then large companies will have superior performance.

We should note, however, that the discovery activities of large pharmaceutical companies have had to change considerably in order to enable the companies to survive. They do not necessarily possess inherent R&D competences that cannot be challenged.

Of more enduring importance may be the development and commercialisation competences. These appear to be hard to replicate. In spite of the rise of subcontracting in clinical and non-clinical R&D and in manufacturing and marketing there have been very few new entries into this end of the pharmaceutical industry. An exception, as we have noted, has been the introduction by biotech companies of orphan drugs to the US market place (Kettler, 2000). However, there are unusual circumstances in the cases of these US orphan drugs. Whilst there is a package of 'push' incentives (tax credits, help with R&D costs, and fast track approval) which may also be present in PPP situations, other factors are different. Active patient groups and hospital-use reduce selling costs and the need for commercial

infrastructure. Most importantly, companies are guaranteed seven years market exclusivity, can charge very high prices, and have often been successful in getting use outside of the orphan indication or patient group. It is not clear that this kind of ‘niche’ activity requires the competences that a PPP seeking to get products to patients in less developed countries would need.

3.6 What will the R&D market place look like?

Given the research findings we have discussed what conclusions is it possible to draw about the future shape of the R&D market place? Is it one in which it will be possible for PPPs to contract with a variety of public and private sector organisations and achieve their R&D objectives?

On the basis of this evidence we have presented we are skeptical of the ‘traditional model’, in which the major pharmaceutical companies use alliances and licensing as a ‘stop gap’ to catch up with new technologies. Under this scenario, the large integrated company remains the dominant competitive force in the discovery, development and delivery of new products. If this were the case then the implications for PPPs would be severe, as, over time, the number of potential partners would diminish and be reduced to the major established pharmaceutical companies.

An alternative ‘dynamic’ model is the specialist division of labour model set out by Pammolli and others. This could take the form of large companies establishing longer term relationships with biotech companies, either by way of long-term, renewable contracts or by acquiring shares. Although this has occurred, we think a more likely version of the model will be a dynamic network. The R&D process might differ depending on the therapeutic category and the product, leading to more short term, project specific, contracting between biotech suppliers and large company customers. In some cases this dynamic model may be more virtual with biotech companies developing products on their own, perhaps through collaborations or alliances with each other, sometimes using major pharmaceutical companies, sometimes not, relying on research organisations and

contract sales organisations to do work that major pharmaceutical companies have done in the past.

Our assessment of the evidence is that it supports the second scenario, of a 'dynamic' network model of R&D, but with major pharmaceutical companies playing the central (although not exclusive) role in co-ordinating discovery activities and in bringing products through development to market.

We should note however that there is little evidence to date of a successful pay-back to those large pharmaceutical companies making a significant investment in biotech and in an external network. A study by Pammolli and Ricaboni (2001) of in-licensing of R&D projects by the top 100 pharmaceutical companies by sales found that licensed in projects achieve consistently and significantly better success rates in moving from Phase I to Phase II to Phase III in the trial process. This suggests that the investment in selection that large companies make before signing deals is paying off (Pisano, 1997, Teece, 1986). It was too early, however, to assess the ultimate commercial success of these projects. The sustainability of a dynamic model of the R&D process will depend on its ability to generate commercial success in terms of valuable products for patients.

3.7 What are the implications for R&D costs and time to market?

Kettler (1999) reanalysed earlier estimates (Di Masi et al 1991, OTA 1993, Myers and Howe, 1997) of the cost of bringing an NCE to market and concluded that \$600m was a reasonable estimate. More recently Di Masi et al have produced an estimate of \$800m (Di Masi et al 2001, 2003). The issue arises as to whether PPPs are going to have to find this sort of money to bring a new product to an LDC market. There are at least five key issues to consider.

First, the opportunity cost of capital accounts for half of these costs. If PPPs are funded up-front and do not have to provide a return on this investment then these costs will be lower. However, if commercial contracts are to be signed at some point in the process these costs will kick in and will need to be funded up-front as part of

the contract or via the returns a company obtains from selling the product.

Second, the cost of failures is a significant factor in overall R&D per successful product. If PPPs have higher success rates costs will come down. However, we should note that large pharmaceutical companies have not been able to reduce their attrition rates despite many years of trying (CMR International, 2000).

Third, discovery costs, before capitalisation, according to DiMasi's work, made up more than half of out of pocket costs. Other studies suggest they are around 33 per cent of out of pocket expenditure (CMR International, 2000). It is unclear whether PPP discovery alliances with companies and universities will be able to reduce this cost.

Fourth, time to market averages 10-15 years. Large companies have had very limited success in reducing the time from discovery to launch despite efforts to outsource stages and stream line decision making (CMR International, 2000). Studies suggest that new biological entities take less time to get to market than new chemical entities – implying that biotech company involvement may reduce time to market. However a study by Gosse and Manocchia, (1996) finds that many of these products were recombinant versions of products whose therapeutic properties were well understood.

Finally, despite predictions by Lehman Brothers (1997) and others that technological improvements in the discovery process could reduce attrition rates and speed up time to market, there is no evidence to date that this is happening.

The costs to a PPP of getting a product to market may be substantially below \$800m, but unless discovery costs are much lower than the industry norm and partners are found to take on the risk associated with clinical development and commercialisation, then the up-front requirements for cash will be large. Again, the US orphan drug experience suggests that costs can be lower, but this is largely because of 'push' packages of the sort we discussed earlier.

3.8 What are the implications for PPPs?

In summary, this review of the new dynamic R&D market place has a

number of key implications for PPPs:

- early evidence from the private sector suggests that the ‘virtual’ approach is contractually feasible and would give each PPP maximum flexibility in identifying public and private partners;
- there is a key integrative role that large companies appear to perform in the discovery area. There are also significant ‘spillover’ effects from different, but related R&D programmes. This means that the PPPs should not manage their discovery portfolios as separate discreet entities but should constantly be seeking complementarities across programmes;
- large companies continue to dominate commercialisation activities. There is evidence from the US ‘orphan drug’ market that smaller biotech companies are able to bring products to market, but there are particular characteristics of these markets that may not be applicable to PPP target markets. This means that PPPs have to contract with large companies at some point, or develop substantial in-house co-ordination competencies if they are to manage these stages on a virtual basis¹¹.

To take advantage of the new R&D market place PPPs will need to be expert in a number of corporate activities to support the ‘frontline’ task of finding new products for LDC diseases. We consider these and assess the performance to date of the PPPs in the next section.

¹¹ These conclusions reinforce our concerns that the public-only model of drug development discussed in section 2 may be expensive and inefficient given the comparative advantage of the private sector in many R&D activities.

4 PUBLIC PRIVATE PARTNERSHIPS ASSESSED

4.1 Five key aspects of performance

This chapter is organised around five key issues that have implications for the immediate and long-term credibility and performance of the product PPPs.

First, we discuss the importance of the quality of the executive team and the efficiency of the management and oversight arrangements.

Second, we consider whether the right governance structures have been set up to make sure that the management teams are accountable for the pursuit of their goals effectively and efficiently.

Third, we examine how the different cases plan to organize their R&D effort. We do not know at this stage how successful they will be in using the dynamic R&D market place to obtain effective collaborations. We do know that replicating the skills of large pharmaceutical companies in co-ordinating discovery activities or in development competences will not be easy. However, some biotech companies have brought products to market, and, in principle, a virtual solution is possible.

Fourth, we assess what the financing needs of these PPPs, given their objectives and expectations about R&D costs. The PPPs are committed to seeking commercial partners to bear later stage costs. They also assume that they can cut by two thirds the overall average \$800m cost for major companies of getting a product to market.

Fifth, we highlight the importance of an effective intellectual property policy for the success of PPP deal making. The PPPs are pursuing an aggressive approach designed to obtain maximum leverage for their social purpose. This must be the right approach to maximise bargaining power with collaborators, and so extract value for money.

We conclude with an assessment of their performance up until now.

4.2 The management arrangements

From the outset, it is important to remember that these PPP are still in their infancy. These models are still experiments where through trial

and error they are learning the most effective organisational structure for meeting their goals. And just as there is no one ‘best way’ of organising and conducting R&D in the private sector, so too is this the case for the PPPs.

Nonetheless, the different organisations include the same components as a private company – a management team, a board of directors with representatives who can ‘talk to’ the different areas of business, a scientific advisory committee, and a stakeholder council.

4.2.1 Management team

The list of responsibilities for the full time, in-house management team includes:

- (i) the selection, and management of the research projects;
- (ii) the building and sustaining of trust and co-ordination of relationships between the key research partners involved in specific projects or in researching the disease problem more generally;
- (iii) fund raising;
- (iv) the management of the money and establishment of funding priorities;
- (v) routine information dissemination about the initiative’s progress to the funders, stakeholders, boards and the general public.

Some specialised tasks such as contract writing and tax and legal advice can be brought in on a contract basis but the management team must possess an exemplary set of skills to engage effectively with partners from industry, academia, international finance, governments and international aid and health organisations. The complexity of the R&D process, as discussed in Chapter 3, highlights the need for expertise not only in conventional project management, but in creating networks in which partners learn from each other. Skill is required to ensure that financial contracts provide both value for money for the PPP but also shared incentives to achieve the social goals of the PPP.

The reputation, experience and confidence required of the PPPs’ CEOs in particular cannot be understated, as in the short and medium-term, a critical component of her or his job is to sell the value and potential of their organisation to sceptics from all sides. Their

pitch, however, is only ever as good as the team of people they manage to do the work.

That there is no 'one type' of person for the job is demonstrated by our four cases. Chris Henschel, MMV's CEO has worked many years in the pharmaceutical industry, in large pharmaceutical companies and biotech companies, as a scientist, a manager and most recently, as Chief Scientific Officer and VP at Centacor. Seth Berkley, at IAVI, is a medical doctor by training with a specialisation in infectious disease who was formerly an Associate Director of the Health Sciences Division at the Rockefeller Foundation and one of the key founders of IAVI. Regina Rabinovich is a pediatrician and was 11 years at the National Institutes of Allergies and Infectious Diseases (NIAID) at the NIH prior to accepting her post as Director of MVI.¹² Maria Freire was appointed as the CEO to GATB in September 2001. Between 1995 and mid 2001, she built and directed the Office for Technology Transfer at the NIH.

It is difficult, however, to assess the strength of a management team based on paper credentials. Only a track record will highlight strengths, weaknesses and gaps in the team.

4.2.2 Board of directors

The second critical component of the PPP organisation is the board of directors. These boards work together with the management team in the design of the PPP's strategy and are responsible for making sure that the staff work effectively in pursuit of the stated goals. They must make decisions about selection criteria for initiating and also for closing down programmes, about the scope of the organisation's responsibilities and position of it within the global health and private research communities. Given the unique set of issues addressed, problems faced and stakeholders involved or effected by these PPPs, careful selection of board members is important. Major funders, founders and in-kind contributors are represented. In our cases that includes the global pharmaceutical industry, the WHO, the World

¹² Regina Rabinovich has been appointed the Director of Infectious Diseases at the Gates Foundation as of November 2002. At the time of publication MVI had not initiated the search for a new CEO.

Bank, universities and research institutes (disease or country specific or both), major corporate funders, patient groups and researchers from the afflicted regions of the developing world, and NGOs.

The composition of the board is also important because prior to the establishment of a track record, it is their background and reputation along with that of the top management that will be assessed by those considering pledging funds or committing to research contracts. Appendix 6 compares the Boards for our four cases. In particular we see that all four cases have successfully put together teams of reputable representatives from industry, international health organisations and academia.

4.2.3 Scientific advisory committee

The same can be said about the scientific committees. These advisory committees help the PPP determine the overall structure, goals and progress of the project pipeline, help the management team assess the quality of the proposals, and then, in smaller teams, contribute to the monitoring of key research projects. They help the Board of Directors and management to assess gaps in the pipeline, to identify potential new partners, and to decide whether to renew funding for existing projects at key milestones or redirect those funds towards other priorities and projects. It is important that members of this committee understand not only the disease but also how it operates in the developing world. Our cases include representatives from the global R&D-based pharmaceutical industry and key research institutes from both the developed and developing world.

The participants volunteer their time to sit on the Scientific Advisory Committee and Board of Directors. The calibre and quality of the boards, at least on paper, in our four cases, suggest widespread interest among key constituents in helping the global health research cause and considerable consensus that it is worth the risk to back the PPP model as a way to move forward.

4.2.4 Stakeholder board

Finally, each PPP is ultimately responsible to their stakeholders. Important questions have been raised about the extent to which the

composition of these councils are weighted too heavily in favour of the global industry, scientists and the funders, at the expense of inter-governmental global health organisations and less developed countries (or the targeted recipients) (Buse and Walt, 2000c, Interview, Roy Widdus, May 2001).

The stakeholders have played a critical role in getting the PPPs established and their missions specified. Ultimately they will again be called upon to make difficult policy and ethical issues as products move towards market approval. In particular, they will help decide what vehicles to use to purchase, and distribute the products, what countries or populations will receive first priority, and who should pay and how much (Interview, Trevor Jones, July 2001). Appendix 7 lists our PPPs' key stakeholders and funders.

4.3 The effectiveness of the governance arrangements

In a discussion of governance, we need to address three key questions:

- who makes the strategic and organisational decisions?
- who are the major stakeholders who these decisions directly affect?
- what processes are in place to ensure that those stakeholders can contribute to the establishment of priorities and evaluate the activities following from the strategic decisions.

4.3.1 The debate about PPPs and governance

As new, 'hybrid' organisational forms, the establishment of PPPs in general, and for health in particular, have prompted important debates about how they should be governed and to whom they should be accountable (Buse and Walt (2000a), (2000b), and (2000c)).

Buse and Walt (2000c) quote Rosenau (1995) as defining governance as 'the process whereby an organisation or society steers itself' – the system of rules, norms, processes and institutions through which power and decision making are exercised. They go on to say that 'good governance has four components: a. representative legitimacy; b. accountability; c. competence and appropriateness; d. respect for due process'. This is taken from the World Bank report (1994) and in particular they adapt the OECD's Development

Assistance Committee's (DAC) own adaptation of the World Bank's 1989 definition of governance. The DAC refers to governance as the: 'legitimacy of government (degree of democratisation); accountability of political and official elements of government (media freedom, transparent decision making, accountability mechanisms), competence of governments to formulate policies and deliver services; and respect for human rights and rule of law (individual and group rights and security, framework for economic and social activity, and participation.)' (p xiv).

The World Bank itself uses a narrower definition, which reflects its terms of reference. These do not allow it to comment on the form of the political regime. Its interest is in getting economic and social development. To this end it has four major components of governance:

- public sector management, where the emphasis is on 'a smaller state, equipped with a professional, accountable bureaucracy that can provide an 'enabling environment' for private sector-led growth, to discharge effective core functions such as economic management, and to pursue sustained poverty reduction.' (p xvi)
- accountability, which can be achieved by a number of measures including decentralisation of government, improved financial management, encouraging beneficiary participation in projects, and competition in service delivery;
- transparency and information, to help achieve accountability;
- legal framework, with appropriate protection of private property rights and regulation of private economic activity.

The difference in emphasis is important. The DAC and Buse and Walt's interpretation of governance issues is most relevant when the government is providing services and making all the decisions. It must have legitimacy and respect the rights of its citizens. The World Bank approach is applicable to a more pluralistic view of society. It assumes that the government has policy objectives but seeks to achieve them by creating a framework in which civil society and a market economy can function and help to deliver these objectives. In this model when the government is seeking to fund services it will use the private sector to provide them if it has the expertise to provide them efficiently.

PPPs only make sense in a pluralistic model of the world. If the only issue is democratic legitimacy and delivery is assumed to be straightforward then the case for PPPs is weak. It is precisely because delivery is extremely difficult (and costly compared to the size of existing international agency budgets for this type of product development) that PPPs become an attractive option. In the case of drug discovery and development the expertise of the private sector is well understood. The objective is to harness this expertise and engage its resources through a mechanism whereby the public sector takes on much of the cost and risk involved at the discovery stage. It has been argued that the private sector will not, ultimately, respond. This is not, however, a governance issue, although an important one which we have discussed and will return to.

4.3.2 The governance challenge for PPPs

Buse and Walt raise a number of key governance issues of relevance to our PPPs.

First, they argue that the motives of the private sector must be considered. These will include some combination of positive publicity, expectations of some kind of commercial return on the activities they undertake, or influence on policy making. In our view, it is not clear why this is an issue, assuming that the public objectives of the project are achieved and rules are in place that do not allow inappropriate behaviour on the part of any participants (public or private). Significant gains to the reputations or profits of those involved will only be achieved if the PPPs are successful.

Second, they ask the question of whether the private sector presence in governance will distort public sector priorities. There are two aspects to this. Firstly, the public sector must make its own decisions about which PPPs (or other projects) to back if resources are constrained. Secondly, if private resources are required to make a PPP, or one of its projects, viable then inevitably private choices will influence the ability of public bodies to achieve their objectives. The alternative is for the public sector to fund a 100 per cent public delivery project. Sadly there is no guarantee that this would be successful, or that the public sector can raise the sort of funds that would be necessary – indeed the evidence suggests the opposite.

Third, they are concerned that key groups of potential recipient countries are not represented in PPPs. Here we return to our distinction between the ‘centralist’ and ‘pluralistic’ approaches to legitimacy. The PPP model, if it is to achieve its goals, requires recipient countries to be involved in key decisions about projects. If new drugs will not be used effectively because of local logistical or social obstacles then unless the PPP can overcome these obstacles there is no point in developing the drug. We have already discussed how some of these factors (dosage regimen, ease of manufacture, and stability) will be taken into account at early milestone stages of project viability. However, the local input that is required is expertise, not token political representation on a PPP Board or Council.

Fourth, they find that the PPPs lack transparency, and it is not clear how Board members and expert group members were chosen. Transparency is essential for accountability. Decisions must be justified. However, they must be made on efficiency grounds and not political grounds. If PPPs fund units, or don’t cancel projects, or don’t pay key staff at market rates because of fears about the political repercussions then they will not succeed. Indeed an important advantage they have over the in-house public sector approach will have been lost.

Our comments should not be taken as meaning that the Buse and Walt challenges are not valid ones. They are. PPPs must be efficient, effective and accountable. In particular the issue of transparency needs to be addressed and a more explicit mechanism must be found to involve potential recipient countries. The private sector goes to great lengths in commercial drug development to understand how the medical profession, governments and other third party payers will perceive the usefulness, and therefore the value, of products they have in development. Exactly the same processes must be applied by the PPPs in relation to their potential customers – in particular to understanding the views of the scientific and health professionals in less developed countries and of those who would be expected to fund use of the product.

In summary, PPPs are established to do a specific job. They should first and foremost be made accountable to the funders and

stakeholders engaged in the specific R&D problem. The key questions are whether they are organised in such a fashion that they are likely to accomplish that job and if their performance is transparent enough for those on the boards, and ultimately for external stakeholders, to assess it. Our view, subject to the points we raise in our previous paragraph, is that their governance is organised in a way that is most likely to enable them to achieve their objectives.

4.4 The organisation of the PPP R&D process

So how do the PPPs plan to meet their ambitious targets of bringing new products to market in the next 10 years at a fraction of the cost that pharmaceutical companies spend to bring their products to market? MMV, for example, seeks to create a portfolio of properly funded and adequately resourced projects on a par with industry-run discovery projects. In the long term the goal is to secure the production on average of one licensed new anti-malarial every five years for a cash outlay of \$150m (TDR Press Release, May 2000 and Introducing MMV, <http://www.mmv.org/about.htm>). By 2007, IAVI hopes to have 8-12 vaccine partnerships in their pipeline (they are currently supporting five), to double their existing fund of \$230 million, and to have two vaccines in Phase III clinical trials (two of their five are currently entering Phase I trials) (Cowley, 2001).

The PPPs have set themselves a set of difficult challenges. First, they seek to develop a 'virtual R&D organisation' that works from a scientific and an organisational stand point – i.e. will result in effective, safe, products at competitive costs. Second, they seek to apply this, as yet relatively untested model, to 'orphan developing country diseases' and ensure that the resulting products not only meet FDA regulatory requirements, but are also inexpensive to produce, relatively easy to transport, store and distribute, and 'affordable' – however that might be defined. Finally, they aim to achieve this through public and private partnerships that can, in and of themselves, be potentially difficult to achieve given significant differences in goals, cultures, and expectations.

4.4.1 Opportunities and obstacles to virtual R&D development

Our discussions in Chapter 3 point to a number of potential opportunities but also difficult obstacles to establishing an effective virtual R&D unit. These are summarized below.

Opportunities:

- success in R&D is already contingent on deals and collaborations in publishing and patenting between universities, public research organisations and private companies. Therefore a culture of collaboration already exists.
- increased development of specialists at various stages in the R&D process and the move by all actors to exploit resources and leverage their own comparative advantages by way of deals, alliances and contracts provides opportunities to conduct R&D ‘virtually’ by way of a network of actors.
- there are success stories of small biotechnology companies getting products to market by way of a series of deals rather than through in-house resource or through a development deal with a major pharmaceutical company. There are also teams of researchers attempting to conduct R&D ‘virtually’ where their main contribution is a knowledge of the science and the technology, how the process works, and who the right partners are (e.g. Triangle Pharmaceuticals, The Medicines Company and Vernalis Group plc).
- our review of evidence suggests that key architectural competencies that are needed to conduct R&D can, in principle, be ‘acquired’ from the market for R&D.

Obstacles:

- costs, attrition rates, time to market remain high and there is no evidence that the move towards ‘network R&D’, and other technological advances in discovery and in basic science, have led to significant savings. In anything, costs and time lines may have increased over the past 15 years (CMR International 2000).
- success in discovery is contingent on realising spillovers that exist between projects within the same disease, between projects across

diseases and across types of organisations. It is unclear whether an integrating force, such as a large pharmaceutical company, is needed to realise these spillovers.

- despite the move towards use of the network, the major pharmaceutical companies continue to dominate in other critical areas – notably development, regulation, and marketing.

The specific details for each case are different but there are a number of common elements across the product development PPP's approach to R&D.

First, our PPPs seek to make strategic investments in a portfolio of projects from a range of stages in the R&D (in part dictated by the gaps and the projects on offer).

Second, they seek to establish innovative intellectual property contracts that allow them to both incentivise industry involvement and retain control over the pricing and distribution process for success products.

Third, they work to monitor and assist partners to ensure their projects retain research priority and make progress.

Deals are used strategically to move the products through the process as quickly and cheaply as possible. Though alternative routes exist, the models all ultimately seem to depend on the PPP being able to do a late stage development deal with a major pharmaceutical company.

Finally, the PPPs utilize their in-house resources and their position within the global health and disease networks to reduce total R&D costs.

4.4.2 'Social' venture capitalists

The PPPs explicitly distinguish themselves from 'grant givers' using the title of 'social venture capitalists' instead. Like traditional venture capitalists, they are in the business of assessing the field of projects and proposals, and selecting those that best fit their criteria for funding. Once selected, however, the projects receive funds but also assistance in managing their work, accessing related technologies, setting up clinical trial sites, and so on. They are thus more interventionist than a venture capitalist. Like venture capitalists, the PPP's own success

depends on the success of their investments. Instead of exchanging funds for equity in the company, however, the PPPs provide funds and management resources in exchange for ‘guarantees’ that the product developed will be ‘accessible’ to patients in less developed countries once approved for market.

For example, the ‘IAVI concept is to invest in companies or academic labs with good ideas, then do everything possible to help them succeed including orchestrate clinical trials, coordinate regulatory approvals, work to establish purchase funds and distribution systems. In return, partners pledge to sell (or license) their products simultaneously in rich and poor countries and offer break even prices in the developing world while reaping higher profits elsewhere’ (Cowley, 2001).

The Types of Projects Sought

The types of products any one PPP seeks out and selects depends on an analysis of the disease specific needs, the state of the science, and the gaps in the R&D pipeline. The primary concern of MMV, for example, is the growing rate of disease resistance faced by the top of the line malaria drugs currently used in the developing world, combined with the lack of new drug projects in the pipeline. It strives, therefore, to develop a complete new pipeline by building up some early discovery work but also by funding later stage development projects. To meet its goal of cheap, easy to use drugs, its selection criteria also includes questions of how easy the product would be to manufacture, how much that would cost, and the dosage regime.

GATB has a two pronged strategy: to address the gaps in late discovery and pre-clinical phases where no research is going on and to license-in later stage candidates currently ‘sitting on company shelves’ for accelerated development through other public or private partners. Any product receiving funding must meet one or more of the following criteria:

- shorten or simplify TB treatment. This will improve patient compliance (and hence treatment efficacy) as well as potentially reducing the total cost per treatment episode;
- provide a more effective treatment of multi-drug-resistant TB; and

- improve the treatment of latent TB infection.

IAVI's scientific programme seeks to accelerate the development of new and innovative AIDS vaccine designs and prioritise the best candidate vaccines for large scale efficacy testing where the epidemic is spreading fastest in the developing world. IAVI's emphasis on product development and targeted research is intended to complement national AIDS vaccine research programmes, which have focused primarily on basic research. Vaccine candidates that focus on HIV clades of the type predominant in the developing world and explicitly involve a north and south partner take top priority.

MVI also focuses on vaccine development rather than discovery. By funding a set of projects in parallel based on a range of different approaches and technologies, it seeks to speed up the entire process, as well as be in a position to co-ordinate work across the projects in their pipeline.

The Types of Partners

Our four PPPs have also targeted and worked with different types of partners. Some of this stems from strategic planning but it also reflects opportunistic recognition of the kind of actors doing research at all in these areas and who are motivated by the PPP's package to do work with them. In the end, however, success will depend on the PPPs being able to incentivise the 'right' combination of companies and organisations to participate. As we established in Chapter 3, while somewhat fluid, there is an identifiable division of labour between public researchers, biotech companies, and major pharmaceutical companies. The most productive R&D organisations have been those that have been able to identify and integrate effective sets of contributions.

Thus far MMV has funded major pharmaceutical company/university collaborations, where the company has contributed in-kind resources and the university the lab space and scientists. The composition of its pipeline might change as it seeks later stage projects, although its second round of projects also includes no biotech-company led deals. The former Chief Scientific Officer speculated that this may be because major companies may be more

willing to hand over rights to intellectual property in the early discovery stages than biotech companies (Interview, Rob Ridley).

IAVI has had the opposite experience. It has thus far failed to do any deals with large pharmaceutical companies working in AIDS vaccines and has so far only partnered with small biotech companies. The difference may in part reflect the state of the science and the types of actors engaged in the two diseases. AIDS vaccines may rely more heavily on the types of new technologies the biotech companies are working in. The difference may also lie in types of deals the two organisations are willing to do (see below). MVI is the only one that has so far established a partnership exclusively with a major pharmaceutical company – GSK in this case.

GATB has to date only finalized one deal but its strategic plans resemble the MMV model where early stage projects are done in collaboration with academic and public researchers supported by industry partners.

4.4.3 Managing the portfolio

The R&D departments of the PPPs, in collaboration with project specific technical assistance committees, monitor the projects. They provide disease, market, and institutional assistance as well as managerial resource. The PPPs must continue to evaluate their pipeline and funding strategies in the light of scientific developments outside their organisations. It is possible that they will at some point need to readjust their priorities in terms of gaps in the pipeline and specific modes of action. Contracts must include escape clauses for both partners. If a company partner wants out for commercial rather than science/effectiveness/cost-effectiveness reasons, the PPP should regain control of the specific IP. As mentioned above, however, for the PPP to be able to license the project on to a new partner it must get rights to background technologies the original partner may have been using as well. It is not clear how the contract would be handled if the PPP wanted out of a contract – i.e. what would happen with the IP.

A critical skill that the PPPs will have to learn is to manage failure. Some analysts have expressed concern that the publicity that has surrounded the establishment of each new project and the pressure to

succeed may lead PPPs to hold on to projects longer than they should. At the same time, they need to demonstrate to industry that they can operate a R&D programme professionally and cost-effectively. While an early failure might set them back, failure to shut a project down when they should would have worse repercussions as it will raise questions about their ability to manage their funds and their projects. Working in their favour is the fact that all the PPPs have more than one project in the pipeline.

4.4.4 Moving through the R&D process

MMV and IAVI both claim that ‘if they had to’ they could bring a product to market on their own. This does not necessarily mean paying for the whole thing if they could find contract research and manufacturing organisation partners who would accept contracts that were linked to future product revenues as well as doing deals of some kind with other service providers to get the product through clinical trials and manufacture. The best case scenario, however, and the one upon which the PPP’s cost and budget estimates is based, is that they be able to do a deal with a major pharmaceutical company at least by Phase III of the development process. We have established in Chapter 3 that these companies have clear competitive advantages in these areas both in terms of resources and know-how. Trying to learn and duplicate these would be expensive and time consuming.

The PPPs are optimistic, at least at this early stage, that they will be able to make a good case to pharmaceutical companies by the time products reach this point. MMV for example, assumes that a pharmaceutical company that licenses in one of the malaria drugs after Phase II (so all the costs up to this point are covered by MMV and its partners) will be able to make a small profit by bringing the product through Phase III and regulation to the market. This calculation is based on specific assumptions that the new product is more effective than those already on the market and that the company can capture a large share of the ‘paying’ traveller’s market as well as selling at cost to the developing country market.

In reality, the PPPs probably depend on other policies and programmes to enhance the attractiveness of neglected disease markets

64 if they are to hope to find major pharmaceutical company partners. We return to this issue in section 5 when we set out our conclusions.

4.5 Funding and cost savings

4.5.1 Funding

A key task is raising money to initiate the R&D process. As we discussed in Chapter 3, the average drug or vaccine can cost up to \$800 million to get from the lab to the market. It is not the intention of any of the PPPs to finance the entire process for any of their products. Their goal is to invest strategically, to establish new discovery projects, to jump-start stalled or shelved projects and to advance the field of science in the specific diseases. They hope that the money they put in will have positive multiplier effects and attract additional corporate investments. But the management teams do need to determine what share of which stages they will help finance and think about where the rest of the money is likely to come from.

MMV aims to spend \$30m per year from 2005 on its research programme. Discovery projects receive between \$0.5m and \$1.5m for two years, development projects more. But even with its optimistic estimate of total cost in the range of \$150m per drug, the work will only succeed if its money is matched from other sources.

The PPPs have made a good start in their fund raising efforts though all, with the exception of MVI, are well short of their 2005 targets. MVI is the exception because its model and current goals have for now been based around the \$50m budget provided by the Gates Foundation. Gates has been the largest contributor to the other three cases as well. Gates has invested \$126 million over 5 years in IAVI alone. Table 4.1 shows Gates' donations to product PPPs.

A critical question going forward is whether there is enough goodwill and 'public' money out there for the PPPs to meet their funding targets (Albert B.Sabin Vaccine Institute, 2000). As more PPPs are established, concerns about donor fatigue and the drying up of new foundation and government funding sources seem justified. However, like biotech companies, the PPPs hope that money plus some early

results, will bring more money. As they mature, PPPs may also widen their net and seek corporate as well as public donations. In addition to increasing their research fund, securing support from a corporation such as a venture capitalist or investment bank could have a positive knock-on effect of helping to encourage the biotech and pharmaceutical companies to participate.

4.5.2 Cost saving by using the ‘global health’ and ‘industry’ networks

There are two issues regarding cost. One, mentioned in the finance section above, involves the question as to where the total sum of money to pay for the entire R&D process will come from. The second relates to the different PPPs’ estimates of how much money it will cost to bring products to market. All assume it will be a fraction of what it currently costs large pharmaceutical companies.

Some expected savings are linked to the unique role that the PPP can play within the R&D process. It can, in principle, help disseminate information and know-how across the projects in its pipeline (although major companies also seek to do this – and appear to succeed, as we found in chapter 3). The management team can also help co-ordinate the pooling of ideas, technologies and partnerships to create new, more effective development solutions. IAVI, for example, seeks to cut development times by pursuing a new model of clinical trial development where Phase 1 and 2 studies are conducted in parallel. Finally it has been suggested that the PPPs may be able to improve R&D success rates because of their disease focus and in-house skills and expertise.

Potential savings may come from conducting clinical trials in the developing world (and product destined for these populations will have to be tested there) though products with a ‘western market’ will need to be tested in the developed world as well. The FDA is unlikely to approve a product based on developing country clinical data. But, as with orphan drugs, opportunities to qualify for fast track exist. In the MMV case, in-kind contributions from industry are expected to save costs, as is the fact that malaria targets are known which allows them to skip some of the early, lengthy discovery searches.

4 PUBLIC PRIVATE PARTNERSHIPS ASSESSED

66

Table 4.1 **Bill and Melinda Gates Foundation contributions to PPPs**

Date	Amount (\$m)	Recipient
04/10/98	1.5	IAVI over 3 years
08/26/98	125	PATH over 10 years for Children's Vaccine Programme
03/22/99	25	IAVI over 5 years
04/01/99	50	PATH over 10 years to support Malaria Vaccine Initiative
08/04/99	25	Sequella Global TB Foundation over 5 years for TB International Vaccine Collaboration
11/22/99	40	International Vaccine Initiative, Korea over 5 years for vaccines; B cholera, dysentery, typhoid B
12/07/99	750	Global Fund for Children Vaccines over 5 years
02/28/00	25	Global Alliance for TB over 5 years
03/15/00	25	Medicines for Malaria Venture over 5 years
03/15/00	18	Albert Sabin Institute for recombinant hookworm vaccine
01/27/01	100	IAVI challenge grant
08/14/02	4.6	Institute for One World Health to fund two projects

Source: www.gatesfoundation.org/about/grantlist.asp

Savings of some two thirds of costs i.e. \$500 million per drug (reducing our estimate of \$800m to \$300m) would certainly ease the funding pressure and improve the PPP's chances of finding a commercial partner to conduct the large scale clinical trials and approval phases. In the ideal scenario, these savings would allow a company to sell the products at affordable prices and still earn some profit.

4.6 Deals and intellectual property

Arguably the most important strategic tool is the partnership research contract and in particular the intellectual property ownership conditions. In the contract, the PPP can specify what it expects from the company in exchange for the funds. A win-win balance must be found. The PPP must be assured that its money will be used efficiently to further research in the global health problem of focus. At the same time the company needs enough leverage to use these funds to help further its own goals – to earn profits.

The critical negotiation point is that over the ownership of IP – both IP created with the PPPs resources and background IP that is essential for the production of the product (International Vaccine Initiative, 1999).

We have established in Chapter 3 that IP is a key weapon for pharmaceutical companies in their pursuit of products and ultimately profits. PPPs must be as aggressive in the way they use IP as any commercial unit but for a different purpose – namely to pursue their social objective of getting quality, affordable products to developing country patients. This involves the negotiation of creative IP arrangements that do not scare off companies but also allow the PPP enough control to ensure their ultimate objective, a difficult challenge. The basic strategy has to be:

- keep what you find. So MMV owns (or shares ownership) of any of the IP created through research it has funded;
- trade over any developed market for control of sales in developing country markets. So IAVI's commercial partners can retain control of the IP to use in the 'paying world' provided that IAVI has access to it to meet demand in the developing world;
- establish explicit volume deals with the company partner so that if the company does not want to manufacture the product at volumes needed to meet the developing country need, the PPP can get rights to the process and use contract manufacturing organisations to meet the supply needs;
- Trade any other disease use for control of the IP for the neglected disease. An alternative option, especially for diseases where the

‘paying market’ is low or non-existent is to give the company partner the right to the PPP funded IP in all but the neglected disease of focus;

- if the partner chooses not to use the IP in pursuit of the designated product, the PPP has the rights to take it back. The PPP therefore has the right not to be held up. IAVI has also tried to arrange contracts where if the product reaches a late stage and the company chooses not to continue development that it also gains access to any background patents it needs to be able to produce the product and continue development through a new partner;
- explicitly address the issue of royalty rights for products sold in the paying markets. Again, using the MMV example, it expects a share of any royalties coming back from IP its funds create. In cases where the IP already exists, prior to the company entering into a deal with MMV, it is more likely to negotiate control over the developing world market only, leaving the paying market to the partner as discussed above;
- clearly determine the IP rights and conditions up front. In an early deal with an academic institute, for example, one of the PPPs took the attitude ‘we’ll sort the IP stuff out later’. The problem is that the research programme now involves a university, the funder of the early university research, the PPP that also contributed funding, a biotech company that has since been created based on the university research, and a device company whose technology they seek to combine with the product in clinical trials;
- when in-licensing products or technologies, seek to control rights to out-source the project to third parties.

PPPs are breaking into completely new territory with their IP negotiations. Some experience can be learned from biotech companies, especially platform technology companies, which are in the business of doing multiple deals with different companies, licensing out the use of their IP. But the conditions PPPs place on IP negotiations – price guarantees, volume guarantees, market specifications – are new and risky. In IAVI’s case, the IP agreements are also used as a mechanism to avoid delay in the introduction of vaccines to developing countries (in previous cases more than 10

years), by insisting that any vaccine will be made simultaneously available in developed and developing countries.

Companies might fear that if they enter into a deal with one of the PPPs, especially one that combines the PPP's IP and some of their own background IP, and early tests fail, that this will limit opportunities to use the background IP for other uses. This is a risk companies take in any collaborative deal but the perception is that there are more risks in doing such a deal with a 'public good' based organisation. Second, and linked to this, is the fear that the PPP will breach the confidentiality agreements and transfer the knowledge they learned in a commercial deal to other ones. 'If the PPP knows it, everyone else will' (Interview, Lita Nelsen, May 2001).

Another potential problem is the fact that PPPs expect to need to do a series of deals with different partners to get products to market. It is therefore important for the PPP to hold on to IP rights in the early stages, so as to have more to bargain with in the late stage when a major pharmaceutical partner is especially important. In cases where the IP has been split across diseases, IAVI, for example, must retain the rights to the IP for the HIV vaccine so it can license it out later.

Biotech companies need money and funding, especially if it helps validate their technologies that may be relevant for other diseases. So cash is a positive incentive. The same can not be said for major companies. Money is not enough. So the challenge is how to make it attractive for major companies to do deals.

4.7 An assessment of performance to date

The PPPs have common aims and comparable organisational structures. All are putting research portfolios together and setting targets. Yet final outcomes are some way ahead, and difficult decisions will need to be made – for example about priorities, choice of partners and closing down failing projects. How should the performance of PPPs be evaluated? Both the progress of PPPs towards their specific goals and the efficiency of the PPP model need to be assessed. However, as relatively few projects have been brought to market in these diseases by other methods it is difficult to find a base line model

to compare the PPP model to. Ideally we would track the progress, time and costs of a product through a commercial model, a PPP, and perhaps through a Tropical Disease Research (TDR) type model (which involves an inter-governmental organisation undertaking in-house work and then contracting work out to private companies). It is unclear whether we could effectively isolate the impact of the R&D process from the differences in priorities and goals that underlie the different models. That might especially be an issue when comparing the PPP and the commercial model. Table 4.2 sums up a number of key differences in the way PPPs and commercial companies conduct R&D.

To track the progress towards meeting goals, intermediary indicators are needed in the absence of any complete projects. Drawing on the methods used to evaluate biotech companies not yet earning profit, indicators for PPPs should include:

- the size, quality, and state of development of the products in the pipeline;
- the type and number of successful deals and alliances;
- the calibre of the partners;
- the reputation and reliability of the board;
- the amount of funds raised and from what sources.

Given the relatively short period of time since their founding, the PPPs in this study have made extraordinary progress in the areas of fund raising, position appointments and project contracts, especially given the obstacles they face.

In total they have raised close to \$500 million in pledges. The Gates and Rockefeller foundations have been among the top donors. The UK and the Netherlands have made the largest country contributions. In the next five years the PPPs need to double this sum.

All have initiated a number of research projects, GATB closing a deal with Chiron for their first TB product in the spring of 2002. MMV has great expectations of having a relatively 'full' pipeline by the end of 2002; IAVI has five partnerships in process with a sixth in negotiation. All of these involve a north and a south partner. Two have already moved from pre-clinical to Phase I clinical trials. According to Jon Horton (formerly of GSK and currently a member of the GATB

Table 4.2 The PPP vs commercial models of R&D

1. IP arrangements – IP assignments in the PPP are linked to ultimate goal of producing affordable, accessible products. In discovery stages, ownership is sought by the ‘funder’ (i.e. the partnership), rather than the finder as is more commonly the case (traditional grant givers don’t expect something in return; traditional venture capital investing in biotech companies look for share in the company rather than IP; the PPP seeks share of IP for their purposes). In the development stage the PPP seeks control of IP for the specific disease (i.e. the company partner retains use for other diseases) or it looks to split the market (the company partner retains control for the non-developing country markets).

2. The Go-No-Go decisions – Scientific reasons dominate the decisions about whether to continue funding a project in the PPP but other features are also important, namely the cost to manufacture, the ability to deliver, affordability, dose regime. An open question is the extent to which PPPs are also taking the relative costs of one product versus another into account. Earning profit is not the issue – but money will always be limited. Will the public goal of improving global health infrastructure more generally interfere in funding decisions? Should, for example, clinical trials for a product in South Africa continue despite poor findings because the investments are helping to build up the clinical trial infrastructure? Or given the severity of the AIDS problems in the developing world, should different ‘efficacy’ standards be applied to the vaccines?

3. Board decisions – In addition to R&D strategy decisions, these boards will eventually need to make ethically difficult decisions about who gets the product first, who will have to pay and who gets it for free etc. In pursuit of their public goals, the PPPs struggle with the question of their responsibility and participation in non-R&D responsibilities; and their interchanges in political arena.

Scientific Advisory Committee), there has been immense show of interest in the GATB programme as well with more than 100 letters of interest in response to the call for proposals. MVI has also already committed a sizable share of its budget on projects. See Appendices 8-11 for complete pipeline detail.

MMV and IAVI present models that, at least on paper, have the potential to save R&D costs for these specific diseases, as compared to the \$800m industry model. Time will be cut and costs at each stage reduced.

The four have been able to attract top people to their key CEO position and present strong teams with business, science, developing world and NGO experience represented. The calibre of board members is also noteworthy.

That said, many problems and uncertainties remain. Most have been mentioned already but to summarise.

It is unclear if the PPPs will be able to meet their funding targets in an environment where the top philanthropic foundations have already contributed and are under constant pressure to give more to ever growing number of different initiatives. The real challenge is to bring in new types of funders and expand the total pot rather than compete for shares in the existing one.

As the pipelines mature, the staffing requirements will also evolve and so the PPPs are under continued pressure to hire and retain top quality staff. This means paying salaries competitive with industry rather than with global health organisations, an approach that has caused some friction between the PPPs and their supporting international aid and health organisations.

Another important issue regards the duplication of skills. An important question is how much does the PPP need to be able to do in-house and how much it can rely on outside organisations and services to fill the skill gaps? How should MMV work with TDR and RBM for example, or GATB with Stop TB? How should their respective activities be divided up?

The pharmaceutical industry has expressed enthusiastic support for the PPP concepts as an alternative way forward towards solving the R&D problem. But not so clear is the extent to which major companies are prepared to participate at a level that is needed for the R&D goals to be achieved. MVI is the only PPP so far to complete a product deal with a major pharmaceutical company, GSK in this case. Factors keeping companies out may include continued uncertainties about the IP arrangements as well as the political and public positioning of these PPPs.

Linked to this problem, therefore, is the fact that none of the PPPs really know whether they will be able to do deals with industry to manufacture to scale any of their products or to cost-efficiently conduct late stage development. All their strategies depend on major company involvement at this stage.

There is also a question as to whether the ever growing number of initiatives produces a risk of duplication (PIU, 2001). This would not be a problem if resources were not so limited for these disease areas as a mix of 'competition' and co-operation in disease R&D often leads to greater success in product development. One proposal is for certain in-house tasks such as IP management be centralised in an entity set up to help PPPs in these areas. However, this would prevent PPPs from learning from each other's experiences.

Beyond the technical accomplishments are the bigger questions of whether the PPPs are adding value to the partners, i.e. the public and the private sectors, and what the overall impact of PPPs on the global health arena will be. IPPPH has picked up both these questions. It seeks, for example, to establish ways to measure 'value added' by the specific partners.

According to Buse and Walt, (2000b), there are gains to be had from both sides:

For the public sector:

- partnerships with private sector are seen to have bestowed more business credibility and authority;
- extension of the UN's ability to fulfil its mandates through increased resources and
- access to private sector skills and management talents.

For the private sector:

- increased corporate influence in global and national level policy-making;
- direct financial returns in the form of cash but also tax breaks and market penetration as well as indirect financial benefits through brand and image promotion;
- enhanced corporate authority and legitimacy through association with the UN and other public bodies.

In summary, the first assessments suggest a win/win model. The

PPP's comparative advantages seem to include (though is too early to confirm):

- cost and time savings through the clinical trials network, possible LDC manufacture, and fast track regulation;
- higher success rates through disease competencies concentrated or at least linked in close networks, with the pooling of resources, technologies, and know-how across locations and projects;
- improvement in the environment for projects outside the PPP's pipeline – spillover effects in the form of information, market size calculations, lobbying for additional incentives, and others pumping funds into disease areas.

There are a number of unresolved or untested potential problems. First is the question as to whether conflicts will occur between the commercial model and goals and the public goal. Second, clear methods for dealing with product failure have yet to be produced mostly because the projects are all still too new to warrant the making of a go-no-go decision. Third, there are concerns about culture conflicts between the public health disease-focused actors driving the objectives, and the companies they depend on to do much of the work. To date, there has been insufficient 'input' from civil society – i.e. the ultimate customers. PPPs are an incomplete solution that depend on deals at later stages with large pharmaceutical companies to succeed. Finally there is the question of whether R&D can be effectively conducted through this model, a key issue given the apparent need for large integrator to facilitate the spillover effects between projects and across organisations.

Just as the PPPs are working to devise creative new ways of organising R&D by designing innovative IPR contracts, funding and alliance strategies, analysts of the PPPs need new tools to assess the organisation and performance of these models. The PPPs do, however, have a well-defined and focused mandate. Regarding their overall contribution or impact on the R&D problem for global health, the most important immediate questions for those concerned about governance and performance are, in our view, whether they are doing an efficient job at furthering the science and the product pipelines in line with their objectives and whether the boards and stakeholder

councils represent the people and organisations best suited to make sure that this is the case.

Despite the list of uncertainties, there seem to be good reasons to be optimistic, going forward, that the PPP model has the potential to make a real contribution to the global health R&D problem. That said, those considering the establishment of new product development PPPs, for example the WHO/IFPMA and MSF's discussions about what to do for leishmaniasis, African trypanosomiasis and Chagas disease, need to take seriously the practical concerns about their being enough money out there to fund new PPPs, especially for diseases with no rich country market at all, and also whether there are enough capable and willing people to sit on the boards and manage these organisations.

5 CONCLUSIONS

76

This paper has outlined the social purposes for which four ‘product development’ PPPs were established. It has discussed the way in which the R&D market place has been changing into a more dynamic model, and the (largely positive) implications of this for these and other PPPs of this type.

The key challenges that the PPPs face are numerous. Our analysis highlights in particular:

- organising their R&D collaborations to take advantage of the dynamic R&D market place;
- managing these activities effectively to deliver products to patients;
- ‘governance’, i.e. being accountable to stakeholders, including those less developed countries where the diseases they are seeking to tackle are prevalent. An important aspect of this is performance measurement – setting realistic targets and tracking progress;
- putting in place an intellectual property strategy that will help achieve the social purposes of the PPP;
- developing a viable financial model for both the PPP and for achieving access in LDC markets to new drugs and vaccines.

Our overall assessment of these four PPPs is that each has made substantial progress. That said, there is a long way to go before their ultimate goal, to bring new products to poor patients in developing countries is met and many uncertainties remain both about the ability of the PPPs to do this job and the ability of the PPPs to solve the bigger problem – the R&D funding gap. In this final chapter we set out our key findings in each of these areas.

Organising R&D

The dynamic R&D market place is characterized by:

- a new division of labour with an increasing number of public and private organisations with skills that can be bought to meet R&D requirements, opening up collaborative possibilities that did not exist even five years ago;
- a partnership of public and private organisations to accomplish R&D in any disease. Whilst public institutes tend to focus on the early discovery phases and private companies invest in all stages (but in particular control most of the know-how in the

development, production, and commercialisation stages in the process), there is an increasing overlap, with the private sector involved in ‘open science’ (publishing as well as patenting) and universities increasingly involved in patenting activities;

- evidence of spillover effects;
- evidence that the major pharmaceutical companies retain important integrative skills.

In establishing the organisational concept of the PPP, much can be learnt from private models especially how companies network and construct deals with different partners.

These characteristics have important implications for the PPPs. Namely:

- the ‘virtual’ approach is contractually feasible and gives each PPP maximum flexibility in identifying public and private partner;
- that there is a key integrative role that large companies appear to perform in the discovery area, there are also significant ‘spillover’ effects from different, but related R&D programmes. This means that the PPPs should not manage their discovery portfolios as separate discreet entities but should constantly be seeking complementarities across programmes;
- large companies continue to dominate commercialisation activities. There is evidence from the US ‘orphan drug’ markets that smaller biotech companies are able to bring products to market, but there are particular characteristics of these markets that may not be applicable to PPP target markets. This means that PPPs have to contract with large companies at some point, or develop substantial in-house co-ordination competencies if they are to manage these stages on a virtual basis.

Effective management

The main requirements for effective PPP management include the presence of high quality managers with commercial experience as well as decision makers with experience in the science of the disease and in the economics and politics of the global health system.

To date, the four PPPs have recruited high calibre people as executives and advisors.

5 CONCLUSIONS

78

The analysis of the four cases suggests a learning process over time by new PPPs from established ones. For example, we find shorter gestation periods and that the more recent PPPs have integrated a more representative set of shareholders from the outset. It is essential that the PPPs continue to learn from each others successes and failures as they progress.

Governance

Accountability is essential but there is an important debate about the form that this should take. The four PPPs in this study have similar objectives, which are reflected in:

- choice of projects and how decisions will be made about whether to move the product forward, award it with additional funding, or cancel it;
- choice of board members.

The trick is to keep a balance between the scientific expertise needed to oversee specific projects and the regional, political, financial expertise needed to pursue a successful PPP in these neglected disease areas.

A pluralist model is appropriate. It assumes that the government has policy objectives but seeks to achieve them by creating a framework in which civil society and a market economy can function. When the government is seeking to fund services it will use the private sector to provide them if it has the expertise to provide them efficiently and manage the contractual arrangements to ensure a 'win-win' situation for the public and private sectors.

Our conclusions are that the main emphasis in scientific committee and board representation must be on expertise rather than representativeness and that LDC involvement at the expert level is essential if products are to be useful in LDC programmes.

Performance measurement

An important discussion is that of how to evaluate the PPPs. Probably a number of indicators need to be developed. The PPPs need to be compared to other models of R&D for neglected diseases, where these exist, from the standpoint of efficiency and accomplishments. They

also need to be assessed on the basis of how well they meet their tasks of bringing products forward, using intermediate milestones to track progress.

Given the immaturity of these PPPs, one way to assess their performance is to rely on intermediate indicators as is done for biotech companies not yet earning revenue. These companies are evaluated for their pipeline, the type and number of alliances, the reputation and reliability of the board, the amount of funds raised through public and private channels.

Acknowledging that these are still early days for these PPPs so any assessment is necessarily preliminary, we find a number of positive trends.

The PPPs have successfully raised almost a half a billion dollars, about half of their targeted R&D funds for 2005. The Gates Foundation and the governments of northern Europe have made the largest contributions so far.

All have successfully initiated research programmes. MMV has introduced development stage projects in its second round of funding to balance the collection of early stage discovery and exploratory projects. IAVI's support has helped to move two vaccine products into Phase 1 trials. MVI has successfully done a deal with GSK to jointly complete Phase III trials on their malaria vaccine.

That said, considerable uncertainties remain about their ability to raise the rest of the funds and secure the deals they need, especially with large pharmaceutical companies to meet their product and cost targets.

Intellectual property

PPP's must pursue an aggressive IP strategy designed to maximise the social value of product and process patents. This can be achieved by:

- acquiring rights over all IP arising from projects directly funded by the PPPs;
- trading rights to rich country markets and use in other indications for low price access for LDC target markets;
- ensuring there are incentives to deliver to these markets – such as requiring simultaneous launch in rich and poor countries;

5 CONCLUSIONS

80

- providing incentives to supply sufficient volume to LDC markets;
- retaining reversion rights, should commercial partners not deliver on their commitments.

The evidence suggests that the PPPs are pursuing these strategies.

Financial viability

All of the PPPs presented here depend on major pharmaceutical company and/ or biotech company involvement in both R&D and commercialisation activities to succeed. For example, MMV assumes that the malaria market is large enough to make investments from Phase III onwards profitable. The other PPPs assume that additional incentives, such as a global purchase fund, are needed. Though companies' total R&D costs will be significantly reduced by their operating with a PPP (because the PPP is making up-front investment in discovery and because other costs, such as clinical trial costs, may be lower) these investments will still not be profitable in the late development and commercialisation stages without a market. So a combination of PPP and push/pull incentives are needed for success.

The amount of money PPPs need to bring products to market will therefore depend on two factors.

First, the extent to which there are other push/pull incentive effects is important. These incentives could be of three sorts:

- potential sales for the product in markets in richer countries, or in the richer parts of middle or low income countries where commercial prices (i.e. including a mark up to recover R&D costs) can be charged. Segmenting markets in poorer countries to identify the size of any potential submarket able to pay commercial prices is work that the PPP can assist with;
- the use of a global purchasing fund to purchase products for the target LDC populations, either at manufacturing and distribution cost or including some mark-up to recover R&D cost;
- other 'push' incentives, such as R&D tax credits for companies undertaking work on products for LDC diseases.

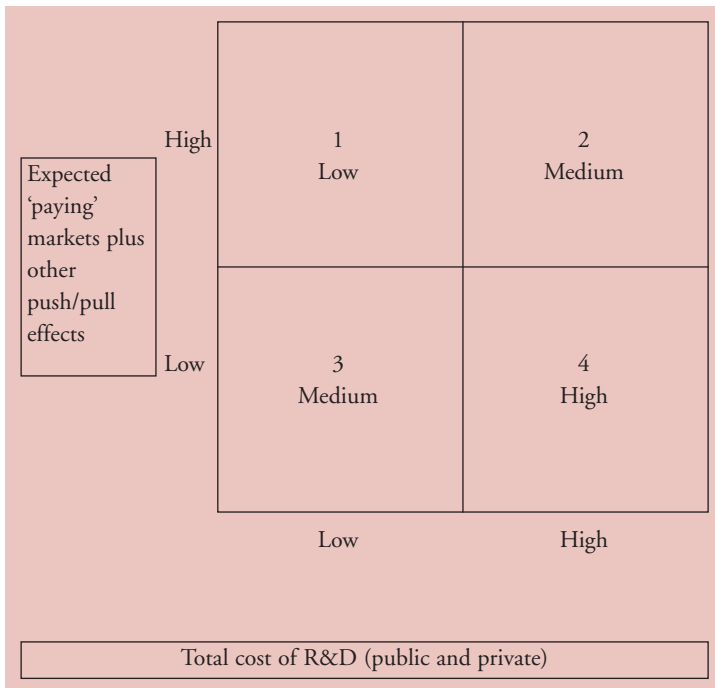
Second, how much money they need to raise will depend on the PPPs' ability to reduce the estimated average cost of \$800m to bring a product to market, by co-ordinating research efforts, reducing

5 CONCLUSIONS

attrition rates, time taken, the cost of clinical trials, and the cost of capital, and by obtaining fast track regulatory approval.

We can represent this in a simple two-dimensional matrix as set out in Figure 5.1. The two cost drivers for the PPP are whether the expected size of the ‘paying’ markets plus other push/pull effects (i.e. points (i)-(iii) above) are high or low, and whether the overall R&D cost (whether paid for by the PPP or by a commercial partner) is high or low. If markets plus other pull/push effects are low then the PPP has to fund much of the work itself. If, in addition, the cost of R&D is high, then the cost to the PPP is high. In the converse situation, with high expected paying markets plus push/pull effects and low total public and private R&D costs, the costs for the PPP of getting this product to market are low. Where both drivers are low, or both are

Figure 5.1 PPP requirements for funding a product



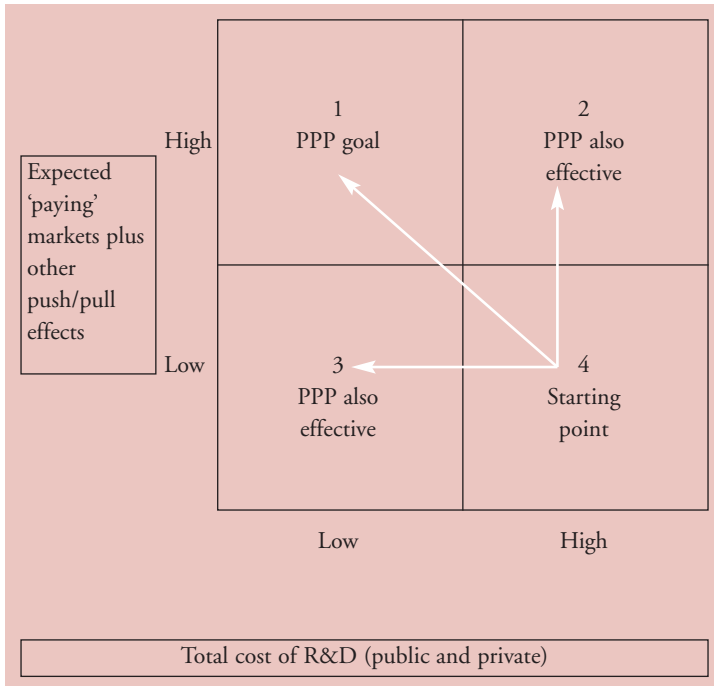
5 CONCLUSIONS

82

high, they should tend to offset each other and the PPP financial contribution is medium. We do not attempt to put figures on high, medium, and low.

We show in Figure 5.2 the direction of travel PPPs are intended to take. The starting point for the international community is quadrant 4. There is no commercial investment because the size of the expected market plus other push/pull effects are low and R&D costs are assumed to be high. The goal of each PPP is to move to quadrant 1 by reducing total (public and private) R&D costs and stimulating other pull/push effects. They may end up achieving only one of these and still be effective. If they achieve neither then, in effect, the PPP will need \$800m to develop a product. Even if it subcontracts all work to the private sector, it will have to pay them – and additional money

Figure 5.2 **Success criteria for PPPs**



will be needed to cover the costs of manufacturing and distributing the product in LDCs. It could be argued that if there is a product, where previously there was not, then the PPP is still a success. However, the expectation is that PPPs will not stay in quadrant 4¹³.

In conclusion, our view is that PPPs are in principle a valuable part of a total solution and that in practice the four PPPs we have examined are making substantial progress. But Governments cannot get complacent by assuming that the problem has been solved with the allocation of relatively small amounts of money to the PPPs. The international aid organisations and NGOs, likewise, must not only support PPPs but also continue to support new initiatives such as the Global Fund for Aids, TB, and Malaria, and lobby for other push/pull incentives to operate in these disease areas. PPPs are a viable model to tackle the killer diseases of the poor of the world, but they cannot succeed in isolation.

13 An exception may be very neglected diseases for which there is no market in either high or middle income countries. However, it may be possible to reduce R&D costs in these disease areas.

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List of Interviewees:

Jon Horton, ex-GSK and GATB

Robert Ridley, TDR/WHO

Roy Widdus, Initiative for Public Private Partnerships for Health

Lita Nelsen, MIT Technology Transfer Office and IAVI

Trevor Jones, ABPI

Win Gutteridge, ex-TDR/WHO

Seth Berkley, IAVI

David Phillips, Oxxon and IAVI Partner

Chris Henschel, MMV

APPENDIX 1

MEDICINES FOR MALARIA VENTURE (MMV)

Mission

The mission of MMV is to bring public, private and philanthropic partners together to fund and manage the discovery, development and registration of new medicines for the treatment and prevention of malaria in disease-endemic countries. (Source: CEO, MMV Annual Report 2000, <http://mmv.org>)

Its aims are to discover, develop and commercialise antimalarial drugs at prices that are affordable to the populations worst hit by the disease at a rate of one new product every 5 years. (Source: Introducing MMV, <http://mmv.org/about.htm>). According to MMV's Draft Business Plan (March 2000), this will be achieved by:

- funding and managing cost-effective research and development programmes for the development of new antimalarial drugs;
- and, through the use of public sector funds for drug development, making the commercialisation of antimalarial drugs more attractive and less risky for the private sector.

Background

Disease rationale

Malaria is estimated to kill over 1 million people worldwide each year, disproportionately affecting children under 5, pregnant women and the poor.

MMV was created because the increased cost of developing and registering pharmaceutical products, coupled with the prospects of inadequate commercial return, have resulted in the withdrawal of the majority of research-based pharmaceutical companies from R&D investment in tropical diseases, and especially from discovery research activities. (Source: Dr Gro Harlem Brundtland, WHO Director-General, Press Release Nov 1999, <http://mmv.org/press1.htm>)

At the same time, drugs for treating and controlling the symptoms of malaria are losing their efficacy as the malaria parasite builds up resistance to them. With no prospect of a malaria vaccine in the foreseeable future, MMV's stated focus is the development of new drugs, which are affordable to communities in areas of high malaria transmission.

History

MMV was established by founding partners WHO and IFPMA, and originally operated under the umbrella of the WHO Roll Back Malaria Programme. The establishment of MMV was the culmination of several years of discussions between the industry and international development agencies, in recognition of gap between the need for new malaria drugs and the withdrawal of research-based pharmaceutical companies from tropical disease discovery. The need for an organisation such as MMV was identified through a dialogue between the WHO and pharmaceutical industry leaders, and specifically through a series of roundtable discussions which commenced in 1998. It was the first public-private partnership of its kind established to tackle a major global disease.

To underline its independent status, MMV was established as a not-for-profit Swiss Foundation under statutes dated 15th November 1999. It is located in Geneva.

Strategy and pipeline overview

Strategy and role

MMV operates as a 'virtual' not-for-profit business to develop and discover affordable and appropriate antimalarial drugs for disease-endemic countries. It has created a 'public venture capital fund' to solicit and resource, on a competitive basis, drug discovery projects. The funds for the public venture capital fund will come from governmental funding agencies, foundations, and philanthropic donations. The pharmaceutical industry will contribute in kind (access to combinatorial libraries, high throughput screening systems, laboratory space, and so on).

The aim is to create a portfolio of properly resourced projects on a par with industry-run discovery projects. The most promising development candidates will be fed into a 'virtual' drug development unit, financed and administered by the MMV, capable of taking compounds through to registration. At the appropriate stage during development (usually after proof of principle Phase 2 clinical studies), MMV will seek industry partners for product commercialisation. MMV has stressed that it does not plan to produce and commercialise products itself, but to take compounds through the regulatory process, in partnerships where possible, and license out successful products for late stage clinical trials, and for manufacture and marketing.

MMV has a competitive project selection and review process. To help

identify the best projects, and then to add value to those projects, MMV has assembled an Expert Scientific Advisory Committee whose members come from both industry and academia. MMV has used an open call for project proposals, and attracted 101 proposals in the first round and 87 in the second round. Once a project has been selected, MMV plays a role in helping to shape its goals and mode of operation, and continues to support and monitor the project as it progresses. There remains a strong competitive element to the process after selection, with continued funding dependent on progress and subject to competition from other MMV projects.

The MMV and its academic and industry partners will jointly own the intellectual property rights of any compound patented through this process. The major goal of any licensing agreements will be the commercialisation of products for low-income populations. A royalty income may accrue to MMV on products that earn significant returns for its partners. These returns will be fed back into MMV's fund to offset the need for future donations.

Pipeline and funding

MMV's main challenge, according to its CEO, is to build its pipeline, ... 'and given the inevitably long timelines before new medicines can actually be registered, its [MMV's pipeline's] robustness and scientific credibility will constitute our main deliverable for several years to come'. (Source: Press Release, June 2001, <http://www.mmv.org>)

MMV's strategy is to build on existing scientific knowledge and experience. MMV is currently funding three exploratory projects and four discovery projects for USD 4.2 million in 2001. A total of eight new projects approved for potential funding in 2001 have just been added to this pipeline, bringing the total project funding up to approximately USD 10 million for the current year. (Source: MMV Press Release, June 2001, <http://www.mmv.org>) The funding target for 2002 is USD 16 million, and USD 30 million by 2005. (Source: Press Release, Jan 2001, <http://www.mmv.org/press2.htm>)

MMV expects to be able to bring new antimalarials to market for a cash outlay of some USD 150 million, complemented by substantial 'in-kind' support from the pharmaceutical industry. If funding targets are reached, it is expected that the first product to be generated by MMV will be commercially available before 2010. (Sources: TDR Press Release, May 2000 and Introducing MMV, <http://www.mmv.org/about.htm>)

APPENDIX 1

Current MMV stakeholders include the Bill and Melinda Gates Foundation (recently granted USD 25 million over 5 years), ExxonMobil Corporation, IFPMA, Global Forum for Health Research, Netherlands Minister for Development Corporation, Rockefeller Foundation, Swiss Agency for Development and Cooperation, UK DFID, WHO – RBM and TDR, and the World Bank.

APPENDIX 2

INTERNATIONAL AIDS VACCINE INITIATIVE (IAVI)

Mission

IAVI is a global organisation working to speed the development and distribution of preventive AIDS vaccines. Its mission is:

‘To ensure the development of safe, effective, accessible, preventive AIDS vaccines for use throughout the world’ (Source: IAVI 2000 Year-End Progress Report)

IAVI has a particular focus on the development of vaccines suitable for use in developing countries, where the majority of AIDS cases are. IAVI’s work spans four areas: mobilising support through advocacy and education; accelerating scientific progress; encouraging industrial participation in AIDS vaccine development; and assuring global access.

Background

Disease rationale

Since the beginning of the AIDS epidemic, more than 53 million people have been infected with HIV and more than 21.8 million people have died from AIDS. AIDS now kills more people worldwide than any other infectious disease, and there were an estimated 5.3 million people (including 600,000 children) newly infected with HIV in the year 2000.

More than 95% of all new infections are in developing countries, making HIV/AIDS among the most serious threats not only to global health, but also to global development.

Scientists agree that a preventive vaccine is the best hope for ending the epidemic:

- prevention programmes, including education, condom and clean needle distribution have slowed the spread of HIV, but have not stopped it;
- treatment advances have yielded important new therapies, but their cost and complexity of use put them out of reach for the majority of people in countries where they are needed most.

Despite some very limited progress towards the development of a preventive AIDS vaccine, IAVI believes that there remain significant scientific, political, and economic obstacles. According to IAVI, for example, vaccine research and development commands only about 2% of the USD 20 billion the world spends annually on AIDS prevention,

research and treatment. Moreover, the research effort to date has focused on creating vaccines for industrialised countries, even though more than 95% of 15,000 new infections each day occur in developing countries where there is little access to treatment.

History

In 1994, in the face of an escalating AIDS epidemic and no progress on the development of an AIDS vaccine, the Rockefeller Foundation convened an international meeting in Bellagio, Italy, to bring together scientists, public health officials, and leaders from the pharmaceutical industry and non-governmental organisations to look at ways to move AIDS vaccine development forward.

The Bellagio meeting concluded that there was a gap in applied vaccine development, and, in addition, pointed to a lack of a co-ordinated international scientific and funding strategy. To address these, participants called for a new global initiative whose sole mission would be ‘To ensure the development and availability of safe and effective preventive HIV vaccines appropriate for use throughout the world and, in particular, in those areas most affected by HIV and AIDS’. The Bellagio meeting recommended that both a scientific and a business plan should be developed for the Initiative. Accordingly, two further international meetings were convened:

- The first, held in Paris in 1994, focused on the scientific agenda. An initial seven year scientific research agenda was proposed, with the objectives of:
 - proving a safe and effective HIV vaccine can be produced;
 - developing preventive HIV vaccines that are appropriate for use in developing countries.
- The second, held in New York in 1995, focused on the options for increasing industry involvement in HIV vaccine development, and on financial and structural issues. At the outset, it was recognised that the Initiative would need to focus on two fronts:
 - directly funding research and development activities;
 - creating a more enabling environment for HIV vaccine development. Specifically, working with a range of public and private bodies to resolve issues identified by industry as barriers to HIV vaccine development.

IAVI was established as a non-profit making scientific organisation in 1996. It is located in New York.

Strategy and pipeline overview

Introduction

The ultimate aim of the IAVI is to ensure that a safe and effective preventive HIV vaccine is developed and distributed worldwide to those at greatest risk of infection in the shortest time possible. At the outset it was recognised that in order to achieve this, IAVI would need to be run and managed along the following lines:

- to stimulate sufficient private sector interest, IAVI should be involved in what was described as the ‘push’ component i.e. supporting targeted research and the ‘pull component’, creating a more enabling environment for HIV vaccine development;
- IAVI should focus on vaccine product development and not on basic research. In addition, a number of approaches should be pursued in parallel until a definite choice can be made between alternative strategies;
- IAVI would not conduct research or development itself, but rather award contracts or grants to the most appropriate companies, universities and research institutions. This would also allow it to be a small and flexible organisation;
- funding was initially most likely to come from philanthropic funds. However, as progress is made in the development of a vaccine, it may be possible to draw on other funding sources;
- there was a need for IAVI to have a wider remit than just funding and research. Other roles envisaged for IAVI included monitoring progress in vaccine development in order to facilitate information exchange and communication between organisations working in the field, and developing a global education/information campaign aimed at educating the general public, politicians, financiers and other key parties about the need for vaccine development.

IAVI currently has four key programmes. Summaries of these are given below. (Full descriptions and back-up materials are available through IAVI’s website – <http://www.iavi.org>)

1. Scientific programme – accelerating the development of AIDS vaccines for the world

IAVI’s scientific program seeks to accelerate the development of new and innovative AIDS vaccine designs and prioritise the best candidate vaccines for large scale efficacy testing where the epidemic is spreading fastest in the developing world. IAVI’s emphasis on product development and targeted

research is intended to complement national AIDS vaccine research programs, which have focused primarily on basic research.

Recognising that most vaccine development expertise resides within private industry, IAVI seeks to develop strategies that encourage increased involvement of pharmaceutical and biotech companies in AIDS vaccine development. IAVI aims to move candidates into clinical trials faster than would otherwise be possible.

There are three key areas within this programme:

- **Vaccine development partnerships (VDPs).** These are the cornerstone of IAVI's scientific programme, and are designed to move promising experimental vaccines into clinical trials as rapidly as possible. VDPs link researchers from academia or biotechnology companies with vaccine manufacturers and with clinical researchers in developing countries. Beyond providing funds, IAVI also brings in expertise, as needed, in areas ranging from project management to regulatory affairs and infrastructure for clinical trials. In selecting which experimental vaccines to move forward, IAVI looks for novel approaches that have shown significant promise in non-human primates and can progress to clinical trials within approximately two years. The candidate vaccine is then tailored to match the predominant HIV strain in the VDP's developing country (where clinical trials will take place) – a mechanism which ensures that vaccines are developed for the world's poor nations and not just for the profitable markets in industrialised countries. The IAVI currently has six VDPs in place [excluding Maxygen].
- **Intellectual property agreements.** In keeping with its mission to secure HIV vaccines for use throughout the world, IAVI has secured unique intellectual-property and technology-transfer agreements. IAVI invests 'social venture capital' which enhances the value of its partners' intellectual property, and in return seeks a commitment that a successful vaccine will be provided to the poor in developing countries at a reasonable price. Under the IP agreements, partners usually retain rights to the products in profitable markets. The IP agreements are also used as a mechanism to avoid delay in the introduction of vaccines to developing countries (in previous cases more than 10 years), by insisting that any vaccine will be made simultaneously available in developed and developing countries.
- **Scientific blueprints for AIDS vaccine development.** IAVI has published two documents aimed at stimulating debate, building

consensus and guiding global scientific endeavour. The first, published in June 1998, outlined a global strategy to accelerate product development and human testing, recommending the creation of VDPs. This was subsequently updated with the publication of a second Scientific Blueprint in July 2000, in which IAVI called for an additional USD 0.75-1.0 billion over the next seven years for accelerated AIDS vaccine product development and testing.

2. Education and advocacy programs – Mobilising support for an AIDS vaccine

IAVI is committed to raising international understanding of and support for the need for an AIDS vaccine through education, advocacy, and outreach programs. IAVI works across sectors and across borders to influence the agendas of the scientific community, public health officials, governments, multilateral organisations, community-based organisations and others involved in global health and development issues. IAVI seeks to increase the prominence of vaccines on national and international agendas.

Current key activities include:

- **Vaccine trial preparedness in developing countries.** IAVI recognises that providing accurate and timely information to trial participants and the general public is a key to successful clinical trials. IAVI supports these efforts with advocacy and clinical trial information programs. Currently, IAVI funds programs in the UK and Kenya. The organisation is also working to set up programs in China, India and Uganda, all countries where large-scale clinical trials are likely to be carried out.
- **Outreach to policy and decision-makers.** By bringing together leaders from industrialised nations and those from the most highly-affected countries, IAVI helps to raise support among key decision makers for an international AIDS vaccine effort. IAVI's Call for Action on HIV Vaccine Development was signed by 83 organisations and presented to the G-8 leaders in June 1997. Since then 160 additional organisations have signed the Call. Advocacy by IAVI and other vaccine supporters led to U.S. President Bill Clinton's call for the creation of a vaccine by 2007.
- **Monitoring the state of AIDS vaccine research and development.** IAVI publishes a bimonthly *IAVI Report*, which is the world's only periodical devoted solely to chronicling AIDS vaccine research and

development. It has an estimated readership of 10,000 in 129 countries, and covers AIDS vaccine issues from both scientific and political perspectives. The Report covers the AIDS vaccine industrial sector and provides important information on these efforts not published elsewhere.

3. Encouraging Industrial participation in AIDS vaccine development

Industry's participation in the AIDS vaccine effort is critical. However, at present, there is little incentive for companies to invest heavily in this area, particularly in vaccines designed for developing countries. IAVI is working on a number of initiatives to improve market forces, including:

- providing public financing for vaccine development and testing, particularly for those with limited commercial potential;
- The World Bank, G-8 leaders, the EC and other international partners are working with IAVI to establish Vaccine Development and Purchase Funds – financial instruments intended to encourage the commercial sector's investment in the AIDS vaccine enterprise. A Vaccine Purchase Fund would create a guaranteed paying market of known minimum size in the developing world. By encouraging industrial investment in vaccine development, the Vaccine Purchase Fund may help to mobilise private capital and allow market forces to work, incorporating the efficiency of the private sector in creating vaccines for the developing world;
- IAVI also promotes legislation, such as *The Lifesaving Vaccine Technology Act* pending in the U.S. Congress, that would provide tax breaks and other incentives for private industry to invest in vaccine development.

4. AIDS vaccines for all: assuring global access

IAVI believes that simultaneous access to AIDS vaccines in both North and South must be addressed before a vaccine is developed, so that there is no delay in providing it to those who need it most. The aim is to put policies in place now and avoid potential delays of around 10 years for vaccines to be available in developing countries.

IAVI has proposed a number of mechanisms to achieve this, including innovative intellectual property rights agreements for its partners developing successful vaccines. In addition, IAVI published a blueprint document in July 2000, calling for a global action plan for AIDS vaccine

distribution that would assure timely use of preventive vaccines in all at-risk populations, regardless of where they are found.

Pipeline and funding

IAVI's pipeline comprises five VDPs with academic, government and industry partners. Most projects are at the discovery and pre-clinical stages. However, one VDP, the Oxford/Kenya Partnership, which involves collaboration between Oxford University in the UK and the University of Nairobi, Kenya, and which commenced in November 1998, has just moved to Phase 1 testing for its DNA vaccine.

IAVI's goal is to achieve a USD 550 million vaccine development workplan through 2007. As of January 2001, IAVI had achieved 40% of this, securing commitments for USD 230 million. (Source: Press Release, Jan 2001, http://www.iavi.org/press_/50/bill_and_melinda.htm) Over half of this funding will come from the Bill and Melinda Gates Foundation, which, following earlier donations of USD 1.5 million in 1998, and USD 25 million (over five years) in 2000, has subsequently issued a USD 100 million challenge grant to IAVI at the beginning of 2001. Other contributors include philanthropic organisations, including many AIDS charities, government and non-governmental organisations, and individuals. IAVI also received a recent donation from Yahoo! Inc for USD 5 million over 5 years, which is the largest single donation Yahoo! has made.

APPENDIX 3

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT (GATB)

Mission

GATB is an international non-profit organisation whose vision is the provision of new medicines with equitable access for the improved treatment of tuberculosis (TB). The organisation's mission is to accelerate the discovery and/or development of cost-effective, affordable new TB drugs that will:

- shorten or simplify TB treatment. Shortening the current 6 month treatment to 2 to 3 months and/or significantly reducing the total number of doses to be taken under the supervision of a health care worker could improve patient compliance (and hence treatment efficacy) as well as potentially reducing the total cost per treatment episode;
- provide a more effective treatment of multidrug-resistant TB; and
- improve the treatment of latent TB infection.

GATB aims to have a new drug that achieves these improvements registered by 2010.

(Source: GATB website, <http://www.tballiance.org>)

Background

Disease rationale

According to the WHO, every year 8.4 million people develop TB and almost 2 million die from the disease. In addition, an estimated 1.86 billion people worldwide are infected with the bacterium that causes TB. TB remains one of the largest killers of youths and adults, and the problem is growing as a result of the spread of HIV/AIDS and drug-resistant strains of TB.

Despite this, no new drug for TB treatment has been developed in the last 30 years. Moreover, the prospects for new drugs have been poor given:

- a widespread, but inaccurate, belief that there was no need for new agents; and
- the high cost of development, coupled with a perception that the potential global market was insufficient to generate a return on investment, which had resulted in a lack of investment in TB from pharmaceutical companies.

History

To address the issues described above, the Rockefeller Foundation convened a meeting in February 2000 in Cape Town, bringing together 120 interested parties from academia, industry, major agencies, non-governmental organisations and donors. This meeting provided the impetus for the creation of GATB, which was launched only eight months later in October 2000. At GATB's launch, Dr Gro Harlem Brundtland, Director-General of the WHO, acknowledged the financial support of the Bill and Melinda Gates Foundation and the Rockefeller Foundation, which had made the organisation's establishment in such a timescale possible.

GATB operates as a non-profit making, public-private partnership and has offices in Brussels, Cape Town and New York.

Strategy and pipeline overview*Strategy and portfolio development*

In its Scientific Blueprint for TB Drug Development, GATB states that although it could potentially invest in projects at every stage of the R&D process, it will prioritise projects which assist in overcoming major bottlenecks that occur relatively early in the process, specifically, late discovery and preclinical research.

Two separate analyses, a 'gap analysis' and a portfolio modelling exercise, have led GATB to adopt a multi-pronged R&D strategy:

- first, GATB will concentrate resources to help fill the current largest gaps in late discovery and pre-clinical work on TB drugs;
- second, to reach its goal of a new compound being registered by 2010, GATB will focus on acquiring or in-licensing later-stage compounds, specifically candidates at the phase I clinical trial stage or later;
- third, to pursue its mission cost-effectively, GATB will look to 'leverage' its investments by courting partners in the public or private sectors and using creative business development (for example, taking limited rights with respect to candidate compounds). Furthermore, it will actively manage the costs and time frames at each stage of the R&D pipeline through dedicated project management.

To achieve this, it is intended that GATB will employ an incubator model, functioning as a, 'lean, virtual research and development organisation that outsources R&D projects to public or private partners'. This model is to allow GATB the freedom to constantly survey possible

leads in TB drug discovery and then selectively intervene when its actions will move a drug candidate towards registration and use in therapy. GATB therefore aims to build a portfolio of projects where it provides varying levels of funding, management and ownership. A further aim is that 30% of GATB's portfolio should be projects which include North-South collaborations.

The process to be used to identify potential projects is two-fold:

- a request for proposal process. The first of these was issued in autumn 2000, and received 103 letters of interest. Of these, 21 have been under further consideration (7 discover, 7 pre-clinical and 7 clinical) by GATB's Scientific Advisory Committee. A recommended shortlist was due to be considered by GATB's Board of Directors in June 2001. GATB announced its first, and to date only deal, with Chiron in February 2002;
- proactive investigation. This includes ongoing monitoring of the status of development projects worldwide, and includes discussions with pharmaceutical companies.

Partnerships

GATB is dedicated to working with organisations across the public/private spectrum. Examples of the range of partners and types of relationships it will seek include:

1. Public/not for profit

- academic institutions – their activity is strongest in basic research, drug discovery, and new target identification. However, due to the lack of pre-clinical funding from grant-making agencies, many meritorious projects are stalled in this stage. GATB may fund academic projects through pre-clinical development in order move them forward to clinical trials.
- associated interest groups/partner networks – works particularly closely with the Coalition for TB Research and Development, which is predominantly a research network of parties from countries with a high burden of TB. The Coalition seeks to mobilise researchers worldwide to share expertise and gather resources for R&D related to TB drug development and research.
- government institutions.
- NGOs – for example, the WHO, whose DOTS programme is the basis of TB treatment in endemic countries, has an international

network useful for clinical trials. It is also developing programs for drug distribution in developing nations. Programmes like Tropical Disease Research and organisations such as the TB Trials Consortium may provide GATB with the means to accelerate both pre-clinical development and clinical trials.

- regulatory agencies

2. Private partners

- Pharmaceutical companies – a range of areas for partnership are envisaged, including providing access to libraries and high-throughput screening, working together on shelved products, which could be acquired or donated and/or co-developed, and arrangements to co-market and co-distribute existing products. GATB sees the greatest promise in ‘co-operating with pharmaceutical companies to seek donations of these ‘shelved’ compounds. In return, the pharmaceutical companies may expect positive humanitarian publicity and access to any research findings or additional indications’;
- Biotech companies – co-develop products sharing IPR (splitting the market) or purchase/licensing the companies to bring forward by their own network;
- CROs – help develop acquired products.

Intellectual property agreements will be important mechanisms for encouraging industry to develop new vaccines.

Publications

Since its inception, GATB has been working on two key publications:

- The *Scientific Blueprint for TB Drug Development*, published in April 2001. This document is the organisation’s definitive approach to the science behind the TB drug development process. The Blueprint lays out the strategy to target each stage of the R&D value chain and to support multiple targets across multiple partners. It also contains guidelines for the discovery and development processes which are aimed at increasing the chances of regulatory approval for new drugs.
- The *Economics of TB Drug Development* was published in October 2001. This report serves as a comprehensive source on the epidemiology of TB, the potential market for new TB drugs, the cost and potential return on development investment and options for funding and conducting drug development. It is targeted at providing the data required for investment appraisal decisions.

Funding

GATB has a funding target of USD 40 million.

GATB has published very little information about its current and required funding levels, nor how much it is likely to commit to projects. However, according to the Gates Foundation website (<http://www.gatesfoundation.org>), Gates made an initial contribution of USD 25 million over five years to GATB in February 2000.

APPENDIX 4

MALARIA VACCINE INITIATIVE (MVI)

Mission

The mission of the MVI at PATH (Program for Appropriate Technology in Health) is:

‘to accelerate the development of promising malaria vaccine candidates and ensure their availability and accessibility for the developing world.’

Within this, MVI’s prime focus is on children.

To accomplish the first part of its mission, MVI is identifying the most promising vaccines and technologies, and implementing targeted partnerships with scientists, vaccinologists and development projects. To help ensure access to the eventual vaccines, MVI will work with other vaccine programs, vaccine development partners and the Global Alliance for Vaccines and Immunisations (GAVI) to explore commercialisation, procurement and delivery strategies that will maximise availability in the countries most affected by malaria.

Background

Disease rationale

The World Health Organisation (WHO) estimates that at least 2.3 billion people are at risk for malaria and that between 300 and 500 million people are currently infected. Malaria causes the deaths of more than 2 million people every year – more than almost any other infectious disease. Over half of all malaria deaths are among children in sub-Saharan Africa, and malaria also takes a high toll on pregnant women and their foetuses.

Malaria was virtually eradicated in most of North America and Europe using insecticides and environmental management. Widespread and increasing resistance to malaria drugs and insecticides has hampered similar efforts in Africa, Asia, and Latin America.

Given the challenge of controlling the mosquito vector and the success of childhood immunisation for other communicable diseases, a malaria vaccine suitable for young children (and women of childbearing age) is considered to be an almost ideal solution. However, there are two key obstacles to this:

- scientific obstacles. Vaccines can prevent many viral and bacterial infections. There has, however, never been a vaccine developed against a complex multi-cellular parasite. Since malaria is caused by

such an organism, developing a vaccine to prevent it is especially challenging. Despite the difficulties, advances in biotechnology and the mapping of the malaria genome make a vaccine against malaria more feasible now than before;

- market obstacles. Malaria vaccine research has made painstaking gains over many years. Now, targeted efforts are needed to move viable malaria vaccine candidates beyond the laboratory, into field trials. Traditionally, there has been relatively little interest in supporting these early development activities. In addition, special efforts are needed to bring together scientists, manufacturers, antigens, adjuvants, vaccine platforms, and testing sites.

According to MVI, a neutral party with significant funding and technical expertise has the potential to address these issues.

History

The MVI was established in June 1999 following a grant of USD 50 million from the Bill and Melinda Gates Foundation to PATH. PATH is an international, non-profit organisation dedicated to improving health, especially that of women and children.

The MVI follows an earlier grant to PATH by Bill and Melinda Gates to support the Children's Vaccine Program. MVI will be administered through PATH, and will have access to the same group of international health experts assembled to provide guidance to the Children's Vaccine Program. Unlike the other PPPs considered in this paper, MVI is therefore not a stand-alone entity.

MVI is located in the Washington DC area.

Strategy and pipeline overview

Strategy and role

MVI aims to co-ordinate its efforts with malaria vaccine programmes at various organisations and agencies around the world, identifying opportunities in current vaccine development efforts, and applying its resources to advance promising malaria vaccine candidates. This approach is based on several key assumptions about the malaria vaccine field:

- a strong foundation of malaria research already exists;
- progress along the malaria vaccine development pathway will be measurable;
- current market forces requiring a return on investment cannot drive

malaria vaccine development alone, requiring a balance of push and pull mechanisms for success; and

- effective disease prevention will ultimately require combination vaccines that include several antigens from different stages of the *Plasmodium* life cycle and elicit a breadth of immune responses.

Given the existing malaria vaccine development participants, activities, and environment, MVI has determined it can be most effective by seeking opportunities, seizing those that present themselves, and collaborating with a variety of partners.

MVI's strategy also focuses on vaccine development rather than discovery, adopting an industrial model of management, ensuring that MVI funding translates into a net increase in funding for malaria vaccine development. It proposes working on different approaches simultaneously rather than one at a time, further speeding up the overall process. This includes pursuing development of candidate vaccines that employ different platform technologies or target different antigens thought to be critical for generating a protective immune response.

MVI will focus primarily on vaccines against *Plasmodium falciparum*, but will also undertake a smaller effort against *Plasmodium vivax*. While *Plasmodium falciparum* is responsible for most of the mortality from malaria, which occurs in Africa, infection in other parts of the world is often mixed, and effective disease prevention will require immunity against both falciparum and vivax malaria.

Projects supported by MVI will meet high standards for both product and trial quality and ethics.

MVI works with other programs within PATH, in particular the Children's Vaccine Initiative, to help realise the delivery of any malaria vaccine that does come down the MVI pipeline. 'We have to work in recognition that even if we had the best vaccine cheaply available, manufactured in large quantities in our hand right now, we could not deliver it effectively to the children who are dying from it. So the linkage across PATH between the malaria vaccine initiative and the rest of the children's vaccine program is very focused on developing strategies to purchase and deliver vaccine to children.' (Source: interview with Regina Rabinovich, MVI website, <http://www.malariavaccine.org>)

MVI's business development team is examining and employing a variety of strategies to assist the smooth introduction of malaria vaccines. These include:

- in negotiating with potential partners, MVI seeks to achieve a

workable balance between ensuring that malaria vaccine development moves forward and ensuring that successful, appropriate vaccines will be sold at affordable prices in the public sector;

- MVI plans to conduct a study to help the vaccine field better understand the potential markets for a malaria vaccine;
- MVI is participating in INVI efforts to design 'pull' mechanisms that will attract potential manufacturers.

Pipeline projects

MVI has a number of projects in place with private and public sector organisations. These include:

- an agreement with GSK Biologicals to fast-track the development and testing of GSK's malaria vaccine for children;
- a deal with Apovia Inc, to fund further development of a malaria vaccine using the biotech company's proprietary technology;
- a partnership with Emory Vaccine Research Center, Yerkes to undertake a series of malaria vaccine trials in primates;
- an agreement with NIAID to allow for greater collaboration in malaria vaccine research providing access to NIAID's clinical testing sites and manufacturing capability.

It actively works with a range of existing players in the field, from across the private/public spectrum, but does not appear to have the aim of positioning itself as an umbrella organisation for all malaria vaccine development work. For example, in June 2001, MVI announced an alliance with the European Commission's European Malaria Vaccine Initiative (EMVI) and the USAID's Malaria Vaccine Development Program (MVDP).

The alliance is to facilitate malaria vaccine development – from testing and manufacturing of vaccine candidates to ensuring their accessibility and affordability in developing countries. Each programme will bring resources and experience to the fight against malaria. MVI brings a flexible international structure and considerable expertise; EMVI has the support of the EU, access to European science and a partnership with the African Malaria Vaccine Testing Network; and USAID has a 35-year history of supporting malaria vaccine development through a global network of partners. The three groups will strategise about how to break through technical and financial barriers to vaccine development. They will also share information useful for the design of clinical trials and vaccine development, where permitted by confidentiality agreements. (Source: Press Release, 22 June 2001, <http://www.malariaivaccines.org>)

Funding

MVI has an initial grant of USD 50 million. Further funding will be sought, but, according to MVI's Director, there are no current guarantees. 'If all we do is spend USD 50 million wisely and advance the field, we'll have done part of our job. But I think the greater part is to bring credibility and enhanced commitment from other partners. It's going to take more than USD 50 million.' (R Rabinovich, Director MVI, Dec 1999).

APPENDIX 5

THE MEDICINE R&D PROCESS FROM THE LAB TO THE PATIENT

This appendix discusses the R&D process from target identification through to patient consumption of a medicine. It also considers how vaccine development differs from the pharmaceutical model. The scenario described below represents the state of the art. The methods used to discover and validate compound candidates have advanced considerably over the past 15 years, although, in reality, companies apply a combination of state of the art and conventional tools.

Discovery

As a result of scientific advancements in microbiology, scientists now seek to initiate the drug discovery process by identifying the disease ‘target’ that accounts for the symptoms. Improved understanding of how a disease works will, with time, improve the quality of the compounds designed to block or turn off the target. Where there is thought to be a genetic component to a disease, genomic databases will be used to assist in this process. A target then has to be validated, i.e. the key question is whether its elimination is likely to lead to a modification of the progression of the disease to the benefit of patients. This can be tested in the laboratory using animal models including transgenic animals.

The next task is to find compounds that may have an effect on the target. To do this a library of compounds is screened. This can be done using computer modelling (*in silico*) to see which molecules ‘fit’ into the structure of the target, or biologically, using high throughput screening in which robotics are used to test the reactions of thousands of assays of different compounds against the target.

A lead series of compounds is then identified, i.e. those with the chemical structures that appeared to have the greatest impact on the target. Lead optimisation is then carried out in which a subset of more promising compounds are identified, again using chemistry and/or computing, on the basis of their apparent efficacy and safety. Genomic databases may again be helpful at this stage if one factor influencing response may be pharmacogenetic (i.e. dependent on a patient’s genetic make-up). Other factors will also be important, including the likely difficulty of turning the compound into a drug (e.g. is it likely to be

available in a convenient dosage regimen, how stable is it likely to be and how difficult to manufacture.) Candidates for pre-clinical and clinical work are then selected. Usually a lead candidate is identified together with some back ups.

Pre-clinical development (toxicology or safety evaluation)

Toxicology or safety evaluation has three purposes. These are to test for carcinogenicity and teratogenicity, and to identify general side effects. Screening can take place *in vitro* prior to testing in animals. Acute tests in animals are then carried out and then long term animal studies.

Clinical development

On the basis of pre-clinical toxicology and animal study data, the compound developer applies for IND (investigational new drug) status from the FDA (in the US) or equivalent elsewhere in order to obtain the right to test the drug on humans. In Phase I of clinical development the compound is tested on healthy volunteers to assess safety and also the pharmacokinetics of the drug, i.e. its ADME (absorption, distribution, metabolism, and excretion) characteristics. In Phase II the drug is tested on patients with a particular emphasis on finding the dose that best balances efficacy and safety. In Phase III the drug is tested on large numbers of patients in at least two well controlled trials (usually double blinded and often with an active control) to enable a regulatory submission to be made to get the drug approved for sale. In Phase IV, (optional post launch testing), additional clinical trials may be needed to identify longer term outcomes, or to compare the product with other treatments. Observational rather than experimental data may be collected, for example using disease registries in which the progress of patients with a particular disease is tracked to enable increased understanding of the disease, patterns of routine care, and the impact of the product and other treatments on patients' health status. Increasingly data is collected on resource use to enable value for money or cost-effectiveness analyses to be done to inform payers of the value as well as of the efficacy of the product. Work will also be done to identify additional uses – new indications – for the drug.

Non-clinical development (preparation for manufacture)

The development of the product itself into a drug that can be manufactured on a large scale to a consistently high quality comprises:

- chemical (or biochemical) development in which different ways of making the active ingredient are explored to find the most 'doable' method;
- pharmaceutical development in which the exact form of the drug is identified, for example can it be delivered as a tablet and what else should go into the tablet along with the active ingredient?
- analytical development. This is about ensuring manufacturing quality standards, for example identifying acceptable levels of impurities and ensuring the product will not degrade over time. Methods are developed to enable quality standards to be set and monitored at production sites;
- scaling up for manufacture. How can laboratory preparation be replicated in a full size production facility?

Some elements of this non-clinical development occur in parallel with the discovery phase and are thus pre-clinical, i.e. they are undertaken before the product enters clinical development. This is because, as noted above, it is necessary to establish that a product can be manufactured, stored and used in a way that is acceptable to those prescribing and taking the product. If this is not likely to be achievable there is little point in testing the compound in humans.

Regulation

There are pre-licensing and post-licensing activities. The pre-licensing activities include:

- a regulatory strategy identifying which markets licenses are required and hence what regulatory requirements have to be met;
- pre-development dialogue with agencies to ensure that, to the extent possible, the clinical and non-clinical development programme that is planned will enable their requirements to be met;
- preparation and submission of the regulatory submissions;
- follow up interaction with the agencies to deal with queries and requests for supplementary information;
- obtaining a licence.

The post-licensing activities include:

- post launch safety data collection;
- maintaining good manufacturing practice (GMP) standards for quality;
- responding to medical and safety queries about the use of the product from doctors and other health professionals;
- obtaining licenses for any additional indications /variations in product form.

Manufacturing and delivery

The active ingredient is made in a primary manufacturing facility and the finished packaged drug is made in a secondary manufacturing facility. Distribution to pharmacies (or to health centres in those countries where doctors or other health professionals dispense) is usually carried out by third party specialist wholesalers, who take ownership of the drug, or may act as an agent for the manufacturer. The drug is dispensed to the patient by a pharmacist, doctor or other health professional.

Selling and using the product

Organisations have to choose the markets they are going to launch the product in and make decisions about the price they are going to charge for a product. In many jurisdictions price has to be negotiated with the third party payers (often governments) running the health care systems. In some cases 'value for money' or cost-effectiveness hurdles also have to be overcome. The product has to be promoted so that doctors are aware of its existence and are persuaded to use this product in preference to other forms of treatment. It may also be necessary to promote awareness to patients (although in most countries, if this does occur, it is done by the third party payer running the health care system, rather than by the manufacturer of the product). The patient needs to present at the doctor's surgery, a correct diagnosis be made, a prescription issued and the patient has to comply or concord with the treatment regimen in order to obtain the health benefit.

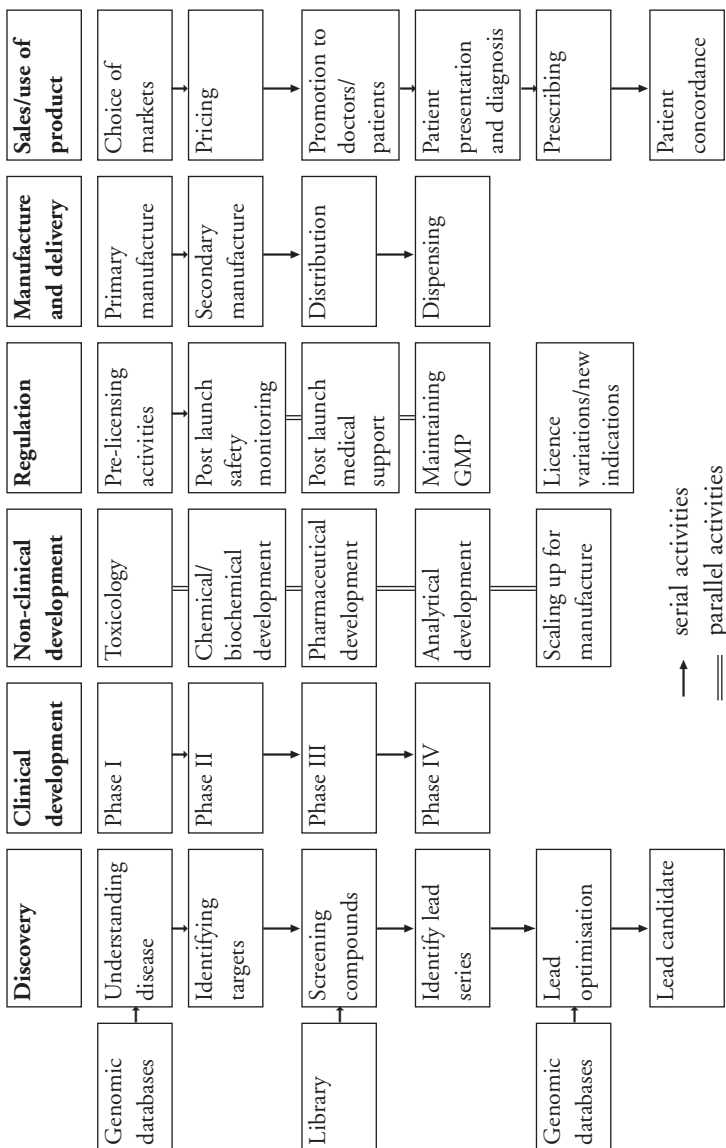
Vaccines

Vaccine discovery varies in part from NCE/NBE development. Once a target has been identified, instead of a 'screening' stage there is a comparable process of identifying proteins which serve as antigens that will stimulate the body to produce antibodies when the disease attacks. The process of identifying a lead series and optimising for a lead candidate has to address the question as to whether the antigen can be made synthetically.

Summary

We summarise in Figure 1 the R&D process we have set out above. Figure 1 breaks down the 'frontline' activities into the major sub-components of activity through to patient consumption of the medicine.

Figure 1 Major sub-components of R&D activity through to patient consumption of the medicine



APPENDIX 6 PPP BOARD OF DIRECTORS

116

MMV Board of Directors

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Prof. Francis Nkrumah, Director, Noguchi
Memorial Institute for Medical Research, Ghana

Prof. Leon Rosenberg, Dept of Molecular Biology,
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Mr. David Alnwick, Project Manager,
Roll Back Malaria

Area of Expertise

Resource mobilization

Finance

R&D

Business

Science & Technical

R&D, India

Clinical &

Operational Issues

N/A

WHO, Disease

Sources: www.mmv.org as of July 2002.

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R. Gordon Douglas Jr, MD,

Former VP Merck & Co.,

Former President Merck Vaccines

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Awa Coll Seck, Minister of Health and Prevention,

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Immunization, PAHO

Board Role

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Treasurer

(Chair of Scientific
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Secretary

Chair

Source: <http://www.iavi.org/about>

APPENDIX 6

118

GATB Board

Board Role

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Source: <http://www.path.org/about>

APPENDIX 7

PPP STAKEHOLDERS AND DONORS

120

MMV

Stakeholders

Bill and Melinda Gates Foundation (\$50 million)

ExxonMobil Corporation

IFPMA

Global Forum for Health Research

Netherlands Minister for Development Corporation

Rockefeller Foundation

Swiss Agency for Dev. And Corporation

UK DFID

WHO – RBM and TDR

World Bank

Source: MMV Annual Report 2000

Note also that BCG co-funded MMV's Draft Business Plan

IAVI**Donors**

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Department for International Development (DFID), UK

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The World Bank

UNAIDS

United States Agency for International Development (USAID)

Until There's A Cure Foundation

Vanderbilt Family Foundation

Viacom Inc.

Yahoo! Inc

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African AIDS Vaccine Programme

AIDS Fondet, Denmark

AIDS Fonds, Netherlands

AIDS Vaccine Advocacy Coalition, USA

Association Francois-Xavier Bagnoud, France

Australian Nat. Coun. AIDS, Hep C, Australia

Canadian AIDS Society

Commonwealth Medical Association Trust

Deutsche AIDS Stiftung, Germany

European Commission

The Foundation Marcel Merieux, France

Grupo de Trabajo Sobre Tratamientos del VIH/SIDA, Spain

International Council of AIDS Service Organisations

The Joint United Nations Programme on AIDS (UNAIDS)

Microsoft Network

Ministry of Health and National AIDS Programme, Brazil

National AIDS Control Organisation

National AIDS Trust, UK

Real Networks Inc.

San Francisco AIDS Foundation, USA

South African AIDS Vaccine Initiative, S Africa

The World Bank

Viacom Inc.

World Economic Forum

Yahoo! Inc.

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American Thoracic Society
ABPI
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EC
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Global Forum for Health Research
International Union against TB and lung disease
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Sequella Global TB Foundation
Stop TB Initiative
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UK DFID
US AID
US CDC
US NIH/NIAID
US NIH/TB Antimicrobial Acquisition
Wellcome Trust
World Bank
WHO/Special Programme for Research and Training
WHO/Stop TB
WHO/TB Programme

APPENDIX 8

MMV's Pipeline

Title	Partner	Stage	Money	Key Milestone/Project Goals
<i>Exploratory Projects from 2000</i> Heme polymerisation inhibition	University of California Berkeley, USA		\$100,000	to synthesise compounds for a novel class of heme polymerisation inhibitors that lack the quinoline structure, overcoming resistance limitations, that are efficacious in animal models as well as in culture.
Dihydroorotate dehydrogenase inhibition	University of Leeds, UK		\$100,000	to synthesise compounds that inhibit the malarial enzyme over the human enzyme and demonstrates good activity against malaria parasites both in culture and in animal models.
Dihydrofolate reductase inhibition	National Science and Technology Department Agency, Bangkok Thailand		\$50,000	This laboratory has developed the ability to construct, clone and express synthetic genes for DHFR from both sensitive and drug-resistant malaria parasites, including a highly resistant tetraivalent mutant. The objective is to identify compounds active against the drug resistant parasite.
<i>Full Drug Discovery Projects, 2000</i> Lactate dehydrogenase inhibition	Bristol University, UK, LSHTM, UK, GSK, Madrid		\$880,000	Bristol/LSHTM/GSK consortium aims to target the glycolytic pathway of Plasmodium falciparum in design and discovery of novel anti-malarials. Also to discover a drug that acts on malaria LDH and is cheap, fast acting and orally bioavailable.
Cysteine protease inhibition	UCSF, GSK		\$1,800,000	UCSF and GSK scientists have established a collaboration to exploit the therapeutic potential of falcipain inhibitors. The aim is to develop promising compounds for human testing within 5 years. An ideal compound arising from this project will be oral.

MMV's Pipeline (continued)

Title	Partner	Stage	Money	Key Milestone/Project Goals
<i>Full Drug Discovery Projects, 2000</i> Synthetic peroxide	U. of Nebraska, Swiss Tropical Institute Basel, Monash U., Australia, Roche, Basel		\$1,100,000	identify an orally active low cost antimalarial peroxide more potent than any of the currently available semisynthetic artemisinins and with a treatment regimen of no more than three days to ensure good patient compliance.
<i>MMV Projects in Discussion for Funding, 2001</i>				
Discovery Drug discovery focused on Plasmodium falciparum fatty acid biosynthesis				Texas A&M U., Albert Einstein College of Medicine, Pharmaceuticals
Plasmodium falciparum protein farnesyltransferase inhibitors				UW Seattle, Yale, Schering Plough Research Institute
Interface between Discovery and Development Development of a semi-synthetic endoperoxide				Bayer, Hong Kong U of S&T
Development of 3rd generation antifolate malaria drug combinations				WRAIR – US Army, Jacobus Pharmaceuticals
Development of a novel and superior 4-aminoquinoline				U.of Liverpool, GSK
Development of intravenous artemisinin for severe malaria				WRAIR – US Army
Development Projects Development of chlorproguanildapsone-artesunate combination				U. of Liverpool, GSK
Development of pyronaridine-artesunate combination				Shin Poong Pharmaceuticals, WHO/TTD

APPENDIX 9

LAVI's Pipeline

Title of VDP	Description/Concept	Partners	News
VDP #1 – Oxford/Kenya	Combination vaccine approach utilising a 'prime-boost' approach combining 2 vaccine technologies: DNA followed by MVA. The candidate DNA vaccine is derived from HIV subtype A – the principal strain of HIV circulating in Kenya.	Collaboration between Oxford University, UK and University of Nairobi, Kenya. Also involving Cobra Pharmaceuticals, UK and IDT, Germany in the manufacture of pilot lots of DNA and MVA vaccines (respectively). Powderject Ltd, UK to be involved in future clinical trials involving new gene-gun delivery system	Launched Nov 1998. Since then, vaccine candidate has been moved from lab to regulatory approval for human testing. Phase 1 trial for DNA vaccine began Aug 2000 in Oxford, followed by Phase 1 trial of MVA vaccine commencing in Feb 2001. Phase 1 trials of DNA vaccine started in Nairobi in March 2001. Phase I/II trials started in London and Oxford in April 2002. One is planned to start in Nairobi at the end of 2002.
VDP #2 – AlphaVax/ South Africa	Development of a vaccine based on Venezuelan Equine Encephalitis (VEE) Alphavirus replicon particles. Strategy is to fast-track the testing of a prototype vaccine expressing a single HIV gen (gag), while concomitantly developing a multigenic candidate vaccine expressing several HIV genes.	Collaboration between AlphaVax Inc, (small US-based biotech company) and, from South Africa, the University of Cape Town, the National Institute for Virology and the MRC. The University of N Carolina and the Children's Research Institute, Columbus, Ohio are also involved in the development of a HIV-1 clade C vaccine. Other contributors include NIH (funding, support for preclinical testing), WRAIR (undertaking its own Phase 1 trial, upgrading pilot production plant to support this), Greer Labs for manufacturing	Launched Nov 1998. Still in pre-clinical stage. Goal to start Phase 1 by end of 2001. This deal was not renegotiated in mid 2002 and is no longer going on.

IAVI Pipeline (continued)

Title of VDP	Description/Concept	Partners	News
VDP #3 – Targeted Genetics/Children’s Research Institute/South Africa	Development of a vaccine based on the subtypes of HIV most prevalent in Southern and Eastern Africa (subtypes A & C), using Targeted Genetics Corporations Adeno Associated Viral Vectors (AAV).	Vaccine candidates are derived from AAV vectors developed by Dr. Johnson, President CRI, Children’s Hospital, Ohio. Targeted Genetics will develop and manufacture the vaccine in collaboration with the CRI and the South African Partnership. IAVI also working with South African AIDS Vaccine Initiative and the Ugandan Government to identify sites for clinical tests.	Launched Feb 2000. In first 10 months, HIV gag genes for Clade A and C have been successfully cloned after unforeseen technical difficulties. Next steps include construction of recombinant AAV (HIV gag) vectors and a study to evaluate the persistence and bio-distribution of their genomes in animals. Trials in South Africa are due to start in 2003-2004.
VDP # 4 – Institute for Human Virology/Uganda	Use of an attenuated live bacterial vector to deliver a DNA vaccine. Vaccine based on HIV subtype A. Project will conduct a clinical comparison of the Oxford DNA+MVA vaccine and a Salmonella-delivered DNA vaccine in Uganda.	Institute for Human Virology, University of Maryland and scientists in Uganda (possibly involving the Uganda Virus Research Institute and Joint Clinical Research Center for clinical and lab teams) Berna Biotech AG is to manufacture doses for clinical trials.	Launched May 2000. Still in pre-clinical phase, plus regulatory issues to be resolved, manufacturing partners to be identified and clinical trials in Uganda to be agreed. No date given for initiating Phase 1 trials. Uganda and US trials are targeted for early 2003.

LAVI's Pipeline (*continued*)

Title of VDP	Description/Concept	Partners	News
VDP #5 – India/Therion	Two separate projects: (1) agreement between IAVI and India's Ministry of Health and Family Welfare and the Indian Council for Medical Research to develop and evaluate one or more vaccines for use in India; (2) VDP bringing together researchers from India with Therion Biologics to build vaccines for India.	Therion Biologics, a US-based biotech company; Indian Ministry for Health and Family Welfare, India's MRC, NIH/ NIAID (partnership and partial funding for development and manufacture of Therion HIV technology – also MVA-based vaccines),	Initiated March 2001. For clade C – India, IAVI to fund work in design, engineering, manufacture novel AIDS vaccine specific for Clade C. Therion already has HIV vaccines in Phase 1 trials – presumably for Clade B (in collaboration with NIAID). Trials due to start in India in 2003-2004. Therion will manufacture the doses for trials. If approved, the company plans to ultimately transfer the technology to an Indian company for large-scale manufacture.
VDP #6 – A DNA-MVA approach to an antigen based on HIV type C in China	A DNA-MVA approach to an antigen based on HIV type C in China.	Aaron Diamond AIDS Research Center; Vical Inc. will manufacture the doses needed for the clinical trials.	Trials targeted for 2003 in China, US, and possibly Africa.
VDP #7 – Bioption AB – HIV subtypes	Bioption AB – HIV subtypes A and C delivered in Semliki Forest Virus cells based on Bioption AB technology.	Bioption	The Trials are targeted for 2004-05 in India and Africa.

IAVI's Pipeline (continued)

Title of VDP	Description/Concept	Partners	News
<p>Maxygen</p>	<p>Agreement between Maxygen, IAVI and DBLV LLC for three year collaboration to use Maxygen's proprietary MolecularBreeding (TM) directed molecular evolution technologies. Under the agreement, DBLV will provide full research and development funding to Maxygen to expand its HIV vaccine development program.</p>	<p>Maxygen Inc, US-based biotech company, DBLV LLC, an entity established and funded by the Rockefeller Foundation.</p>	<p>Under the agreement, IAVI will be granted a royalty-free license to develop and distribute HIV vaccines to those who cannot afford them in developing countries. Maxygen will retain all rights to commercialise vaccines in all developed countries and some developing countries.</p>
<p>Sources: IAVI 2000 Year-End Progress Report. IAVI website, http://www.iavi.or</p>			

APPENDIX 10

130

MVI's Pipeline

Title of VDP	Description	Partners	News
MVI-GSK	March 2001. To fast-track development and testing of GSK's malaria vaccine for children. MVI to provide funding and to fully participate in overseeing accelerated development. GSK provides know-how and proprietary technology.	GSK, UK's MRC, Gambia Unit, MVI	Candidate in development since 1983, initial trial WRAR, subsequent field trial in adult men in Gambia. Clinical trial on children in Gambia to start May 2001. Partnership to include joint Steering Committee and MVI funding of \$6.7 million to support accelerated clinical trials.
MVI-Apovia Inc	Established in Jan 2001, this was MVI's first major private sector agreement. Multi-million dollar, multi-year deal. Apovia to bring the novel, proprietary vaccine technology and MVI to provide funding and assist managing the development process.	Apovia Inc (US) is subsidiary of Apovia AG (German biotech), NIH, MVI	Apovia already done small mammal studies. Under partnership move into larger primates and then humans in US (w/ NIH collaboration), followed by Africa. MVI help to guide product through pre-clinical, mft, regulation, trials.
MVI-Emory Vaccine Research Centre, Yerkes	January 2001. Partnership to undertake a series of malaria vaccine trials.	Emory, MVI	To start with multiple trials in primates
MVI-NIAID	Memorandum of Understanding signed Feb 2000 to speed development of vaccines.	NIAID, NIH Office of Technology Transfer (to oversee patents and inventions that might arise from research conducted in government labs)	Agreement to allow for greater collaboration in malaria vaccine research between MVI and NIAID. Will gain access to NIAID clinical testing sites, capability to manufacture sufficient quantities of vaccine for field testing.

MVI's Pipeline

Title of VDP	Description	Partners	News
Development of MSP1-42 and AMA 1	to enable the NIAID's Malaria Vaccine development unit to produce and evaluate several plasmodium falciparum blood stage antigens.	NIH/NIAID/Malaria Vaccine Development Unit, Bethesda MD. ; Yerkes Regional Primate Testing Facility, Walter Reed Army Institute, Amgen Inc.	
Development and initial clinical testing of Plasmodium vivax Duffy binding protein	To conclude pre-clinical development, manufacture under cGMP conditions, and conduct initial human clinical safety trials on the PvRII fraction of the Plasmodium vivax Duffy Binding Protein.	International Centre for Genetic Engineering and Biotechnology, New Dehli India. ; Bharat Biotech Int'l, Yerkes Regional Primate Testing Center.	
Dev., m.f., and test recombinant modified vaccinia Ankara and fowlpox-9 malaria vaccines	to develop two strains of R-non-replicating pox virus constructs (MVA and FP9) and test vaccine alone and in combination.	Oxford University. ; Oxxon Pharmaccines, Impfstoffwerke Dessau-Torman.	
Develop Merozoite surface protein 2 (MSP2) as a vaccine against P. falciparum	to support the process development, cGMP manufacture and formulation of MSP2 (3D7 and FC27) as malaria vaccines and demonstrate the safety and immunogenicity of MSP2 formulation in Ph 1 clinical trials.	La Trobe University, Melbourne Australia; GroPep, Ltd, Cooperative Research Center for rVAccien Technology, Royal Brisbane Hospital.	

MVI's Pipeline

Title of VDP	Description	Partners	News
Pre-clinical development and manufacture of MSP 4 and 5	to complete all pre-clinical development including preparation of regulatory documentation for two recombinant protein vaccine candidates.	Monash U, Progen Industries, Brisbane, Australia; BPRC, Rijswijk, Netherlands	
Development, manufacture, and clinical testing of RAP-2	To develop and begin clinical trials of the recombinant protein rhoptry associated antigen 2 (RAP-2)	Queensland Institute of Medical Research, Brisbane, Australia. : Progen Industries, Brisbane, Australia; CRC-VI, Brisbane, Australia; BPRC, Rijswijk, Netherlands	
Clinical development of MSP-1/AS02A (FMP1) Candidate malaria vaccine lead	Demonstrate the safety, immunogenicity, and protective efficacy of FMP1 in Western Kenya	Walter Reed Army Institute of Research (WRAIR), Forest Glen, Maryland, Kenya Medical Research Institute (KEMRI); WRAIR's U.S. Army Medical Research Unit-Kenya(USAMRU-Kenya) U.S. Agency for International Development (USAID), Washington, DC	

Source: all from MVI's website: <http://www.maliavaccines.org>

APPENDIX 11

GATB Pipeline

Title of VDP	Description	Partners	News
Develop PA-824 and related nitroimidazole compounds for TB	In February 2002, Chiron granted GATB exclusive worldwide license to develop PA 824 and related nitroimidazole. Chiron obtained the compounds, which are in pre-clinical development, through its acquisition of Path Genesis Corp. GATB will under take further development.	Chiron granted GATB the worldwide license to develop the compounds. Chiron has an option to manufacture and commercialize products in developed country markets but will not receive royalties for drugs marketed in LDCs.	

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