

ABRIDGED VERSION

Combating Diseases Associated with Poverty

Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships

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*Based on a workshop of the same title organized by the
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Initiative on
Public-Private
**Partnerships
for Health**

Combating Diseases Associated with Poverty Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships

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¹ The complete text of annexes is included in the full version of this report.

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- Rockefeller Foundation
- Wellcome Trust
- World Bank

Abbreviations and acronyms

ADIPs	Accelerated Development and Introduction Plans (GAVI)	FTE	full-time equivalent
AHRF	African HIV Research Forum	GATBDD	Global Alliance for Tuberculosis Drug Development (TB Alliance)
AMANET	African Malaria Network Trust	GAVI	Global Alliance for Vaccines and Immunization
ARVs	antiretrovirals	GCP	good clinical practice
CABs	Community Advisory Boards	GDP	gross domestic product
CANs	development candidates	GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
CDC	Centers for Disease Control and Prevention (United States)	GFUNC	Gates Foundation/University of North Carolina Partnership for the Development of New Drugs
CIDA	Canadian International Development Agency	GMP	Global Microbicide Project
CMM	Capital Markets Mechanisms working group (World Bank)	GSK	GlaxoSmithKline
CONRAD/ CICCR	Contraceptive Research and Development Program/Consortium for Industry Collaboration in Contraceptive Research	HepB	hepatitis B
DAH	development assistance for health	HHVI	Human Hookworm Vaccine Initiative
DECs	disease-endemic countries	Hib	Haemophilus influenzae type b
DFID	Department for International Development (United Kingdom)	HRP	Human Reproductive Programme (WHO)
DNDi	Drugs for Neglected Diseases Initiative	IAVI	International AIDS Vaccine Initiative
DSMB	data safety and monitoring board	IBRD	International Bank for Reconstruction and Development (World Bank)
DSS	demographic surveillance systems	ICH	International Conference on Harmonization
DTP	diphtheria-tetanus-pertussis	IDA	International Development Association (World Bank)
EDCTP	European and Developing Countries Clinical Trials Partnership	IDRI	Infectious Disease Research Institute
EMA	European Medicines Evaluation Agency	IFC	International Finance Corporation (World Bank)
EMVI	European Malaria Vaccine Initiative	IFF	International Finance Facility
EU	European Union	IFPMA	International Federation of Pharmaceutical Manufacturers Associations
FDA	Food and Drug Administration (United States)	IOWH	Institute for OneWorld Health
FIND	Foundation for Innovative New Diagnostics		

IP	intellectual property	PH-ROI	public health return on investment
IPM	International Partnership for Microbicides	PMA	portfolio management approach
IPR	intellectual property rights	PneumoADIP	Pneumococcal Vaccines Accelerated Development and Introduction Plan
IPPPH	Initiative on Public-Private Partnerships for Health	PPPs	public-private partnerships
IRB	Institutional Review Board	R–D–A	research–development–access
JICA	Japanese International Cooperation Agency	R&D	research and development
LAPDAP	Lapdap Antimalarial Product Development	RFPs	requests for proposals
LMICs	low and middle income countries	ROI	return on investment
MCA	Millennium Challenge Account (USA)	RotaADIP	Rotavirus Vaccines Accelerated Development and Introduction Plan
MDGs	Millennium Development Goals	SAAVI	South African AIDS Vaccine Initiative
MDP	Microbicides Development Programme	SOPs	standard operating procedures
MHRA	British Medicines and Healthcare Products Regulatory Agency	STIs	sexually transmitted infections
MMV	Medicines for Malaria Venture	SVI	Albert B. Sabin Vaccine Institute
MSF	Médecins sans Frontières (Doctors without Borders)	SWAps	sector-wide approaches
MVI	Malaria Vaccine Initiative	TAM	traditional African medicines
MVP	Meningitis Vaccine Project at WHO/PATH	TB	tuberculosis
NEPAD	New Partnership for Africa’s Development	TBDI	Tuberculosis Diagnostics Initiative
NGO	non-governmental organization	TDR	UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
NIH	National Institutes of Health (United States)	TPPs	target product profiles
ODA	official development assistance	UNAIDS	Joint United Nations Programme on HIV/AIDS
OPIC	Overseas Private Investment Corporation	UNDP	United Nations Development Programme
PABIN	Pan-African Bioethics Initiative	UNFPA	United Nations Population Fund
PAHO	Pan American Health Organization	UNICEF	United Nations Children’s Fund
PATH	Program for Appropriate Technology in Health	USAID	United States Agency for International Development
PD	product development	USAIDMVDP	USAID’s Malaria Vaccine Development Program
PDVI	Pediatric Dengue Vaccine Initiative	VF	Vaccine Fund
PEI	polio eradication initiative	WHO	World Health Organization
		WRAIR	Walter Reed Army Institute of Research

Preface

Public-private partnerships for health product development: Why a critical review now?

In the mid-1990s, some fundamentally different ventures began to emerge addressing the development of products for combating diseases associated with poverty. These have come to be known as public-private partnerships (PPPs) although some prefer other descriptive phrases. Collaboration on an ad hoc basis and around individual candidate projects had, however, occurred previously between public sector agencies and private sector pharmaceutical companies.

What distinguishes these new ventures is that they take as their starting point not a ('favourite') specific candidate product, but a survey of the field and then promote the parallel development of a range of different candidate products (a 'portfolio'). Management of a portfolio, borrowed from the pharmaceutical and venture capital fields, is designed to manage the risk of failure accompanying any individual project. Prior to the mid-1990s, no public-interest venture engaged in product development had articulated 'portfolio management' as a conscious strategy. Some of the product development ventures considered at the 15–16 April 2004 meeting convened by the Initiative on Public-Private Partnerships for Health (IPPPH) in London have, as yet, only small portfolios. However, the older ventures have at least five to six years of operational experience and sizeable portfolios, some over 25 projects.

The emergence of these new ventures was initially fostered by the Rockefeller Foundation and subsequently, around the turn of the millennium, by substantial funding from the Bill & Melinda Gates Foundation. Their number is presently approaching 20. More new ventures to address currently unmet needs (for example, for control of noncommunicable diseases) may possibly emerge.

While they draw upon skills and procedures that are well established in the commercial sphere, these product development PPPs are essentially 'social experiments'. 'Best practices', proven by the delivery of products, are not yet available. The desire to know how to assess the added value of these ventures, as well as 'partnership proliferation', are high on the agenda of concerns for both existing and prospective funders such as bilateral aid agencies. These funders also need to know the scale of future resources needed.

These same funders and many other entities, including the World Bank, UNDP, WHO and developing country governments, are currently seeking ways to achieve the UN Millennium Development Goals (MDGs), adopted in September 2000, and other internationally agreed targets.¹ Of these MDGs, half relate directly or indirectly to health, and one specifically calls for a partnership with the pharmaceutical industry to provide access to affordable essential medicines.²

At present, however, it seems very unlikely that the MDG targets for 2015, and particularly the health-related ones, will be achieved in most of the poorer countries. Unfortunately, the debate on achieving the MDG targets has not recognized that the array of 'tools' available to meet the international targets on child mortality, HIV/AIDS, tuberculosis (TB) and malaria are inadequate for the poorer countries. Major

¹ The UN General Assembly Special Session on HIV/AIDS Declaration of Commitment: Three million people – 2 million in Africa – receiving treatment by the end of 2005.

The Abuja targets for malaria in Africa: By 2005, ensure 60% of those with malaria have access to appropriate treatment.

The Amsterdam target for tuberculosis: By 2005, 70% of people with infectious TB will be diagnosed and 85% cured.

² Goal 8, Target 17, Indicator 46.

causes of child mortality, such as pneumococcal pneumonia and rotavirus diarrhoea, lack preventive vaccines. There is no vaccine or microbicide to prevent HIV infection, no vaccine for malaria and no vaccine to prevent the majority of TB cases (in adults). Existing diagnostic tools or therapies for most diseases associated with poverty are old and/or difficult to use. Most drugs are threatened by increasing resistance.

Given this situation, the Initiative on Public-Private Partnerships for Health concluded that taking stock of

experience to date would help a range of constituencies to maximize the value of their future investments of money and effort in product development. Partnerships, we hope, can learn from each other; existing donors can compare and contrast practice for adjusting their support; and prospective funders can see what types of ventures most closely align with their missions. Finally, a new dimension can be added to the debates about achieving the MDGs, namely improving the array of tools that can facilitate their achievement.

Roy Widdus, Ph.D.

Project Manager

Initiative on Public-Private Partnerships for Health

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Geneva, Switzerland

Public-private partnerships to combat health problems associated with poverty

Message from the World Health Organization

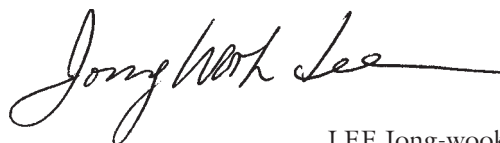
The mission of the World Health Organization (WHO) includes fostering research and product development to address the health problems that burden its Member States, particularly the poorer ones.

Significant contributions to this goal have been made by various WHO implemented programmes, such as the World Bank/UNDP/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research in Training in Human Reproduction (HRP), and more recently the Initiative on Vaccine Research. We anticipate a continuing role for these programmes.

Over the last few years, WHO has also participated in the development and launch of some new not-for-profit ventures that complement WHO core role. These include, the Medicines for Malaria Venture, the Global Alliance for Tuberculosis Drug Development, and

the Foundation for Innovative New Diagnosis, as well as broader coordination mechanisms, like the Global Alliance for Vaccine and Immunization and the Stop TB Partnership.

Such collaborations strengthen the overall global movement for better health. WHO welcomes these and the other new ventures addressing neglected diseases. They support our shared goal, and WHO's underlying mission, to ultimately break the deadly cycle of diseases and poverty in which – even in today's globalizing world – too many individuals are still trapped.



LEE Jong-wook
Director-General
World Health Organization

Message from the International Federation of Pharmaceutical Manufacturers Associations

For decades, the research-based pharmaceutical industry has fostered the development of new medicines and vaccines that have saved lives and improved the health of millions of people around the world. Not only have these innovations helped the poor by dealing with major causes of the global burden of disease, but the pharmaceutical industry has also developed products needed to combat conditions that affect primarily the health of poor populations.

Some commentators have expressed misgivings that as global competition among companies increased, there would be less attention to the needs of the poor, particularly as the costs of bringing new innovative

products to the market increased. Fortunately, all major R&D-based companies continue to address the needs of poorer populations through a variety of mechanisms. These include research collaborations; donation programmes or differential pricing policies for poorer populations; special packaging and formulations; initiatives to assure quality and discourage counterfeit medicines; and educational, training and other programmes to strengthen the infrastructure and human resource capacity for the delivery of healthcare services.

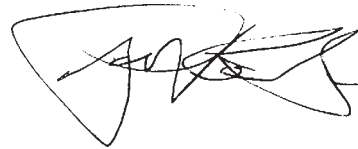
The accumulated expertise and experience represented in research-based pharmaceutical companies is

a major resource for global health. It would be wasteful to duplicate this or not to recruit it to social purposes, such as those represented by the Millennium Development Goals. Linking private sector expertise with public sector goals to combat global health problems obviously makes sense.

R&D-based companies welcome the emerging array of new ventures – so-called public-private partnerships – specifically addressing diseases associated with poverty. These ventures facilitate the processes by which industry can utilize its unique strengths – expertise for innovative product development – to address the needs of the poor. These new ventures also represent disciplined ways of working toward success in a timely manner, approaches familiar to industry and necessary for the efficient and effective use of everyone’s resources.

IFPMA, the official representative of the pharmaceutical industry’s innovator companies worldwide,

welcomes the opportunities that these new ventures create to address the critical needs of those who still suffer disproportionately from the health problems associated with poverty. Investing in health is the surest way to find the path to economic development and greater wealth. Public-private partnerships have an important role to play in achieving that worthy and ambitious goal.



Raymond V. Gilmartin
*Chairman, President and
Chief Executive Officer, Merck & Co., Inc.
President, International Federation of Pharmaceutical
Manufacturers Associations, 2002–2004*

Executive summary

Background

In the mid-1990s, a new group of not-for-profit ventures addressing the development of health products for combating diseases associated with poverty began to emerge. This phenomenon resulted from trends in the late 20th century including awareness of disease burden distribution and pharmaceutical industry economics and the emergence of ‘champions’ for tackling specific health inequities. To mitigate risks arising from individual project failures, these ventures adopt the pharmaceutical industry approach of developing various candidate products simultaneously and recruit, to varying degrees, industry collaboration in their efforts. Hence, they have become known as ‘public-private partnerships’ (PPPs), although some prefer other descriptive phrases. About 20 PPPs now exist, some relatively new with small portfolios; others having over six years’ experience and managing sizeable portfolios of more than 25 products.

While they have underlying similarities, these ventures also vary, particularly owing to factors arising from their choice of disease target (HIV/AIDS, malaria, tuberculosis or other) and product focus (drugs, vaccines, diagnostics, microbicides or other health product).

Workshop summary

On 15–16 April 2004, a workshop entitled *Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships* was organized by the Initiative on Public-Private Partnerships for Health (IPPPH), part of the Global Forum for Health Research, in collaboration with the Bill & Melinda Gates Foundation, the UK Department for International Development, the Rockefeller Foundation and the

Wellcome Trust which hosted the workshop at their London headquarters.

The workshop was organized around five objectives:

- Provide background on the emergence and operations of these ventures.
- Consider how product development (PD) PPPs and other players operate and interact.
- Assess the current and future financial needs of PD PPPs.
- Assess if innovative financing options for diseases of the poor exist.
- Identify questions and issues requiring further attention and study.

During the workshop and an associated consultation among existing PD PPP funders, it became clear that PD PPPs could be considered a coherent grouping or field albeit with differences around individual ventures arising mostly from their choice of disease and product focus which significantly affects the context in which they operate.

The main themes in the discussions were:

- Agreement, generally, that the PD PPP model (albeit with variations) was a sound and cost-effective approach to product development for diseases associated with poverty, probably the best that could be currently identified.
- Interfaces with other organizations in the research–development–access (R–D–A) continuum were critical and a major management challenge for PD PPPs. This encompassed both upstream interfaces with basic research, downstream interfaces with potential delivery systems, effective management of interfaces with private sector collaborators and ‘contractees’ in the specific steps of product development and links with

researcher- and policy-makers in disease-endemic countries (DECs).

- Effective portfolio management is a critical factor allowing PD PPPs (and donors) to spread risks of individual project failure and ultimate success. In addition, the technical expertise of PD PPP staff and Scientific Advisory Boards provided added-value to funders who may not have, or wish to have, the in-house scientific capacity to manage product development themselves.
- Consideration was needed of the activities required to achieve optimal access for the poorer populations in need of the anticipated health products. Identifying necessary actions becomes more important where delivery systems are not easy to identify or function poorly. The PD PPPs may be in a good position to advocate for the necessary actions but responsibility for implementation probably more appropriately rests with other players.
- The financing required for product development will vary given the disease/product choices of the PD PPP. Based on estimates of funds committed by early 2003, and cost estimates for the portfolio of products underway, the financing shortfall through 2007 for major PD PPPs appears to be at least US\$ 1.2 billion and possibly over US\$ 2.2 billion, depending on assumptions. Techniques for assessing the amounts necessary need to be refined. Nonetheless, PD PPP projections and estimates from independent sources prepared for the workshop using industry costs as reference suggest a large shortfall in the near term. This shortfall exists, even for the best-

funded PD PPPs, as well as across the field. Credible certainty about financing can affect the level of collaboration from industry.

- Judging ‘success’ is important to funders and requires the development of comparative performance measures.
- Communication and coordination among all players is critical to the field, as cooperation of so many players (funders, PPPs, industry, DECs, etc.) is required to ensure progress of candidate products along the R–D–A continuum. Current levels are probably suboptimal, but mechanisms need to be ‘light’ as most players are already stressed by current obligations.

Areas for future attention

Participants did not prioritize conclusions and recommendations at the workshop. However, subsequent consultation among the meeting chairs and session co-chairs, funders and PD PPPs identified some consensus on areas for future attention:

- Development of common performance measures.
- Coordination of clinical trial capacity development.
- Harnessing the potential of disease-endemic countries.
- Ensuring financial sustainability of the PD PPPs.
- Communication and coordination.
- Fully recruiting potential industry contributions.

These are discussed further in the full report from the workshop, along with possible approaches to moving forward.

Historical context

Why public-private partnerships for product development emerged and how? A summary¹

Roy Widdus

The reason that a wave of new multi-candidates/portfolio-based ventures for product development to combat ‘neglected diseases’² arose in the late 1990s has not been subject to extensive analysis. What follows is a short analysis of the trends that probably created an environment conducive to the emergence of these new ventures, and some commentary on their early history.

Trends in the late 20th century conducive to emergence of PD PPPs

The late 20th Century saw a number of trends that created a fertile environment for the emergence of new ventures against diseases associated with poverty. Briefly, these included:

- Systematic analysis of the global burden of disease highlighted ‘diseases associated with poverty’ and deficiencies in tools to combat them.
- Pharmaceutical companies faced increasing R&D costs, consolidation, and greater competitive pressures, increasing their aversion to commercially risky or unattractive projects.
- Vaccines increasingly became ‘orphan’ products, despite their public health importance, especially in developing countries.
- The HIV/AIDS pandemic drew global attention to the need for greater action on health needs of low and middle income countries.
- Public sector and public interest organizations improved their understanding of industry motivations and product development expertise.

Coupled with the emergence of ‘champions’ in the right place at the right time, these factors may explain the growth of this new field.

The emergence of discrete ventures dedicated to product development for neglected diseases

Adoption of the multi-candidate/portfolio approach by ventures committed to global public health (as a means of enhancing likely success) appears to have occurred, somewhat surprisingly, in two independent circumstances in the mid to late 1990s. Each, however, represents moving towards common ground – the necessity of effective public-private collaboration – from different starting points.

The emergence of the first PD PPP – International AIDS Vaccine Initiative (IAVI) – for vaccine development

On 7–11 March 1994, the Rockefeller Foundation convened a meeting entitled *Accelerating the development of preventive HIV vaccines for the world*. The Rockefeller Foundation has a long history in philanthropy for global public health and the meeting’s principal architect was Seth Berkley, a public health epidemiologist with experience of the early HIV/AIDS epidemic in Uganda, then working at the Foundation.

Under Berkley’s guidance, the Rockefeller Foundation sponsored further meetings on a scientific agenda (co-sponsored by the Fondation Mérieux)³ and on financial and structural issues⁴ which laid the ground-

¹ A complete version of this discussion will appear in the unbridged report from the IPPPH workshop of 15–16 April 2004 in London, UK (in preparation).

² The term ‘neglected diseases’ is used generally to designate diseases that differentially affect poorer populations in developing countries.

³ Rockefeller Foundation, 1995. *Summary report and recommendation of an international ad hoc scientific committee*. 27–28 October 1994, Le Val de Grâce, Paris, France. 24 pp.

⁴ Rockefeller Foundation, 1995. *Summary report and recommendations of an international meeting: Financial and structural issues*. 17 August 1995, New York. 16 pp.

work for the International AIDS Vaccine Initiative (IAVI). IAVI became an independent legal entity in 1996.

IAVI therefore has its origins in the recognition by the private philanthropic sector of a global public health need. Industry expertise was recognized as necessary, but so was the need to go beyond industry's usual role, into advocacy and access for poor populations to anticipated products.

Medicines for Malaria Venture: The first drug development PD PPP

Shortly after the Rockefeller Foundation initiated the process which led to IAVI, staff at the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases started discussions which ultimately led to the creation of the Medicines for Malaria Venture (MMV). Two individuals, Win Gutteridge and Robert Ridley, initiated these discussions. Both knew about product development and the benefits of a portfolio approach in increasing the probability of success from their prior experience in the pharmaceutical industry.¹

The major issues that arose in discussions of revitalizing anti-malarial drug development to meet developing country needs were those relating to industry engagement and the nature of the venture which would be able most effectively to catalyse new product development. An independent, not-for-profit legal entity status was eventually accepted as the most appropriate structural arrangement. Various other groups, including the Global Forum for Health Research and the Rockefeller Foundation, facilitated the creation and early operations of the nascent venture. MMV was established under Swiss law as a foundation in 1999.

Role of foundations in nurturing and expanding the field of PD partnerships

Two foundations have been instrumental in the start-up and funding of various PD PPPs. These are the Rockefeller Foundation, through its Health Equity Program, and the Bill & Melinda Gates Foundation,

whose greatly expanded endowment in 1998–1999 allowed it to become a major investor in combating diseases associated with poverty.

Ventures launched following 'incubation' by the Rockefeller Foundation (other than IAVI and MMV) include:

- Global Alliance for Tuberculosis Drug Development (TB Alliance) (2000), which also benefited at its launch from endorsement and significant 'seed' funding from the Gates Foundation.
- International Partnership for Microbicides (IPM) (Early 2001)
- Pediatric Dengue Vaccine Initiative (PDVI) (2001)

In 1998–1999, the Bill & Melinda Gates Foundation provided significant resources to PD PPPs already established at that time, such as IAVI, MMV, Sequella Global TB Vaccine Foundation (see also discussion of Sequella/Aeras below) and the Tuberculosis Diagnostics Initiative (the antecedent of FIND). Other PD PPPs were in an independent process of formation at this time or later and also benefited (for example, the Institute for OneWorld Health, IPM and PDVI).

In other cases, ventures were re-launched, e.g., the Foundation for Innovative New Diagnostics (FIND, as it evolved from TDBI), or launched exclusively (Human Hookworm Vaccine Initiative – HHVI) or overwhelmingly (Malaria Vaccine Initiative – MVI) with funding from the Gates Foundation.

The Bill & Melinda Gates Foundation has also funded a number of single candidate product development ventures. These include the Meningitis Vaccine Programme at PATH.

Emergence of other PD PPPs

A number of the PD PPPs addressed here, such as the Institute for OneWorld Health (IOWH), originated independently from the foundations/processes noted above. Some, e.g., FIND and Aeras/Sequella, evolved into their current model from earlier, significantly different, incarnations.

The processes for creating PD PPPs evolve, as do the ventures themselves

Champions appear to play a significant role in the establishment of PD PPPs but other elements seem to

¹ Ridley RG, Gutteridge WE, Currat LE. 1999. *New medicines for malaria: A case study of the establishment of a public/private sector partnership*. Presented at 3rd Global Forum for Health Research, Geneva.

be emerging as reasonable predictors of a successful launch with broad-based support. These include:

- An inclusive process for achieving consensus on the mission of a new venture and the activities most needed;
- A scientific review/blueprint;
- A pharmaco-economic study, to define the need and possible market;
- A business case/business plan, which describes the problem that the venture will address, the activities needed to accomplish the goal, how they will be undertaken and the resources required to do them;
- An access plan in some cases, particularly those where the path to use is otherwise unclear, since no delivery system is immediately apparent.

Product development partnerships examined at the IPPPH London meeting¹

As alluded to in the Preface, public-private collaboration for development of products to combat ‘neglected diseases’ did not arise de novo in the mid to late 1990s. The defining feature of the new ventures emerging at that time is that they elect to foster the simultaneous development of a number of candidate products portfolio, rather than starting with any specific (‘favourite’) project. This category was considered to include the following ventures:

HIV/AIDS

International AIDS Vaccine Initiative (IAVI)
 South African AIDS Vaccine Initiative (SAAVI)
 Global Microbicide Project (GMP)
 International Partnership for Microbicides (IPM)
 Microbicide Development Project (MDP)

Malaria

Medicines for Malaria Venture (MMV)
 Malaria Vaccine Initiative (MVI)
 European Malaria Vaccine Initiative (EMVI)

Tuberculosis

Global Alliance for Tuberculosis Drug Development (TB Alliance)
 Aeras Global Tuberculosis Vaccine Foundation (Aeras)
 Foundation for Innovative New Diagnostics (FIND)

Other ‘neglected infectious diseases’

Drugs for Neglected Diseases initiative (DNDi)
 Institute for OneWorld Health (IOWH)
 Pediatric Dengue Vaccine Initiative (PDVI)
 Human Hookworm Vaccine Initiative (HHVI)
 Rotavirus Vaccine Accelerated Development and Introduction Plan (RotaADIP)
 Pneumococcal Vaccine Accelerated Development and Introduction Plan (PneumoADIP)

This listing may be incomplete due to ventures using a portfolio approach on which IPPPH does not as yet have adequate information.

Information on the various types of public-private partnerships for health is provided in a background paper prepared for the meeting that also included specific information on these organizations.²

A current snapshot of the PD PPPs addressed Similarities among PD PPPs

The significant underlying common characteristics across this group of new ventures are:

- They use some private sector approaches to attack research and development challenges.
- They target one or more ‘neglected diseases’.
- They use, or intend to use, variants of the multi-candidate/portfolio management approach.
- Their primary objective is public health rather than a commercial goal.
- They are focused on developing products suited for use in developing countries.

The other similarities among existing PD PPP ventures are their specific ‘needs’ that stem from the nature of the product development process. Common needs of partnerships aimed at developing and delivering health products for the poor include:

- Engagement of industry, public/governmental agencies and civil society organizations as necessary.

¹ This listing, and the IPPPH London meeting of 15–16 April 2004, focused on ventures addressing infectious diseases. The Contraceptive Research and Development Program and its Consortium for Industry Collaboration in Contraceptive Research (CONRAD/CICCR) uses a portfolio approach to new contraceptive development. See Partnerships Database: www.ippph.org.

² See annex 3a (Widdus R. 2004. *Background on PD PPPs under consideration at the workshop*).

- Sufficient resources to implement their chosen strategies.
- Strategies for management of intellectual property and leveraging R&D investments to assure product access for the poorest populations.
- Access to clinical trial capacity.
- Access to regulatory experience including that relevant to low and middle income countries (LMICs).
- Access to expertise in assessing need, demand and markets for their products particularly in LMICs.
- Access to expertise in assessing production options and their costs.
- Knowledge of the best strategies for delivering products to the poorest, including ways to work effectively with/within the existing health services infrastructure.
- Ways of measuring progress, in product development or delivery, or health status.
- Strategies for ensuring that non-contractual allies in the collective efforts to develop and improve access to health products actually fulfil their responsibilities and obligations.

For success in development and application of products to combat neglected diseases, a range of complementary activities must also be undertaken in parallel, but not necessarily by the PD PPPs themselves. These include strengthening research, clinical trials and health services delivery capacity in disease-endemic countries.

Variations among PD PPPs and their origins

One background paper prepared for the London meeting documents the variation among the PD PPPs under consideration along four themes:¹

- Strategic variations.
- Financial variations.
- Sector roles and contributions.
- Operational variations.

One means to understand this variation, and even perhaps predict it, is to examine the consequences of the choice of mission made by those responsible for founding the new venture. Specifically, the choice of disease

and product focus determines to a significant extent a wide range of factors around which PPP operations vary. A totally new or a badly funded field will generally have fewer potential collaborators. The product/disease focus chosen also has significant implications for the potential uptake of products. Partnerships developing products for which purchase or delivery systems are less easily identifiable or function less efficiently, face the quandary of how to ensure uptake of their products.

Thus, variations around ‘**advocacy**’ may reflect the perceived shortage of collaborators and those around ‘**access**’ activities, the absence, or deficiencies, in downstream uptake systems.

Partnerships with fewer potential overall collaborators are more likely to be active along the whole R–D–A continuum (including advocacy) and to undertake more activities ‘in-house’. These ventures are therefore likely to need greater resources, principally because of the environment their mission bestows upon them.

Advocacy

Some PD PPPs elect to undertake various general communication and advocacy activities in addition to those activities strictly connected with product development. The extent and nature of these are, to a large extent, governed by their perceptions of the status of the ‘field’ in which they operate and the position that they wish to occupy in it.

Access

By access we mean a range of activities that are needed to make sure a product actually gets to intended recipients at an affordable price. They include expediting regulatory approval, planning production to meet the size of demand, the lowest sustainable cost of production, planning for financing purchase, and the delivery systems needed for appropriate use. To some extent even appropriate product design (e.g., oral administration) can affect access.

If no delivery system is identifiable, a PD PPP may see a need to outline an ‘access’ plan. Where identifiable delivery systems exist but function poorly, it is arguable that an access plan could facilitate actions, in parallel to actual product development, to strengthen delivery, so that more of the potential impact of a new

¹ See annex 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*).

product was eventually achieved. Suggesting the PD PPPs prepare a plan identifying steps necessary to achieve access does not imply that they would necessarily be the implementers. Others might be more appropriate and indeed have formal responsibility for the necessary actions.

Understanding typical PD PPP operations

Although it is difficult to generalize PD PPPs and their operations, because there are so many variations among them, some attempt to do so is necessary so that readers new to the field have a general understanding of the way most of the PD PPPs considered here operate.

Candidate products need to be moved at the fastest possible speed and at reasonable cost through the various steps of product development. These have been described in most detail for drugs,¹ and are somewhat similar for vaccines, particularly at the clinical testing stages.

It is possible for a candidate product to come under the influence of a PD PPP in a variety of ways and at any point in the R–D–A continuum.

To move any candidate product through the various product development stages requires certain types of testing and subsequent decisions on whether it has sufficient promise to move through the next stages. Failures, rather than successes, are the norm and it is most cost-efficient if decisions to abandon projects are made quickly and with the lowest expenditures.

To maximize the chances of success, it is best to have a number of candidate products at each different stage and to replace routinely those that are abandoned because the results of testing indicate problems, e.g., low efficacy or toxicity. This process of portfolio management has been refined for drugs (see Schmid²) but less studied for vaccines.

Each testing step in product development requires particular expertise and resources, e.g., laboratory equipment for synthesizing chemical variants of a candidate drug, animal models for toxicology testing or access to human populations at risk of the target disease or patients for testing candidate efficacy in preventing or treating it.

This expertise typically exists outside a PD PPP in other organizations individually (e.g., pharma companies) or can be brought together in project teams. PD PPPs normally draw upon these companies or assem-

ble collaborative teams through contracts for the activities connected with moving candidates through specified testing steps and based on the results decide to pursue the candidate further or abandon it. A deal is generally sought that combines contributions from different players and ultimately provides benefits to all – a so-called ‘win-win’ situation.

Sufficient expertise and staff need to reside in the PD PPP to manage the organizations or project teams contracted by it. If fewer potential collaborators can be found to take on the necessary work, a PD PPP will need to have a proportionally larger staff to manage or conduct activities ‘in-house’. The length, complexity and expense of product development means that where there is a paucity of candidates and few collaborators, the funding needed by the PD PPP and the likely time to success will be greater.

The necessary expertise and composition of teams assembled to move candidate products through different stages in the R&D process vary with product type and development step. As the vast majority of collaborators engaged in moving candidate products through testing steps are at a distance – physically and organizationally – from the PD PPP, the term ‘virtual R&D’ has been coined to describe these arrangements, to contrast it with the process as historically practised in large pharmaceutical companies, where most employees and activities were ‘in-house’.³ In recent years, smaller ‘biotech’ companies have pioneered virtual operations as a way of conducting R&D with lower in-house investment in staff and equipment, thus maintaining their flexibility. Even large pharma is moving in this direction.

Some commentators have noted the extra management demands that virtual R&D places on its sponsors. However, there seems to be general agreement that it is a cost-effective alternative when compared to financing expensive physical infrastructure and staff for possibly short-term projects.

¹ Nwaka S, Ridley R. 2004. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews Drug Discovery* 2: 919–928

² See annex 9d (Schmid E. *Portfolio management in the pharmaceutical industry*).

³ Recently, pharma companies themselves have been adopting ‘virtual R&D’, for example, through contract research organizations.

Most PD PPPs are not currently funding activities intended to translate ideas from basic research into candidate products (see Nwaka and Widdus¹). Translational activities are hence reliant on major biomedical research funders, if they are undertaken at all.

The foregoing needs to be recognized as a general description of PD PPP operations. Readers interested in more detail are referred to the Sander and Widdus background paper, plus the websites and annual progress reports of the individual organizations.

¹ See annex 9f (Nwaka S, Widdus R. *The current research-to-development 'hand-off' process for product concept/candidate products and possible improvements in it*).

Meeting summary

Katherine White

Background

A workshop “Combating diseases associated with poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships”¹ was organized by the Initiative on Public Private Partnerships for Health (IPPPH)² in collaboration with the Rockefeller Foundation, the Bill & Melinda Gates Foundation, the UK Department for International Development and the Wellcome Trust. Prior to the workshop, IPPPH commissioned a comprehensive set of background papers to help prepare participants (see annex 9). In both the background materials and meeting discussions, attempts were made to elucidate the significance of the many differences among product development public-private partnerships (PD PPPs) for their funding requirements and probabilities of success.

Participants at the meeting represented a broad array of current and potential actors in the field from the PD PPPs, their funders, the private sector and other constituents.³

The workshop was organized around the following five objectives:

- Provide background on the emergence and operations of the PD PPPs.
- Consider how PD PPPs and other players operate and interact.
- Assess the current and future financial needs of PD PPPs.
- Assess if innovative financing options for diseases of the poor exist.
- Identify questions and issues requiring further attention and study.

Meeting discussion themes

During the two days of discussion it became clear that as a group, PD PPPs could be thought of as a coher-

ent field, albeit with broad differences driven by the environment in which they operate. As product developers for ‘neglected diseases’, or diseases of poverty, the PD PPPs share underlying similarities, as well as differing on many features and the context in which they operate.

Discussions during the meeting covered a number of areas surrounding the current understanding of the PD PPP field and its future needs. The main themes of this discussion are summarized in the following sections:

- PD PPP model
- Key interfaces with other organizations
- Role of portfolio management
- Preparing for access: availability and adoption
- Financing
- Judging success
- Role of coordination

PD PPP model⁴

There was general agreement that the PD PPPs are a coherent group and that the model is a sound approach to bridge the gap that has existed between basic research and the need for new products to control/ combat diseases of poverty. Their activities are generally characterized by:

¹ Held at the headquarters of the Wellcome Trust, London, UK, 15–16 April 2004.

² A component of the Global Forum for Health Research, established to monitor, analyse and support ventures in public-private collaboration to reduce global health inequities associated with poverty.

³ For full list of participants see annex 2.

⁴ See annexes 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*) and 9l (Ridley R. *PD PPPs for diseases of poverty. Are there more efficient alternatives? Are there limitations?*).

- A focus on product development for diseases of poverty.
- Use of private sector management practices including portfolio management and industrial project management.
- Advocacy for their own work and often for global attention to their disease(s) of interest.

However, there was also recognition of the differences in approach across PD PPPs as a result of:

- Technical differences in drug, vaccine, microbicide and diagnostics/device development.
- The extent to which individual PD PPPs have implemented portfolio management.
- The specific context in which an individual PD PPP is operating, including scientific development and political will associated with the disease(s) of focus.

One challenge is to communicate the core strengths and perceived benefits of the model with simple messages that cut across the entire field of PD PPPs to encourage a broader support base (see also subsection on financing, below).

PD PPPs are not an end in themselves but are a practical way to help address a specific public health inequity that characterized the 1990s: the near-total lack of development of essential new products for the diseases of the poor. In particular the use by PD PPPs of portfolio management is a key distinguishing feature of this new field, very different from the linear approach to vaccine and reproductive technology development that has sometimes been pursued by the public sector in the past. On their own PD PPPs are necessary but not sufficient to address the global health needs outlined in the Millennium Development Goals.¹

Each pursues its own strategy, driven by the economic and social context in which they are operating to ensure development and access to its products. This affects every decision point along the product development pipeline from acquisition of candidate products, to the choice of manufactures, to the need for strong partnerships with donation programmes, procurement programmes and/or other ‘pull’ mechanisms to ensure the neediest and poorest populations around

the globe benefit from the products that result from the PD PPPs efforts.

Open questions

- Should the PD PPP field continue to proliferate or have the most important opportunities already been addressed?
- How should funders balance their investments in PD PPPs with other approaches to product development (e.g., funding the private sector directly, or funding individual projects)?
- How should funders balance investments in access to existing products with investments in new product development?
- What is the right balance of public and private sector goals, staff and managerial approaches for the PD PPPs? How will this vary as the PD PPPs mature?

Key interfaces with other organizations

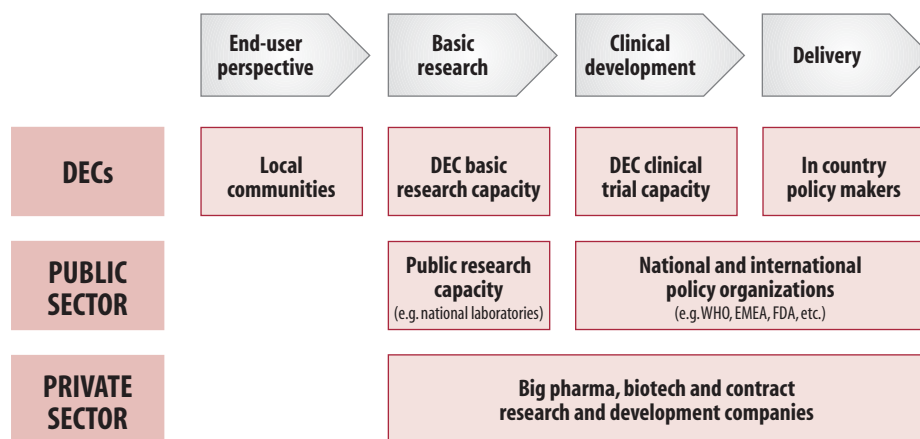
Within the commercial world of product development, effective management of interfaces with other companies and institutions is critical for success. Due to the cross-functional nature of the development process there is an increasing emphasis on the complex outsourcing networks throughout the R&D continuum. The private sector also benefits from the focus and essential discipline instilled by a commercial market, in which success is easily quantified by the bottom line.

Traditionally for big pharmaceutical companies, many of the connections that need to be made are internal. In pre-clinical development, for example, in-house chemists, biologists and toxicologists must work together to determine a target molecule’s suitability for progression to clinical trials. This is not the case for PD PPPs.

Most PD PPPs, like many biotech firms, are relatively small and achieve a large portion of their work through others, by connecting the requisite people, communities, organizations and companies to achieve their goals. Depending on the state of the science and the nature of the products and disease targets, the focus of activities along the spectrum from research to development to access may vary. Whatever role a PD PPP itself takes on, effective management of interfaces with, and “hand-offs” to, others remains central to its

¹ See annex 5 (United Nations Millennium Declaration, *United Nations Resolution 55/2 2000*).

Potential interfaces for PD PPPs along the development chain



strategy. Since product development is at the core of all PD PPPs, interfaces with the following players were recognized as important to all PD PPPs:

- Disease-endemic countries (DECs)
- Public sector
- Private sector

Disease-endemic countries

Disease-endemic countries already provide valuable contributions to product development all the way from research to end product delivery and use. Increasing DEC involvement will help build ownership of potential products and increase the potential for successful delivery and adoption of new products.

As discussed above, there may be further opportunities to link directly investment in basic research and system strengthening in these countries with the work of the PD PPPs. The DECs are also integral to three other components of the development process, providing the end-user perspective, clinical trial capacity and in preparation for access.

End-user perspective

Developing drugs and other products that will be used and embraced by those in need requires early consideration of their needs and perspectives. Within both big pharmaceutical and biotech companies, the involvement of their commercialization groups (those with the greatest customer insight) begins early in the proc-

ess as the candidates' transition into pre-clinical and clinical development. It is just as important for PD PPPs to get the same kind of market input; a product has no value if it is not used. Many of the PD PPPs are already getting some involvement through their boards, scientific advisory bodies and through sophisticated market analyses. It was very clear that involvement of the ultimate customers and generating ownership at the country level is integral to success and is not an optional extra.

Basic research

There was a strong feeling during the discussions that in the longer term research from DECs could play an important role in contributing to the overall success of the PD PPPs. In the shorter term, one idea to increase the flow of leads that was discussed was strengthening the links between PD PPPs and existing research communities in disease-endemic countries. Another area of discussion included the potential for traditional medicines, widely used throughout Africa, China and South-East Asia, to provide an additional source of potential candidates.

Today, while there may be applicable research, these communities often do not have strong technology transfer skills. It may be beneficial to go further than creating direct links to PD PPPs by setting up centres of excellence around specific disease areas in some countries. Centres of excellence could help provide the criti-

cal mass and focus characteristic of successful research groups in the commercial drug world and would provide a natural interface point for linking into specific PD PPPs. It could also have the added benefit of bringing the local ‘customer’ (or intended beneficiary) perspective into the development process earlier and building research capabilities in these countries. It was generally agreed that PD PPPs should not be expected, as a principal goal, to address the need for research strengthening in disease-endemic countries.

Clinical trial and regulatory capacity

Effective clinical trials require physical sites, ethical review capacity and the appropriate regulatory bodies to support the trial and ultimately approve the product for use. In sub-Saharan Africa, where many of the products will need to be tested, there is a shortage of all three. Bridging this gap will require scientific and regulatory leadership as well as significant investment in funding.

- *Trial sites:* With more than 300¹ products for ‘neglected diseases’ in development globally there is not the trial capacity to support the current pipeline. In response many groups are independently investing in trial site capacity (e.g., individual PD PPPs and the European and Developing Countries Clinical Trials Partnership [EDCTP]). Given the high cost of such investment there may be benefits from increased coordination in this area where possible. Once established it will also be necessary to ensure a steady flow of projects to sustain them. (See also IPPPH 2004.²)
- *Regulatory capacity:* In many of the countries where trials could be conducted, there is limited local regulatory capacity to provide approval for such trials and successful products. While trials can be run under the guidelines from other recognized regulatory bodies (e.g., the United States’ Food and Drug Administration [FDA]) the absence of such capacity is one of the reasons many industry players choose not to run trials in these countries.
- *Ethical review capabilities:* Credible research cannot be conducted anywhere without two review capabilities: the ability to gain informed consent; and the presence of effective ethical review committees. While committees are being established they are

often of poor quality due to the limited training and awareness of international standards.³ In cases where researchers work with an international Institutional Review Board (IRB), the board may not be as sensitive to the issues raised by the local culture⁴ (e.g., the need for consultations with families and communities). Local researchers need to be trained so that they can play a role in determining the nature and type of ethical guidelines used in international collaborative research.

For sub-Saharan Africa, one of the options discussed was to develop capacity in a representative set of African countries; balancing the potential benefits of focus with the benefits that capacity building in a broader set of countries could bring. However, increased DEC involvement in product development cannot be the lone burden of the PD PPPs (e.g., capacity building for research, regulatory infrastructure, etc.). While it is clear that PD PPPs will need to work closely with developing countries in this area, leaving the task to the PD PPPs would risk losing the focus that they bring to the product development. A challenge for the PD PPPs is how to leverage their collective voice to facilitate increased focus and momentum from organizations such as WHO, which can help by working in parallel with them.

In the future it might be possible to see some PD PPPs basing themselves in DECs. However, this is unlikely while R&D and innovation primarily occurs in developed countries.

Delivery

Disease-endemic countries will also play a critical role in working with the PD PPPs to ensure access and delivery of the products that are developed. See subsection Preparing for access: availability and adoption, below.

¹ See annex 9h (Kimanani E, Clements V. *Current status of clinical trials in Africa*).

² IPPPH. 2004. *Clinical Trial Capacity in Low Income Countries: Experiences, lessons and priorities for strengthening*.

³ See annex 9g (Leke R. *Ethical review capacity: Country needs, role and responsibility of partners and researchers*).

⁴ “83 per cent of the developing-country researchers surveyed criticised US IRBs for being insensitive to local culture” Ethical review of health research: a perspective from developing country researchers, Hyder et al. *J Med Ethics*. 2004.

Public sector

Basic research

PD PPPs have three primary sources of product concepts for drug development:

- Development or modification of an established product for new indication(s).
- Continued development of previously abandoned products (often abandoned due to lack of commercial market).
- Development of totally new products.

Development of totally new drugs requires novel product concepts or leads from the basic research community (e.g., academic laboratories) to be fed into the product pipeline. ‘Translation’ is the term used to describe this transfer from basic research into product development. Ensuring that a flow of high-quality ideas are translated into products requires clear communication of the target product you are trying to develop, as well as awareness in the research world of how to channel ideas into PD PPPs or other development mechanisms.

In recent years there has been a significant increase in the flow of leads from basic research into commercial drug development. Universities and other research institutes are paying more attention to the benefits they can reap from successful translation of their research with many employing technology transfer managers. While there is often funding of basic research for most of the neglected diseases being targeted, there is still a struggle to translate this investment into potential medicines. From the discussions during the meeting translation efforts today appear to be facing two main challenges: scarcity of practical product-directed research; and the mechanisms to flow potential leads into PD PPPs.

For most academics working in research there is little incentive to focus on practical product-directed research when credits and accolades are more prevalent for basic research. Given that academics are primarily judged on the number of publications they produce and how much grant money they bring in, funding organizations could play an important role in changing some of the incentives. They could help make it attractive for PhD students and academics to push research until product developers can adopt it. For most of those funding basic research today this would re-

quire an increase in understanding about the importance of translation and the process.

Even where there is a high level of awareness of the benefits of technology transfer and there are potential leads or candidates that could be applied to neglected diseases, many of the technology transfer managers are not aware of the public health impact they could be having. There may be opportunities for them proactively to include intellectual property clauses in their agreements to ensure potential applications for neglected disease are not lost. For example, Yale University recently licensed a compound for commercial development for athlete’s foot and reserved the rights for any indications in support of Chagas disease. Technology transfer in universities is largely driven by metrics, such as numbers of patents licensed and income to the universities, raising the question of how to encourage consideration of public health issues as well as raising awareness of the routes into global health.

Even if promising leads are generated and identified there is the challenge of translation itself. In many cases the skills and resources needed to help ensure successful translation reside largely within the private sector (e.g., development of assays, compound libraries, production scale-up, development of analogues, medicinal chemistry, etc.). Many PD PPPs are already working with subcontractors or negotiating in-kind contributions from the pharmaceutical industry to help enable the flow of novel product-focused leads into the pipeline, but more attention in this area is still required.¹ There was strong feeling during the workshop that any investment and capacity building to improve translational capabilities should pay equal attention to opportunities in both the developing and the developed countries.

For the future of the field it is imperative to increase awareness and the level of investment in product-focused research and translation mechanisms. Without a steady flow and successful translation of potential leads, the PD PPP model will not be sustainable.

Clinical development, regulatory approval and delivery

Much of the work the PD PPPs do to develop and manufacture new products requires either approval

¹ See annex 9f (Nwaka S, Widdus R. *The current research-to-development ‘Hand-off’ process for product concept/candidate products and possible improvements in it*).

from existing regulatory authorities (e.g., FDA and the European Medicines Agency [EMA]) or, where available, from country regulatory bodies. As discussed above, in many of the countries for which the products under development are intended, there is not sufficient regulatory capacity. As a result PD PPPs must work within existing regulatory frameworks which often have a very different risk benefit threshold. In other cases, such as microbicides, the existing regulatory bodies do not have the necessary experience in approval and registration of the class of products. During discussions at the workshop there was strong feeling that coordination amongst PD PPPs and those organizations supporting them could help increase pressure on existing bodies to address the desperate need for regulatory harmonization and simplification.

As the PD PPPs plan for the success of their development efforts, they must also work in parallel with other organizations and groups to ensure that public policy, financing and infrastructure are ready once a product has been successfully developed.¹ Many of the gaps in resources or capacity highlighted during the workshop's discussions could be addressed through existing public sector organizations (e.g., WHO, UN and bilateral organizations). In particular some of the capacity building (e.g., translational capabilities, regulatory capacity, delivery infrastructure, etc.) and systemic issues (e.g., rapid public policy formulations, regulatory harmonization, etc.) are already within the remit of these organizations. The issue appears not to be one requiring new organizations but an increase in focus and attention on the issues. (See also subsection Preparing for access: availability and adoption, below.)

Private sector

Many of the skills required by the PD PPPs – both now and, increasingly, in the future – lie within the private sector. While many PD PPPs have links to private industry there was strong agreement that increased private sector involvement would be beneficial. The private sector today has been a source of both candidate products and access to technical expertise and physical resources, areas that will continue to be important in the future. Examples include:

- *New research technologies*: While the exact benefits are not yet clear technologies such as genomics or platform technologies should offer opportunities to improve the quality and flow of leads.
- *Manufacturing*: Formulation, scale-up, quality control.
- *Regulatory*: Management of the process of submission and reviews.
- *Market assessments*: Market sizing and economics.
- *Post-launch activities*: Pharmaco-vigilance, product liability.
- *Intellectual property*.

A better understanding of the current barriers to private sector participation is required if the level of involvement is to be increased significantly. Historically one of the greatest barriers to greater involvement, in addition to the opportunity cost, has been reputational risk given the political nature of the diseases and settings involved. Among some of the workshop participants, there was a strong belief that such an increase will only come from top-down support, driven by chief executive officers or senior research officers.

While big pharmaceutical companies have many of the significant expertise and physical resources required, the biotech community also offers a valuable source of resources. The biotech may not have all the resources of big pharma available but they are likely to have different opportunity costs than their larger counterparts. The private sector could have several motivations for getting further involved with PD PPPs, starting from a humanitarian desire to do the right thing, opportunities for good public 'image' and the benefits that come from people in the company feeling good about what they are doing. However, their involvement needs a good business case, as private companies must ultimately satisfy their investors. One of the challenges for PD PPPs is to encourage the private sector to articulate what it will take to get them involved and to explore innovative ways to work together.

One promising area of opportunity is innovative licensing agreements with the private sector. This is especially the case in instances where a private drug company has already started the development of a particular product for which there may be both a commercial and a public health market, but where the

¹ See annex 9i (Ghosh G. *Emerging lessons in preparing for uptake of new vaccines*).

development risks outweigh the potential commercial benefits to the company. PD PPPs are already benefiting from licensing high-potential products in such a way as to ensure technical support in conjunction with the product while reserving the benefits from potential commercial applications for the private company. The recent deal between the International Partnership for Microbicides and Tibotec (affiliated with the Johnson & Johnson companies),¹ is just one example of the types of deals PD PPPs for both infectious diseases and contraceptives have been able to reach.²

The biggest opportunity, however, is to build markets where companies can expect a reasonable return from their investment (e.g., through pull mechanisms and/or tiered pricing structures).

Open questions

- What is the right balance for PD PPPs between getting the product development done and ensuring upstream and downstream gaps are filled?
- What will help ensure that links between the PD PPPs and different sources of research in their field are strengthened? What are the best opportunities to strengthen links with research in disease-endemic countries?
- How could the development of research centres of excellence aligned with specific diseases be encouraged?
- Could incentives for facilitating action be put in place to make it attractive for PhD students and academics to push research to the point where it could be adopted by product developers?
- Can more be done to increase awareness among technology transfer offices of potential routes into meeting global health, as well as commercial, opportunities?
- How can issues of clinical trial, regulatory and ethical review capacity be handled to address the needs of the PD PPP field?
- What will it take to capture the attention of senior management within the private sector and thus increase their involvement with and support of PD PPPs?
- How best to increase speed and focus of public sector organizations on critical path investments that will facilitate successful development and introduction of drugs, devices and vaccines? Can

PD PPPs articulate their needs and priorities collectively?

Role of portfolio management

Many meeting participants familiar with product development repeatedly emphasized the length and the riskiness of the process, with attrition of candidate products expected at every stage along the research-development-access (R-D-A) continuum.³ Portfolio management evolved in the private sector as a vital process by which to limit risk, manage the flow of products to market and minimize the cost of the drug development process.⁴ Portfolio management has two key components:

- Diversification to reduce the reliance on a small number of candidates with similar characteristics and to ensure that the flow of products through the pipeline is smooth (i.e. enough products at different stages of development).
- Rigorous processes to ensure candidates that do not meet the specifications are weeded out.

Since most product candidates will fail somewhere along the development pipeline, management of multiple candidates helps to insulate funders from the risks inherent in health product development. The success of portfolio management is also highly dependant on the quality of the leads fed into the pipeline, reinforcing the importance of effective translation from research to development for PD PPPs. The availability of the right human resources and skills to ensure the process is run effectively is just as important for the PD PPPs as it is for the private sector.

¹ Under the arrangement, Tibotec provides a royalty-free licence to IPM to develop, manufacture and distribute TMC120 as a microbicide in resource-poor countries. Tibotec has already developed a TMC120-containing gel, which is currently in phase I clinical testing. IPM will assume responsibility for development of this compound. Under the agreement, Tibotec will bear the cost of the compound through phase II testing and will remain active as a scientific advisor. *IPM Press Release*, 29 March 2004.

² See Kettler H, White K. 2003. *Valuing Industry Contributions to Public-Private Partnerships for Health Product Development*, IPPPH, and other examples in the full version of this report.

³ See annex 9f (Nwaka S, Widdus R. *The current research-to-development 'hand-off' process for product concept/candidate products and possible improvements in it*).

⁴ See annex 9d (Schmid E. *Portfolio management in the pharmaceutical industry*).

Level of portfolio management

A number of times during the workshop, discussions focused on the different levels at which portfolio management could be conducted within the PD PPP field. Portfolio management could in theory be done at several levels by different players:

- Across the various diseases of poverty (neglected diseases) and across PD PPPs, by funders acting in coordination.
- Across a disease area, by a PD PPP.
- Across the array of products being developed by a particular PD PPP.

One of the challenges of operating portfolio management across the various neglected diseases and across PD PPPs would be how to implement the process efficiently to ensure timely and effective decision-making, which would be respected by all parties involved. Similarly it is unlikely that a single PD PPP would ever hold sway across all development in a particular disease area. However, some PD PPPs today chose to prioritize and select candidate products for development in light of those products already under development in their field; thus helping to reduce the development risk within a particular disease/product area.¹ Other PD PPPs are applying the principles of portfolio management to the array of products they are developing or have direct influence over.

The general conclusion of the discussions was that funders need to be in a position to support the portfolio management process and its outcomes but that PD PPPs are best placed to run the portfolio management process. Many individual donors do not have the depth of technical and scientific knowledge needed to choose winners and losers from among dozens of competing proposals. Most PD PPPs have explicit policies affecting portfolio turnover, with ‘go-no-go’ decisions taken by world-class scientific advisory boards and PD PPP technical staff. Thus the PD PPPs provide a way for funders to ‘outsource’ these decisions to technical experts.

Scale for portfolio management

Many PD PPPs are still in the early stage of developing their portfolios, falling well below the flow of prod-

ucts that would statistically be required to ensure ‘success’. From the work so far and the discussions during the meeting it is not clear what threshold for minimum scale or optimal functioning is required for portfolio management to be most effective. There was concern that to achieve scale there may be incentives to include leads of lesser technical merit or reluctance to kill projects in the pipeline for lack of better alternatives, thus reducing the overall potential for success. However, there was recognition that a rigorous process, with criteria agreed prospectively, can help improve the objectivity and quality of decision-making, one of the cornerstones of the PD PPP model.

To understand effective portfolio management with a smaller number of candidates (as seems a necessity in the vaccine field for practicability), it may be valuable to look at what the biotech field is doing in this area. In the case of some of the vaccine PD PPPs (MVI and IAVI), which have a portfolio of candidates against the same disease target, there may be less opportunity to learn from industry (the norm in industry is to have multiple candidates against different targets). The benefits from a portfolio with multiple candidates focused on the same disease target come more from the lessons and knowledge transfer across the portfolio.

It is also worth noting that in many cases, while a PD PPP may determine which candidates are the most promising to meet a particular need, this does not always mean the PD PPP will be directly responsible for the development of the selected candidate. Depending on the context in which they operate and the availability of suitable partners a PD PPP may outsource either in part or completely the development of the prioritized candidate product(s).

Target product profiles

Establishing agreed target product profiles (TPPs) is a common tool used in portfolio management to facilitate communication and expectation-setting along the development pipeline and to help to ensure that all relevant parties have input (manufacturing, end users, etc.).

In general, TPPs include ideal and minimum criteria across a range of dimensions that reflect the cross-functional nature of product development. The criteria go beyond scientific potential to include usability, manufacturability, costs, time to market and market

¹ See annex 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*).

potential. By defining success prospectively, and early in the process, progression or ‘kill’ decisions are streamlined at a later stage. PD PPPs (in consultation with their disease-control counterparts) are ideally positioned to play a role in developing target product profiles for their diseases. TPPs can be used to solicit submissions in open calls for candidates or as a screening tool for looking at in-licensing opportunities.

Managing the development of the profile and ensuring input from all the relevant stakeholders are almost as important as developing the profile; a good process is the best way to ensure a good profile. The process of portfolio management and TPPs are well established in many big pharmaceutical companies offering another potential area where industry could help with resources or know-how.

Valuing products in a PD PPP environment

In the private sector, products enter the pipeline at all stages of development. Capital markets and financial tools facilitate determination of a ‘value’ for products and thus allow seamless comparison of in-house candidates and external opportunities. Across the PD PPPs, portfolios of products have evolved very differently, coming from basic research, previously abandoned private sector candidates or existing products being considered for a new use. Ascribing monetary value to these products is not particularly valuable given the relative lack of a commercial market for products in the PD PPP world. Given that the common goal of PPPs is public health impact, it seems desirable that an approach be developed to express the potential benefit of the anticipated products, taking into account factors such as:

- Cost and likelihood of successful development.
- Target population and the fraction likely to be reached.
- Cost of ensuring ‘access’.

Funders and portfolio management

PD PPPs have a further challenge when executing portfolio management given the direct involvement of many of the current funders of PD PPPs. A PD PPP that wants to kill a project not only has to say “No” to researchers but also sometimes to funders. In many cases, funders are not currently aligned with a portfolio of products but fund individual products or

projects.¹ Many organizations providing funding today and in the future are not going to be familiar with drug development, the long time frames and the high level of failure during development (a 95 per cent failure rate is the norm^{2,3}) putting PD PPPs in the role of educator and manager of expectations.

The general conclusion during the discussions was that funders should probably let PD PPPs manage the science advice and the portfolio process.

Open questions

- Are there best practices for successful portfolio management in big pharmaceutical companies and the biotech industry that would be applicable for PD PPPs, including those developing vaccines?
- Are PD PPPs big enough to achieve the benefits of effective portfolio management? At what scale is portfolio management most effective?
- Are funders willing to align themselves with a portfolio of product candidates rather than specific projects?
- Do PD PPPs require specific resources and capabilities to support portfolio management (e.g., portfolio models for vaccine candidates)?

Preparing for access: availability and adoption

No drug, vaccine or device will be effective even if it is affordable and of high quality if it does not reach those for whom it is intended. Ensuring access, availability and wide adoption is as much of a challenge as the development of the technologies themselves. Public health experience has shown that uptake of new technologies is not always automatic (e.g., hepatitis B and antiretroviral drugs).

The term ‘access’ is often used to describe a variety of different issues associated with the development of products targeting the diseases of the poor, ranging from public policy to end-user product acceptability. While there is no commonly agreed definition for the purpose of these discussions, two broad categories of issues will be considered under the umbrella of access: availability and adoption.

¹ See annex 9b (op. cit.).

² See annex 9a (Towse A, Mestre-Ferrandiz J, Renowden O. *Estimates of the medium-term financial resource needs for development of pharmaceuticals to combat ‘neglected diseases’*).

³ See annex 9l (op. cit.).

The work to ensure access needs to be started in parallel with the product development process to ensure that the demand, public policy, financing and infrastructure are all in place when a product is successfully developed.¹ There was a general feeling that PD PPPs need to embrace these issues but that they may not necessarily be the best group to address all of them directly. However, PD PPPs may be able to play a role in defining the conditions required to support/ensure access.² Critical steps in preparing for access (beyond the fundamental tasks of appropriate design for disease-endemic countries and user acceptability) include the development of:

- Ensuring *availability* requires:
 - Appropriate regulatory approval and licensing infrastructure
 - Manufacturing capability and sufficient capacity
 - Logistics and delivery networks in-country.
- Ensuring *adoption* requires:
 - End-user awareness about the product and its benefits
 - Effective pricing and financing mechanisms to ensure affordability
 - Supportive social and policy environment (and the research to generate this).

Planning for availability and adoption will take significant investment, which is often neglected. For example, in the case of vaccines accurate uptake curves based on product profiles and projected prices are required five years before licensure to ensure capital investment in properly sized factories to prevent tragic delays in availability.³

At a macro level the leadership in DECAs needs to become champions of health issues for long-term successful adoption of these products. Countries where the most progress is being made in tackling diseases of poverty have significant leadership from the top (e.g., introduction of vaccines in Mozambique and the roll-out of new anti-malarial treatments in Zambia).

¹ See annex 9i (op.cit.).

² PD PPPs may also be able to work with access PPPs in fields where they have been established.

³ See annex 9k (Sadoff J. *The Cost of Trials and Manufacturing Process Development for Vaccines*).

Open questions

- What role can current funders play in mobilizing required resources to ensure delivery systems are in place?
- Who is best placed to build the evidence to influence policy as these new technologies are developed? What evidence will be required?
- How involved should PD PPPs be in the tasks associated with preparing for access? Who should be taking the lead? If the private/governmental sector is not fulfilling their responsibilities, who can hold them accountable?
- How can the attention of the leaders in disease-endemic countries be captured?

Financing

As one of the chief executive officers of a PD PPP who attended the workshop put it “Our job is balancing time and resources to do whatever is necessary to bring a product to market.” Whether done privately or in the public domain drug development is expensive. When we are also talking about enabling access and delivery for these drugs in developing countries where the mechanisms and policy are not yet in place, expected costs rise even higher.

PD PPP needs

A steady flow of funds or a significant amount of money in the bank is important to operate the daily activities of the PD PPPs and give them credibility. One of the most important tasks for PD PPPs is attracting human resources to do the work. Unlike a start-up biotech a PD PPP cannot offer the necessary significant financial incentives like talent stock options, making the stability of funding very important. Having a strong bank balance also helps ensure PD PPPs are taken seriously when they negotiate with potential collaborators from industry. Companies that work with PD PPPs want to know that if they start projects there will be financing to complete them.

One of the challenges faced by PD PPPs is that unlike a venture capital firm which invests in a biotech for an agreed expected return, many of today’s funders have not defined what they are looking for when investing (e.g., absolute public health impact versus impact for the poorest social groups). A venture capital firm investing in a start-up biotech would also want a

good understating of the likely scale and timing of the potential funds required; such clarity is not yet available to funders of PD PPPs.

There was some discussion about the timing with which funds are disbursed to PD PPPs and the merits of incremental year-by-year funding versus lump-sum commitments that represent several years of funding. There was recognition that the larger lump sums bring increased flexibility and credibility but that in practical terms incremental funding was much more likely. In many cases the incremental approach is not very systematic and comes in dribs and drabs from different grants and different funding processes. As the size and complexity of the financial commitments being made by the PD PPPs increases, so too will the importance of understanding the achievements/metrics required for receiving additional support.

Current situation

Based on estimates of funds committed by early 2003, and cost estimates for the portfolio of products underway, the financing shortfall through 2007 for major PD PPPs appears to be at least US\$ 1.2 billion and possibly over US\$ 2.2 billion, depending on assumptions.¹ There was strong agreement about the severity of the funding gap, if not its exact size, and concerns that the current base of funders may not be sufficient to sustain the existing array of early candidates and PPPs as they mature.

Today's best estimates of the funding gap are based largely on estimates of development costs by phase of development and expected failure rates for different phases of development based on historical experience. In some, possibly most, situations the cost of delivering the drugs could significantly exceed the product development costs. During the meeting a strong desire was expressed to expand this work to provide an even clearer picture of the funding gap. Areas that could benefit from further clarification and inclusion in such an analysis include:

- Attrition rates by phase of development,² particularly for newer vaccines.
- Cost of development by stage (see annex 9a).

¹ See annex 9a (op. cit.).

² Including differences between small-molecule drug and vaccine development.

- Investment in capacity required (e.g., clinical trials, manufacturing facilities, etc.).
- Preparation for access (e.g., research to influence policy, delivery systems, etc.).
- Timing of the required funds.
- Variation in the above factors across drugs, vaccines, diagnostics and other products.

While in-kind contributions are recognized as an important resource to the field that is likely to continue, quantifying their value is particularly hard given the unpredictable and sometimes intangible nature of these contributions.

Broadening the funding base

Today the majority of funding for the PD PPPs comes from bilateral organizations and philanthropic foundations focused on development and public health. In some cases PD PPPs are still supported by a single, or very preponderant funding source. The Bill & Melinda Gates Foundation is the sole or major funder in FIND, MVI and HHVI. The sheer weight of future investment required makes it essential for the field to generate support from beyond these traditional funders, which have many competing demands on their resources. On top of this there is growing concern that the growth of the field is stretching the human resources of both existing funders and the PPPs with the amount of time spent on educating and lobbying for funding. In addition many of these funders are working to meet the needs of getting existing technology to people today.

Broadening the funding base beyond traditional 'development' funders will require a focused advocacy effort for both the PD PPP model and investment in product development. Neither traditional funders nor potential funders have historically invested in this type of product development and may not be able, at this point, to grasp the real significance of candidate failures or the magnitude of the investment required. For many there will be the question of the trade-off between investing in getting existing products to people today and investing in R&D for new products. The increasing use by PD PPPs of more business-case style analysis that starts to look at return on investment (both public health and monetary) will help funders assess these trade-offs. The more sophisticated and practised the PD PPPs become at these analyses, the better they

will be positioned to obtain financing from any source. While PD PPPs are not the only vehicle for product development, the model appears to be very well adapted to generating in-kind contributions and support from both the private and the public sectors. Analysis by impartial commentators concluded that the PPP approach, while needing some refinements, is currently the main hope for progress.¹

The good news is that there are still many global players who are not actively supporting investments in product development (e.g., not all members of the G8). However, as discussed earlier, any strategies to increase support will only be successful with clear, simple messages about the benefits and public health outcomes the PD PPPs aim to deliver and why the model is advantageous. For some of the smaller governments and funders, which do not have the capacity to assess each PD PPP investment opportunity, efficient mechanisms to get them involved will be important. Within the private sector there could also be opportunities to get some of the multinational companies involved.

Innovative strategies

Other ways to address the funding gap include exploring other financing mechanisms to attract new funds and looking for potential cost-saving strategies.

Financing

The World Bank's 'Out of the Box' working group² has, as part of its remit, been looking at opportunities to leverage the capital markets to attract new funders or optimize existing financial flows.³ Some of the mechanisms allow funds promised in the future to be brought forward in time (tax exempt debt and securitization); others could bring new capital (project finance and put options⁴). In general, while these mechanisms may be applicable in a small number of situations (e.g., project financing to help enable investment in manufacturing sites), they are unlikely to attract significant amounts of new capital to product development *per se*.

'Pull' mechanisms, including guaranteed purchase, could also benefit the PD PPP field. These mechanisms reduce risk to the developers by providing assurances about the future market for the products under development. Recent work by the Pull Mechanisms Working Group⁵ has shown that these mechanisms are legally

and practically feasible and enforceable, which will increase their potential as a tool for the market. A point made by several groups at the meeting was that 'pull' mechanisms alone will not be sufficient to tip the balance and open the doors to private investment in these markets.

There was also discussion about the potential to encourage more private sector involvement by reintroducing the profit motive. While this is not a new strategy in itself, some of the drug manufacturer representatives highlighted concerns about possible political and negative public relations ramifications of profiting from diseases affecting the poor.

Cost reduction

With such a large amount of funding required, the obvious question of what opportunities exist to reduce the overall requirements must be explored. One of the drivers of cost in the process of developing and gaining approval for a product is the regulatory environment. There could be opportunities even within the current regulatory framework to reduce the burden on phase III trials and perhaps shift some of the work into a phase IV study so that the costs are only incurred if the product is successful.

With some of the later-stage, larger investments, there may also be opportunities for cost savings from sharing resources or investments across PD PPPs, for example development of clinical trials or manufacturing capacity.⁶ Other strategies could involve shifting investments to lower-cost countries. However, there was some concern that benefits might not be that significant; for example, one comparison of manufactur-

¹ See annex 9l (op. cit.).

² Assembled by James Wolfensohn, President of the World Bank, the group consists of senior leaders from industry and the public sector, with particular focus on representation by finance professionals specializing in health care.

³ See annex 9c (Batson A, Shah R, Gingerich C, Rosenquist JN. *PPPs and product development: Innovative financing opportunities and the need for a 'business case' approach*).

⁴ A put option is a contract that gives the holder a right to sell a certain asset to the writer of the option at a specified price up to a specified date.

⁵ See annex 9i (Ghosh G. *Emerging lessons in preparing for uptake of new vaccines*).

⁶ Shared manufacturing facilities are not a possibility for vaccines as current regulations essentially preclude multiple use factories for large scale production.

ing plant costs between India and New Jersey, USA, suggested less than a 20% saving.¹

Open questions

- What is the true funding gap? How much is required and when?
- Who are other potential funders and what constraints/goals influence what they can fund?
- Is there more to be done to garner support from the countries for which these products are destined?
- What role can existing funders play to help attract additional funders?
- What is the right funding balance between PD PPPs and other product development models?
- How to ensure balanced funding for research, translation, product development and uptake?

Judging success

Many of the PD PPPs have established a set of internal metrics to monitor their own performance. However, there does not appear to be a set of commonly understood metrics across the field. Two sets of metrics are important: operating metrics to measure internal performance (R&D and value added of PD PPP model); and output metrics to quantify potential public health impacts.

Operating measures could go beyond funds raised and disbursed, and typical R&D metrics to highlight the progress made by PD PPPs on value-added activities. Some of the additional categories could include:²

- Building unique capabilities and platforms to attract and select the most promising projects.
- Improving their partners' research capabilities.
- Mobilizing funds in line with portfolio and organizational developments.
- Enhancing knowledge and knowledge dissemination among research partners and the broader public health actors involved in turning new products into health impact.
- Progress towards the target (e.g., relative to a road map).

Clear metrics for the field could benefit the PD PPPs in communicating their performance beyond the current audience. In addition, the cost of assessment and monitoring for both donors and PD PPPs will become substantial without common metrics. For funders in

particular, there is a strong desire to have output metrics for the field that allow them to compare investment in PD PPPs with other types of investment. Well-defined and widely utilized metrics will not only serve the funders but if action is taken based upon them, this will help to focus PD PPPs and reinforce the management rigour associated with the model.

Open questions

- What operational metrics are applied by PD PPPs today? For whom? What works?
- What are the best practices from private industry? Could PD PPPs use them?
- How can the value added of PD PPPs be measured or tracked?
- Is there a way to quantify both social demand and scientific maturity to enable comparison across this field and other public health investments?

Role of coordination

PD PPPs and the organizations funding them now constitute an increasingly large group. There appear to be potential opportunities for increased coordination either amongst the funders or the PD PPPs

During the workshop many of the participants expressed the view that coordination would be essential for broadening the funding base for the field. Whether it is the funders or the PD PPPs, working together to develop and deliver a simple set of messages about the PD PPP field will be more effective than a multitude of individual efforts, which may be perceived as competing with one another.

An area that was of particular interest to the PD PPPs was a coordinated effort to address some of the systemwide issues that all PD PPPs now face or will face, but which are too large for an individual PD PPP to tackle alone. Some issues were highlighted, such as regulatory harmonization and simplification, clinical trial and ethical review capacity and investment in delivery infrastructure in disease-endemic countries. However, additional areas would most probably benefit too.

¹ Reference being requested.

² See annex 9e (Pfitzer M. *Demonstrating value: Performance metrics for health product development public-private partnerships*).

The meeting also discussed the potential benefits of investment in shared resources across the PD PPPs in areas such as data management, intellectual property and regulatory skills. Amongst the PD PPPs, a small group of the better-established organizations are connected to varying degrees with information being shared between executives and, increasingly, their staff members. PD PPPs themselves will need to drive any further coordination or even collaboration amongst them. In general, there were some reservations about how much coordination on core operational activities would be beneficial. There was some concern from the PD PPPs that additional umbrella organizations could create additional burdens to getting their work done.

Open questions

- How can donors work together to help address some of the systemic challenges facing the field (e.g., regulatory harmonization, public health policies, etc.)?
- What are the best ways for the field to coordinate work on advocacy for the model?
- Should funders coordinate to reduce transaction costs for PPPs and themselves (e.g., independent assessment of PD PPPs, common frameworks for proposals, etc)?
- Would investment in shared resources for the PD PPPs be beneficial or desirable?
- Is there value to having a body that represents the PD PPPs collectively?

Meeting takeaways

- PD PPPs are at present the best approach to development of products to combat diseases of poverty.
- Product development (customer needs and technical development) should remain the core focus of the PD PPPs; other roles will be determined by the context in which they operate.
- Both similarities and differences across PD PPPs needs to be recognized.
- Increased involvement of the disease-endemic countries along the R–D–A continuum is critical to long-term, sustainable product development and adoption of successful products.
- Currently a funding gap for product development in neglected diseases exists; exact funding needs are still not fully known.
- Development of some common operating performance metrics and measures of likely public health impact would be beneficial to PD PPPs and funders.
- Additional sources and mechanisms for funding product development will need to be mobilized; both ‘push’ and ‘pull’ mechanisms will be required.
- Mobilizing new sources of funding will require a coordinated effort by current funders and PD PPPs.

Areas for future attention

Roy Widdus and Katherine White

As the global commitment to address the burden of communicable diseases associated with poverty increases, so too does the awareness of the need for new treatments and interventions to address these diseases. To date, the PD PPPs have shown themselves to be the most promising vehicle by which to develop these much-needed tools. The momentum that has developed behind the current array of PD PPPs in the past five years is impressive, but there is more to be done if they are to achieve their full potential and provide the best return on investment.

During the IPPPH workshop in April 2004 a number of areas requiring further attention was identified. Addressing these areas will help ensure the continued progress of the PD PPPs. While the participants came to no specific consensus conclusions about the relative priority of these activities during the workshop, its organizers have solicited further input from the overall meeting co-chairs, the session co-chairs, current funders of the PD PPPs, the PD PPP CEOs and participants from African countries to develop some consensus about the priority areas to be addressed.

The following section represents a synthesis of the input from these groups combined with the discussions during the workshop.

Addressing the following challenges will most likely enhance the probability for ultimate success of the PD PPPs:

- Development of common performance measures.
- Coordination on clinical trial capacity development.
- Harnessing the potential of the disease endemic countries.
- Ensuring financial sustainability of the PD PPPs.
- Communication and coordination.
- Fully recruiting potential industry contributions.

Development of common performance measures

The need for the development and implementation of some commonly recognized, comparable measures by which to assess the performance and progress of the PD PPPs was highlighted at the workshop itself, at the donor consultation associated with the workshop and by many of those involved in the post-workshop consultation.

Recognizing that each of the PD PPPs has a different set of objectives and that these will evolve over time, there was still strong feeling that the benefits of recognized quantitative and qualitative measures of performance would be significant for the PD PPPs themselves, current and future funders of PD PPPs, as well as their potential partners.

Desirable performance measures mentioned during the meeting included:

- Estimates of the potential public health impact and cost-utility of new products
- Quantitative productivity goals
- Measures of PD PPP ‘added value’ including the effectiveness of their portfolio management approaches for public health outcomes.

Those funding PD PPPs today and in the future will always have their own strategies and preferences for areas of investment (e.g., specific diseases, specific stages of development, etc.). However, they all need to be able to evaluate the performance of their investments. A common set of measures will help ensure an objective evaluation of how well an organization is performing against specific goals and relative to other similar types of organization. Likewise for PD PPPs, the opportunity to develop a track record may also facilitate longer-term financial commitments from funders as investments are made based not just on achievement

of milestones but also improvements in performance. The availability of public information and the development of a performance track record will also help industry partners, researchers and other stakeholders. Strong indicators will provide valuable data with which they can make the case for getting involved with a specific PD PPP.

Estimates of potential public health impact of new products start within the burden of the disease targeted. However, they also take into account the probability of success in product development *per se*, the time to success and the subsequent time to wide application. They need to incorporate some estimate of the fraction of the theoretical target population that would actually be reached given the likely delivery systems, and the efficacy of the intervention. Combined with the costs of product development and the costs of application, such cost-utility measures would provide investors additional information to help inform decisions. Admittedly, such estimates incorporate projections that are often uncertain but the effects of these on the robustness of conclusions can be determined by sensitivity analyses using a range of plausible predictions.

Such analyses of potential public health impact have been used by the National Institute of Allergy and Infectious Diseases, for vaccines^{1,2} and could be easily extended to other products.

Productivity goals do not necessarily need to incorporate or assume guarantees of success in delivering new products. Where there is higher lack of certainty about scientific success (e.g., some ‘first-in-class’ vaccine development efforts) productivity goals can be framed in terms of process measures (e.g., moving x candidates from development stage b to development stage e). Quantitative productivity goals will enable PD PPPs the better to calculate and negotiate for the funding they need to pursue their mission. Without a clear sense of what will be attempted, funding will be more difficult to negotiate and evaluate.

Some meeting participants informally expressed reservations about the feasibility and use of common performance measures; they argued that the activities of each PD PPP were so different scientifically that no common measures could be found. Some were also apprehensive about the use of such measures for comparison.

Marc Pfitzer³ discussed the ‘value’ that PD PPPs

provide for funders. This value actually lies at levels other than the strictly scientific aspect of product development, where most of the variation between different disease/product targets actually occurs. Such value is represented in the quality of the scientific advice brought to bear on decisions, the quality of project oversight and coordination across multiple players, in the rigorous execution of project management approaches and in cost controls. PD PPPs need to consider their value-added contributions. If PD PPPs themselves define the way in which their approach adds value, they will be contributing to the creation of common performance measures.

This may require extensive consultation to achieve agreement on meaningful approaches, but eventually should help the ventures as well as their funders.

Related to added value is the relatively unquantified area of portfolio management approaches for public health goals. As pointed out by Towse and colleagues,⁴ data and techniques for commercial portfolio management are mostly based on drug candidate attrition rates. Further work specifically for vaccine candidates would benefit a range of PD PPPs addressing vaccines.

PD PPPs apprehensive about use of common performance measures should recognize that comparisons are already being made now by measures that are not identified explicitly. They will be better able to make their case if funders are using specific criteria for comparisons.

Successful establishment and development of such metrics will take time and require the buy-in and long term commitment of both the PD PPPs and their current funders. The challenge for funders (and possibly management consultants or other impartial actors) is to define common performance measures that can be used legitimately across different PD PPPs. Care will also need to be taken to ensure that common performance measures are used appropriately, and that legitimate reasons for differences, e.g., differences in

¹ Institute of Medicine, 1986. *New Vaccine Development: Establishing Priorities*. Volume 1: Diseases of Importance in the USA. 458 pp.; Volume 2: Diseases of Importance in Developing Countries. 432 pp. National Academies Press, Washington, DC.

² Institute of Medicine, 1999. *Vaccines for the 21st Century: A tool for decision making*. 476 pp. National Academies Press, Washington, DC.

³ See annex 9e (op. cit.).

⁴ See annex 9a (op. cit.).

the level of scientific challenge resulting from disease/product choice, are taken into account.

Coordination on clinical trial capacity development

As many of the PD PPPs make progress and bring candidates successfully into the later stages of development, the need for clinical trial capacity in DECs has become increasingly urgent. Phase III clinical trials are one of the most critical and expensive stages of the development process (Di Massi et al. estimates 30 per cent of successful drug products' development costs are incurred during phase III trials¹), and this is probably higher for vaccines.

Today, despite the many groups working to develop clinical trial sites and the predicted demand for such sites, there is still insufficient capacity and overall capability in disease-endemic countries to meet existing demand. This shortage of capacity will lead to undue competition for sites and costly delays to the clinical development of these much-needed products unless it is addressed.

Increased coordination among funding agencies and product developers for 'neglected diseases' will help ensure funds are invested efficiently and in such a way as to ensure the capacity can be sustained. Such coordination may involve groups working together across multiple dimensions including the development of training programmes, sequencing and timing of trials, development of sites and/or establishment of multi-trial sites. From discussions with the African participants they may be well placed to take the lead in coordinating across the PD PPPs (see discussion below).

If, wherever possible, PD PPPs adopted common trials data management systems, then training, trials implementation and analysis would be facilitated.

Without close collaboration between the agencies currently developing sites, the PD PPPs and resources in the disease-endemic countries, it is highly unlikely that the urgently needed trial capacity will be available in time.

Harnessing the potential of disease-endemic countries

During the meeting and in follow-up discussions, there was strong agreement about the importance of legitimate involvement of the various constituents from the disease-endemic countries. While there are many ex-

amples within PD PPPs of DEC scientists and institutions playing critical roles, there still are additional opportunities for increased involvement and needs in these countries, e.g., regulatory capacity strengthening related to rapid uptake. Some opportunities may be immediate, but leveraging the full potential that the DECs have to offer will require investment in new capacity. The African participants highlighted three areas of opportunity (and these are likely to be explored further by them in a workshop scheduled for August 2004).

Clinical trial capacity development

While no specific resources are available in Africa today to assist with the general development of clinical trial sites, many of the activities required to provide such service could, with some targeted training and system development, be handled by personnel trained and living in Africa.

R&D on products from traditional African medicines (TAM)

Throughout Africa there is widespread use of traditional medicinal plants as health measures by traditional health practitioners.² While not developed under recognized regulatory processes, the numerous plant species with potential medicinal used in TAMs could be a valuable source of product ideas and leads. Networking institutions in the field and linking to pharmaceutical development expertise would be useful.

African Scientific and Technical Review Committee

Today product developers make trial applications through bodies in Europe and the United States. As a result IRB members are trained in line with European and US ethics and standards. While these standards are important, so too are experience and credibility with the African communities. Within Africa there are currently enough individuals with sufficient experience of both cultures to enable the establishment of an African Scientific and Technical Review Committee which could help improve the smooth running of tri-

¹ Di Massi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 22(2003) 151-185.

² See annex 11 (Kimanani E, Akanmori B, Gamaniel K, Inyang U, Kilama J, Kitua A, Leke R, Pallangyo K. *Consolidation of the Private Partnership For Product Development: Africa's Role*).

als in Africa. The ‘critical mass’ available at a regional level could help train and develop capacity including that for **regulatory approval** in the individual major countries of the region.

If the full potential of the DECs is brought to bear on the challenges faced by the PD PPPs, there is a much higher likelihood that these countries will feel truly involved. They will thus take greater ownership of the end products that are developed and will contribute both in-kind and financially to their development and rapid utilization.

Ensuring financial sustainability of the PD PPPs

Despite significant success in raising and mobilizing funds the PD PPPs are still under-resourced. While the exact size and timing of future funding required by the PD PPPs is difficult to ascertain precisely, there was strong agreement about the severity of the funding gap and concerns that the current base of funders is not sufficient to sustain the existing field.

Maintaining the current level of funding and attracting additional support beyond the traditional ‘development’ funders will require better understanding of the size and timing of the current funding gap and a clear case for the benefits of investment in product development and the PD PPPs. For some of the smaller governments and potential funders, finding an efficient way to get them involved will also be critical as they do not have the capacity to individually assess all PD PPP investment opportunities.

Both the industry executives and current funders of the PD PPPs will need to work together if they are to develop effectively and deliver clearly the required messages about the potential value of investing in the PD PPPs.

Communication and coordination among players in the research–development–access (R–D–A) continuum

It became apparent during the IPPPH’s London workshop that some level of contact among different players in the R–D–A continuum exists, e.g., occasional contacts between PD PPPs. However, it is unrealistic to believe that the current level of communication and coordination is optimal. Indeed, the meeting was the first time that the PD PPP ‘executives’ and their major funders had met to share information and viewpoints.

Enhanced communication and coordination are needed both across different product development efforts and also along the R–D–A continuum.

While additional coordination should improve overall efficiency and prospects for success, it should be seen as a means to an end, not a goal in its own right. Proposed information exchange and coordination activities should be considered carefully so as not to impose unnecessary burdens on already busy individuals and ventures.

PD PPPs should consider where there is advantage in:

- Information sharing, e.g., on deal making and/or intellectual property management.
- Coordinated action, e.g., possibly on common systems for clinical trials data management.
- Collective advocacy, e.g., for attention to product development to achieve the Millennium Development Goals.
- Collective action for resolution of common problems, e.g., strengthening of regulatory capacity in disease endemic countries.
- Development of methods (especially for vaccines) of portfolio management based on likely public health benefits.

Funders should continue dialogue on:

- Their desire for common performance metrics
- Opportunities to coordinate funding
- Strategies to expand the pool of funding.

Players *along* the R–D–A continuum for particular diseases should consider what communications and coordination vehicles would be useful:

- To ensure that necessary information for policy decisions (e.g., on public health utility) is developed in a timely fashion (not sequentially/subsequently to product development itself)
- To best ensure anticipatory action (e.g., estimating demand, ensuring financing and strengthening delivery systems for rapid uptake) is planned and undertaken in a timely fashion.

One facet of coordination along the R–D–A continuum that particularly deserves additional attention is the translation of concepts relevant to combating ‘neglected diseases’ from basic research to the status of candidate products. This ‘translational research’ is

of concern to both basic research funders who want to see results in terms of health benefits, not only scientific knowledge, and to PD PPPs who need to be assured of an adequate flow of scientifically valid candidate products into their portfolios.

Although not cited by any PD PPP as their major current obstacle, it is a persistent concern, particularly for fields that have been relatively more neglected (e.g., tuberculosis and uniquely tropical diseases like Trypanosomiasis). Hence it deserves attention now to enhance the prospects of return on basic research investment and long-term PD PPP success. A study of current efforts in translational research and workshops to enhance coordination between basic research and PD PPPs (or some other means to achieve this goal) is warranted.

Fully recruiting potential industry contribution

Many participants in the IPPPH's London meeting expressed the view that – overall – the experience and

expertise of pharmaceutical companies, particularly the larger ones, could and should be more fully recruited to the 'enterprise' of product development for diseases associated with poverty. Contributions from industry could assist at various levels: the individual project level; overall portfolio PD PPP management; and in funders' assessments of individual PPP functioning.

Decisions about different sorts of engagement will be taken at the individual company level, and often on a case-by-case basis in response to specific requests. Therefore, it is difficult to devise a general strategy for enhancing the engagement of pharmaceutical companies with PD PPPs and their funders. Suggestions are made in the following section (Moving forward).

Notwithstanding the situation described above, the potential for instituting exchange schemes between public/governmental sector, pharmaceutical companies, and the not-for-profit sector should be explored as a means of improving understanding and knowledge transfer.

Moving forward

Roy Widdus

The workshop convened by IPPPH in April 2004 represents the first time representatives of all major not-for-profit ventures for ‘neglected disease’ product development and their principal funders had ever assembled to discuss issues of common interest in addressing diseases associated with poverty.

While the field is diverse, the *Meeting summary* and the emerging themes in *Areas for future attention* identified a range of issues where further discussion among various players will enhance the prospects for success. The best mechanisms for facilitating these further discussions are also in the process of definition.

Donor coordination

The principal PD PPP funders which had participated in planning the workshop (the Bill & Melinda Gates Foundation, the UK Department for International Development, the Rockefeller Foundation and the Wellcome Trust) convened after the workshop a small consultation among current PD PPP funders to discuss issues of shared concern. Conclusions of that meeting are provided in the Annexes in the full meeting report.¹

As of the time of publication, this Donor Consultation Group is working to define an agenda of work to address their concerns.

To contact the group, write to Dr Charles Gardner, Associate Director, Health Equity, The Rockefeller Foundation, at <gardner@rockfound.org> or Katherine White at <kawwhite@kawwhiteconsulting.com>.

Coordination among PD PPPs

As of publication, the Initiative on Public-Private Partnerships for Health and its parent organization, the Global Forum for Health Research, are assessing its future role. Information on coordination among PD PPPs will be posted on the IPPPH website and can also be obtained from the major PD PPPs.

For further information, visit the IPPPH website or email the Secretariat at info@ippph.org

Coordination among disease-endemic country researchers and policy-makers regarding capacity strengthening

Subsequent to the London workshop, African participants were planning a workshop scheduled for late August 2004 in Nairobi, Kenya to discuss their contributions to product development for diseases endemic in sub-Saharan Africa. It is planned to post a report of the meeting on the IPPPH website with contact details for sources of further information.

Coordination along the research-development-access continuum

Coordination among players and funders along the R-D-A continuum is probably organized most easily on a disease-oriented basis. Hence, the IPPPH Secretariat will be exploring with other parties the level of interest in periodic meetings of relevant players. IPPPH will, therefore, consult with the general coordination secretariats for various diseases, including those for the Stop TB Partnership, the Roll Back Malaria Partnership and the HIV/AIDS and Communicable Diseases Departments of the World Health Organization. For further information, see the IPPPH website or contact the Secretariat via <info@ippph.org>.

¹ See annex 10 (*Donor Consultation on Policy and Programming for PD PPPs, 16 April 2004, The Wellcome Trust, London, UK*).

Recruiting potential industry contributions

As noted above, pharmaceutical companies will most probably make decisions on engagement in different aspects of developing products for disease associated with poverty at individual company level, or even a case-by-case basis, as their in-house R&D activities and policies/philosophies vary.

Given this situation, proposing an overall monolithic approach to more fully recruiting industry expertise may not be as useful as pursuing their fuller involvement in the various forums noted above, particularly the proposed disease-specific discussions that will bring together different players along the research-development-access continuum.

Post-workshop consultation on *Meeting summary* and *Areas for future attention*

All PD PPPs were given the opportunity to respond to drafts of the *Meeting summary* and *Areas for future attention* before their finalization. Significant contributions to or comments on the *Meeting summary* and/or *Areas for future attention* were received from the following meeting participants:

Patricia Danzon, The Wharton School, University of Pennsylvania, USA (Session Co-chair)

Charles Gardner, The Rockefeller Foundation, USA (Co-organizer)

Michael Harper, Consortium for Industrial Collaboration in Contraceptive Research/Contraceptive Research and Development Program (CICCR/CONRAD)

Jane Haycock, Department for International Development, United Kingdom (Co-organizer)

Hannah E. Kettler, Bill & Melinda Gates Foundation, USA (Co-organizer)

Ebi Kimanani, International Biomedical Research Institute, Kenya [On behalf of the African meeting participants, namely: Rose Leke (Cameroon), Bartholomew Akanmori (Ghana), Uford Inyang (Nigeria), Andrew Kitua (Tanzania), Kisali Pallangyo (Tanzania), and John Kilama (Uganda)]

Andrew Y. Kitua, National Institute for Medical Research (NIMR), Tanzania

Adel Mahmoud, Merck Vaccines, USA (Meeting Co-chair)

Sigrun Møgedal, NORAD, Norway (Meeting Co-chair)

Melinda Moree, Malaria Vaccine Initiative, USA

Gwynne Oosterbaan, Global Alliance for Tuberculosis Drug Development (TB Alliance), USA

Sue Perl, Consultant to The Rockefeller Foundation, United Kingdom (Co-organizer)

Adrian Towse, Office of Health Economics, UK

Annexes

(Not included in the abridged version)

1. **Agenda**
 2. **List of Participants**
 3. **Background**
 - 3a. Background on the PD PPPs under consideration
 - 3b. Background on the concept of the workshop
 4. **Purpose of the meeting: Opening Remarks**

Roy Widdus
 5. **Millennium Development Goals**

(<http://www.developmentgoals.com/Poverty.htm>)
 6. **Keynote address**

Gail Cassell
 7. **Questions by Sessions**

Peter Hall
 8. **Background papers' key messages**
 9. **Background papers**
 - 9a. *Estimates of the medium term financial resource needs for development of pharmaceuticals to combat 'neglected diseases'*, Adrian Towse, Jorge Mestre-Ferrandiz and Olwen Renowden, Office of Health Economics, United Kingdom
 - 9b. *The emerging landscape of public-private partnerships for product development*, Alison Sander, Consultant, USA and Roy Widdus, Initiative on Public-Private Partnerships for Health, Switzerland
 - 9c. *PPPs and product development: Innovative financing opportunities and the need for a 'business case' approach*, Amie Batson, The World Bank; Raj Shah, Bill & Melinda Gates Foundation; Chris Gingerich, Wharton, USA; and J. Niels Rosenquist, Consultant, The World Bank and GAVI
 - 9d. *Portfolio management in the pharmaceutical industry*, Esther Schmid, Pfizer, Sandwich, United Kingdom
 - 9e. *Demonstrating value: Performance metrics for health product development public-private partnerships*, Marc Pfitzer, Foundation Strategy Group, Switzerland
 - 9f. *The current research-to-development 'hand-off' process for product concepts/candidate products and possible improvements in it*, Solomon Nwaka, Medicines for Malaria Venture, Switzerland and Roy Widdus, Initiative on Public-Private Partnerships for Health, Switzerland
 - 9g. *Ethical review capacity: Country needs, role and responsibility of partners and researchers*, Rose Leke, University of Yaoundé, Cameroon
 - 9h. *Current status of clinical trials in Africa*, Ebi Kimanani, International Biomedical Research Institute, Canada, Nigeria and Kenya and Valia Clements, Quintiles, USA and South Africa
 - 9i. *Emerging lessons in preparing for uptake of new vaccines*, Gargee Ghosh, Center for Global Development, USA
 - 9j. *The costs of developing vaccines: Case study of VaxGen's HIV candidate vaccine*, Donald P. Francis, USA
 - 9k. *Requirements for vaccine product and field site development at a licensure standard*, Jerry Sadoff, Aeras Global TB Vaccine Foundation, USA
 - 9l. *Product development public-private partnerships for diseases of poverty. Are there more efficient alternatives? Are there limitations?*, Robert G. Ridley, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)/WHO, Switzerland
 10. **Donor consultation on policy and programming for PD PPPs: Minutes 16 April 2004**, The Wellcome Trust, London, UK
 11. **Consolidation of the Private Partnerships for Product Development: Africa's Role** Kimanani E, Akanmori B, Gamaniel K, Inyang U, Kilama J, Kitua A, Leke R, Pallangyo K
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