External Review of Product Development Partnership Grant Framework
Netherlands Ministry of Foreign Affairs

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Acknowledgements

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Cheri Grace
Nel Druce
1 Background to Product Development Partnerships

Product Development Partnerships (PDPs) for neglected disease technology development are a relatively recent addition to the international architecture promoting access to medicines. PDPs have arisen to address the mismatch between need for health technologies to specifically address developing country health problems and the commercial sector’s traditional lack of willingness to meet that need. One of the reasons for the mismatch comes from the difference in disease patterns; non-communicable diseases dominate in the industrialised world whereas communicable diseases dominate in the developing world. There is undeniably significant demand for health technologies to tackle these communicable diseases, but lack of money to pay for it. As a result private research investments are strongly skewed towards developing products for the non-communicable, wealthy market disease patterns, and consequently only 16 of the 1,400 (or 1%) of new medicines developed between 1975 and 1999 were for neglected diseases. ¹

Product Development Partnerships arose about a decade ago as an answer to this gap. PDPs are focused on getting new products developed and in situations where the paying market is non-existent or insufficient to incentivise the private sector to front the costs and bear the risk of development or production on its own. The first PDP was the WHO’s Research and Training Programme on Tropical Diseases (TDR), although it can be argued that TDR is not really structured in the same way as the more recently emerged PDP model of the past decade. The core of PDP work is to bring together research partners from academia and the private sector, along with public sector funding - acting as a sort of virtual non-profit pharmaceutical company. PDPs attract technologies and in-kind contributions from the private sector, and through channelling publicly provided direct research funding, they offset some of the costs and risks that prevent the private partner from engaging in the product’s research, development, production and distribution. Some PDPs also engage in activities to evaluate and demonstrate suitability of existing (whether developed by the PDP or by others) technologies and facilitate their uptake at country level.

PDPs have emerged in the context of, and have also contributed to, a supportive political and policy environment. PDPs have been recognised in international declarations as potentially important contributors to fulfilling the MDGs, particularly MDG 6 (combat HIV/AIDS, malaria and other diseases). In 2001, the report of the Commission for Macroeconomics and Health included recommendations for increased funding for R&D, including through new public-private partnerships. The Mexico Declaration on “Health Research for equity in Global Health” in November 2004, declared as a “necessary action” that “research is needed into the roles of … public private partnerships in creating health products and widening equitable access to them”. The June 2005 G8 Finance Ministers’ conclusions on Development supported “scaling up support for vaccines and medicines research through the successful Public Private Partnership model”. The July 2005 G8 Communiqué on Africa committed to “increasing direct investment and taking forward work on market incentives, through Public Private Partnerships (PPPs) and Advanced Markets Commitments”.

The number of governments providing PDP funding has increased from 9 in 2005 to 12 currently, however the Bill and Melinda Gates Foundation remains the principal funder, accounting for around 50% of total funding for the field. The Rockefeller Foundation played a key role in incubating several PDPs and continues to provide funding. Funding from the European Union and the World Bank remains relatively low. Together with the UK, the Netherlands was one of the first bilateral donors to support PDPs. Funding from the Netherlands continues to have important strategic value to PDPs, as a signal to other European donors that the model is worthwhile. The value increase of the Euro in relation to the dollar during the past year has also made the Netherlands contribution grow in importance where PDPs operate in dollars.

Current PDP funding is a long way from meeting funding needs. One estimate of the funding gap for all PDPs was about one billion dollars per year. This sum represents PDP estimates of additional resources needed, beyond those currently provided, in order to fund the portfolio of products existing in the current PDP landscape. The funding needs are indeed growing - with products moving into the more expensive phases of the R&D pipeline. Sustained and increased funding will therefore become critical if earlier investments are to result in the launch and use of new products.

One of the keys to sustaining and growing the PDP funding base may lie in providing evidence that PDPs are the right way to deliver products for neglected diseases. This requires performance indicators, short of actual product, since product develop timelines are so long. It also requires reviewing the evidence of successes achieved by PDPs as well as critical assessment of potential missed opportunities and improvements that can be made.

A minority of PDPs have been formally evaluated, and both performance metrics and evaluation methodologies are still in development. Several efforts by donors supporting the PDPs are underway to improve understanding of PDP effectiveness and challenges, co-ordinated by for example the PDP Funders Group (initially called the Donor Coordination Group), launched in April 2004 and also supported by the Gates Foundation (e.g. the PDP meeting in Seattle in 2009). This evaluation of eight PDPs may also contribute to the field’s knowledge.

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2 Tara Acharya, Report for the Rockefeller Foundation and presented at the PDP Donor Co-ordination Group Meeting January 2006
2 Background to the Netherlands MoFA Evaluation

In November 2006, the Ministry of Foreign Affairs (MoFA) has decided to award 8 grants, in response to 9 applications for ‘Public-Private Partnership for research and the development of medicines, vaccines and diagnostics aid in the domain of Aids, TB and malaria.” A total amount of € 80 million was awarded, for the period 2006-2009.

<table>
<thead>
<tr>
<th>PDP</th>
<th>Budget (EURO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Aids Vaccine Initiative (IAVI)</td>
<td>16,200,000</td>
</tr>
<tr>
<td>International Partnership for Micriobicides (IPM)</td>
<td>12,000,000</td>
</tr>
<tr>
<td>AERAS Global TB Vaccine Foundation</td>
<td>18,744,000</td>
</tr>
<tr>
<td>Global Alliance for TB Drug development (TB Alliance)</td>
<td>8,000,000</td>
</tr>
<tr>
<td>Foundation for Inovative Diagnostics (FIND)</td>
<td>7,940,000</td>
</tr>
<tr>
<td>Medicines for Malaria Ventures (MMV)</td>
<td>6,954,885</td>
</tr>
<tr>
<td>Drugs for Neglected Diseases Initiative (DNDi)</td>
<td>2,975,000</td>
</tr>
<tr>
<td>European Malaria Vaccine Initiative (EMVI)</td>
<td>7,999,995</td>
</tr>
<tr>
<td>Total</td>
<td>80,813,880</td>
</tr>
</tbody>
</table>

The principal objective of the grants was to promote R&D for drugs, vaccines and diagnostics for HIV/AIDS, tuberculosis and malaria, which are effective, safe, applicable and accessible for the poor population of developing countries.

Secondary objectives were:

- Mitigating the effects of failing free market mechanisms: To help alleviate, as far as possible, the negative impact of the lack of effective market forces in the field of R&D as far as new therapies, diagnostics or preventive interventions for HIV/AIDS, tuberculosis and malaria are concerned.

- Fighting poverty with entrepreneurship: To achieve effective and efficient production of new medicines, vaccines and diagnostic technologies that are important for public health, and thus for the alleviation of poverty in developing countries, on the basis of complementarity between partners from the private and the public sector.

- Expanding knowledge and achieving increased capacity: To provide a powerful incentive towards expanding knowledge and achieving increased capacity within the group of partners in the field of research and development, both in industrialised countries and in developing countries.
3 Purpose of the Evaluation

The current grant period with the Dutch MoFA ends in 2009. In order to decide on an extension of the grant mechanism, the Dutch MoFA contracted a team of two consultants from HLSP to evaluate the following:

1) The relevance, effectiveness, efficiency and impact of the use of funds provided by the Dutch government, in particular in relation to the objectives
2) The impact of the Dutch funds on the PDP, also related to other funds.
3) Lessons learned, as an input for a new call, both related to content (focus of call) and process (funding mechanisms, funding management, progress monitoring)
4 Methodology

Two HLSP consultants were chosen to undertake the MoFA evaluation, bringing public health, evaluation, economics and access to medicines expertise, as well as previous work with Product Development Partnerships. The scope of work and methodology were agreed with the client; the agreement was for a “light touch” review, allowing an average of 2.5 days per PDP, to include document review and interviews with 2-3 informants per PDP plus 6-8 independent experts. It was agreed that the evaluation report would be comprised of approximately 10 pages of summary text, capturing issues across all the PDPs. In order to avoid detail that might be confidential, and allow the report to be shared across PDPs, it was agreed the report would read like a long executive summary. (Section 7 of this report)

The consultants divided up the PDPs, according to their time availability and previous knowledge of the PDPs and disease areas. The consultants made contact with the PDPs, and arranged for confidentiality agreements to be signed. Based on the team’s previous knowledge and a brief initial literature review, a questionnaire was developed, and sent to the client and to the PDP Donor Co-ordination Group Coordinator for comments. Adaptations were made based on feedback received and the questionnaire (Annex 2) was distributed to PDPs. Drawing from the emphasis in the TORs, the questionnaire was organised according to the categories of 4 of the 5 OECD DAC evaluation criteria:

- **Effectiveness**: “Are we doing things right?”
  - Evidence of how the PDP is performing in relation to its overall strategic objectives, and against the objectives of the MOFA grant. How well do the governance and organisational structure as well as management systems support the PDP in achieving its objectives?

- **Relevance**: “Are we doing the right things?”
  - Evidence that the PDP’s objectives are consistent with beneficiaries’ requirements, country needs, global priorities and partners and donor’s policies.

- **Efficiency**
  - Evidence of how economically resources/inputs (funds, expertise, time, etc) are converted into results

- **Impact**
  - Impact on poverty and health for patients in developing countries and on the global architecture for access to medicines

This format allowed for similar reporting and coding of results for each PDP by the consultant team. The evaluation report format has also been deliberately modelled on the format of the questionnaire.

It was recognised that PDPs who have undergone previous independent evaluations would already have much of the questionnaire information available, while PDPs who have not yet been through evaluations would have relatively more work to do in responding to the questionnaire. By requesting that the PDP provide links to references in existing written documents where possible, there was an attempt to minimise workload required of the PDP. In addition, some of the questions asked are those that donors will begin to ask annually and jointly through the PDP performance measurement instrument being developed by the PDP Donor Co-ordination Group. Therefore the learning gained through the exercise of collecting and pulling together information for this evaluation can be used again.
Several PDPs made requests to extend the suggested deadline for returning the completed questionnaire. The consultants agreed to all requests, and the client subsequently agreed to allow the consultants to extend the deadline on submission of this evaluation report.

Once the questionnaires were reviewed, interviews were conducted with the PDPs industry partners or Board representatives, independent external experts and subsequently, with 1 or 2 senior people within the PDP. Fewer external interviews were carried out for the three PDPs evaluated within the last three years (IPM, IAVI and MMV). Thirty-six interviews were conducted (Annex 1). Thus, the analysis of each PDP’s performance was a product of the PDP’s self-assessment via the questionnaire, triangulated against independent document review (including previous evaluation reports); views of partners and independent experts captured through interviews; and the consultants’ knowledge of health technology markets and the access to medicines architecture. The consultants drafted 4 to 6 pages of notes on each PDP, where insights gained from the PDP self-assessment, interviews and document review were intertwined. The consultants shared these notes with each other, discussed common and divergent areas across PDPs, and finally, wrote the synthesis - Section 7 of this report.

Factoring in initial preparation time and final report writing time, 30 days allowed the team to spend an average of 2-3 days per PDP. This allowed the “light touch” review envisaged by the client, with a focus on key findings as well as areas of possible tension, which may require more in-depth exploration. It was not possible within this timeframe to be exhaustive in the treatment of each PDP against each evaluation criteria heading. So instead of summarising what every PDP is doing under each heading, there was only time to focus on performance that was exceptionally strong, where potential problems were identified, or where noteworthy similarities or differences were found amongst PDPs.

It is acknowledged that the treatment of governance and management effectiveness, under the effectiveness heading, is particularly light. A proper evaluation of this subject would have required much more time interviewing and reviewing internal documents and systems; the PDPs would have found this to be more taxing and there was not sufficient time to devote to this. In any case, the working assumption is that effective management and governance reveals itself through the achievements along the effectiveness, relevance, impact, cost-effectiveness dimensions. Therefore, by critiquing performance along these dimensions, there is an indirect assessment of management and governance.

Given the timeframe constraints and the diversity of the PDPs, it was not possible to take an evidence-based judgement on some areas of possible tension. For example, to form a judgement about an appropriate portfolio size or minimum efficient scale of operations, there would need to be a more in-depth exploration of the supply and demand landscape for specific technologies. To form a judgement about whether conflict of interest exists, one would need to conduct more extensive interviews, review policies, advisory group and board composition and project selection criteria, and understand the relationship and power dynamics within a sector.
5 Report structure

We present evidence on the effectiveness, relevance, efficiency and impact of PDPs in general, and then we discuss the findings of the MoFA-funded PDPs specifically in relation to these criteria. We also highlight a few points on the impact of the MoFA funding on PDPs, from which lessons can be drawn about content and process of future calls for proposals. The annexes contain a list of people interviewed and the questionnaire format. The PDP's completed questionnaire, as a self-assessment against the criteria, was sent to the client as a separate zip file and other documents submitted by PDPs have been provided to the client on CD-Rom.
6 Evidence on the Performance of PDPs

PDPs require increased investment to bring products to market and donors need evidence that investing in PDPs is justified. In a resource-scarce environment, one of the challenges for donors is justifying the need for investment in research to develop new technologies versus investment now in scaling up existing health technologies. New technologies are intended to be substantial improvements upon existing technologies, allowing higher uptake at lower cost of superior products in terms of quality, safety, effectiveness, etc. Even though their uptake is delayed versus uptake of existing technologies, on a cost per DALY basis, and assuming a long term horizon, investment in new technologies should compare favourably. Rockefeller-commissioned research (figure below) illustrates this; dollars per DALY averted for new PDP-developed technologies were well within the acceptable range of $15 to $120 and favourable in comparison to investment in existing technology scale-up.

![Cost-Effectiveness of Existing Interventions v. PDPs](image)

**Cost-Effectiveness of Existing Interventions v. PDPs**
(for HIV and AIDS, TB and malaria in LMICs)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Existing Intervention</th>
<th>PDPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS: ARV therapy</td>
<td>$100</td>
<td>$10</td>
</tr>
<tr>
<td>HIV/AIDS: home care</td>
<td>$1,000</td>
<td>$100</td>
</tr>
<tr>
<td>TB: DOTS therapy (endemic)</td>
<td>$100</td>
<td>$10</td>
</tr>
<tr>
<td>HIV/AIDS: mother-to-child prevention</td>
<td>$1,000</td>
<td>$100</td>
</tr>
<tr>
<td>HIV/AIDS: opportunistic infection treatment</td>
<td>$100</td>
<td>$100</td>
</tr>
<tr>
<td>HIV-TB co-infection prevention &amp; treatment</td>
<td>$100</td>
<td>$100</td>
</tr>
<tr>
<td>TB: DOTS therapy (epidemic)</td>
<td>$1,000</td>
<td>$100</td>
</tr>
<tr>
<td>TB: BCG vaccine</td>
<td>$100</td>
<td>$10</td>
</tr>
<tr>
<td>Drug and Vaccine PDPs</td>
<td>$100</td>
<td>$10</td>
</tr>
<tr>
<td>HIV/AIDS: STI diagnosis with Treatment</td>
<td>$100</td>
<td>$100</td>
</tr>
<tr>
<td>HIV/AIDS: voluntary counseling &amp; testing</td>
<td>$100</td>
<td>$100</td>
</tr>
<tr>
<td>Malaria: residual household spraying</td>
<td>$100</td>
<td>$100</td>
</tr>
<tr>
<td>Malaria: insecticide-treated bed nets</td>
<td>$100</td>
<td>$100</td>
</tr>
</tbody>
</table>

**Slide Source:** Chad Gardner, based on Disease Control Priorities Project [www.dcp2.org](http://www.dcp2.org) and unpublished research by the Office of Health Economics, London UK (latter commissioned by The Rockefeller Foundation)

Accepting that investment into new technology research is justified on cost-effectiveness grounds, how should donors channel support to new technology development for neglected diseases? There has been some empirical analysis to show that the PDP model is performing well, helping to justify it as an effective channel through which to support neglected disease product R&D. Wellcome Trust funded research led by Mary Moran – the Pharmaceutical R&D Policy Project - found that, within the drug sector, PDPs have been responsible for increased
neglected disease R&D activity, increased effectiveness of that activity, and increased cost-efficiency of R&D activity.

The figure below contrasts the pre and post PDP world, in terms of neglected disease drug R&D activity.

What has been the result of PD PPPs versus 'pure' industry participation in neglected disease R&D?

... More R&D activity


Of the 63 neglected disease drug projects underway at the end of 2004, three-quarters were being conducted by PDPs. At standard attrition rates, it was projected that these projects would deliver 8 to 9 new neglected disease drugs between 2004 and 2009, as compared with the 13 new drugs developed for neglected diseases in 25 year period from 1975 to 2000. As revealed later in this report, these projections have proven to be accurate.

Although increased activity is a positive sign, donors are obviously interested in more details: is the activity well targeted to the needs of developing countries (i.e. relevant to their needs), and is it resource efficient, for example. The LSE group consequently devised a range of metrics, such as health value of the final products, level of innovation, development times and cost-efficiency. Measurement of the various drug development approaches against the metrics showed that industry working alone and public groups working alone performed less well on these parameters versus PDPs.

Highlighting just two examples: time to market (development times) and cost efficiency, we find:
- PDP drug development trajectories were significantly faster than public alone drug development times and they matched or exceeded industry standards for neglected disease research, and
- The overall cost-efficiency of PDPs was superior to other approaches, partly due to their ability to leverage in-kind contributions from partners and the exclusion of cost of capital.
What has been the result of PD PPPs versus ‘pure’ industry participation in neglected disease R&D?

... and it would seem, better performance than public or private individually

$112 million all PD PPPs 2000-2004 versus $400 million = industry average for 1 drug


Expanding on the latter point, the total collective PDP drug development activity from 2000 to 2004 was $112 million including cost of failure but excluding cost of capital for 40 projects. The industry cost for developing a new chemical entity for Western markets is substantially higher – estimated to be $800 million including cost of capital and cost of failure in one study and $400 million if cost of capital is excluded.

In addition to the LSE work looking at the PDP model overall, there have been studies of individual PDPs that have also been positive. The joint donor review of MMV in 2005 concluded that “MMV has made tremendous progress, ahead of its predicted milestones” and has successfully mobilised academic institutions and pharmaceutical companies in highly productive partnerships; within a relatively short period, MMV and its partners have established an “impressive portfolio”, with drugs about to emerge from the pipeline, as well as other, more novel compounds, at earlier stages of development. The World Bank evaluation of MMV in 2007 stated, ‘The specific value added of MMV lies in its proactive management of the R&D pipeline. It functions as an efficient allocator of public and private resources to finance potential new malaria drugs. MMV’s relatively large portfolio permits it to enjoy internal efficiencies in resource allocation across candidate drugs that could not be realized with a small portfolio.’

IPM’s multi-donor evaluation (2008) found that IPM “has contributed significantly toward the goal of developing safe and effective microbicides.” Furthermore, the evaluation found that “across IPM’s key activities (portfolio and product development, clinical trials, access, and advocacy), IPM has largely pursued the right strategies and appropriately assessed and managed risk.”
The evaluation of IAVI commissioned by the World Bank in 2009 concluded that “IAVI’s work has been highly relevant to the search for an HIV vaccine” and that “IAVI has added significant value to that search”, with “its unique focus on the development and uptake of a vaccine that meets the needs of the developing world”, and its “ability to identify and fill gaps in the design and development of HIV vaccines”.

7 Performance of the MOFA-funded PDPs

7.1 Overview of MOFA PDPs

It may be helpful to begin this section with an overview of selected characteristics of the MoFA-funded PDPs. The table below details the disease and technology sectors of focus to each one.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Microbicide</th>
<th>Diagnostic</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmaniasis</td>
<td></td>
<td></td>
<td>DNDi</td>
<td></td>
</tr>
<tr>
<td>Chagas</td>
<td></td>
<td></td>
<td>DNDi</td>
<td></td>
</tr>
<tr>
<td>Human African Trypanosomiasis</td>
<td></td>
<td></td>
<td></td>
<td>DNDi</td>
</tr>
<tr>
<td>Malaria</td>
<td>EMVI*</td>
<td></td>
<td>FIND</td>
<td>DNDi, MMV</td>
</tr>
<tr>
<td>TB</td>
<td>Aeras</td>
<td></td>
<td>FIND</td>
<td>TB Alliance</td>
</tr>
<tr>
<td>HIV and AIDS</td>
<td>IAVI</td>
<td>IPM</td>
<td>FIND</td>
<td></td>
</tr>
</tbody>
</table>

*During the time period of the Dutch grant, EMVI has been single disease focused

The figure below reveals the size of the MOFA-funded PDPs, as a function of 2008 expenditure, showing wide variation from 2.6 million Euros for EMVI to 62.8 million Euros for IAVI.

The figure below reveals the number of full time employees, divided by those based at headquarters versus those based at regional/country offices and research programmes. There is some correlation between size of expenditure (above) and size of staff, although size of staff is also a function of the PDP’s specific business and operating model. Some PDPs operate like mini biotech companies, e.g. Aeras, IPM, IAVI where key assets may be owned, expertise located in-house, and product development takes place internally of the PDPs own candidates as well as by external partners, co-financed by the PDP. Towards the other end of the spectrum is

Source: Question 1.c. of the MOFA Evaluation self-assessment questionnaire. NB: Dollars have been converted to euros at the spot exchange rate, Oct 14 2009
the project management organisation (e.g. DNDi, EMVI) where the PDP contracts for
the assets and expertise needed and primarily finances activities of external partners,
performing a project management function.

The difference in the percentage of regional versus headquarters-based staff is also
noteworthy. Interpreting this would require further work, but it may indicate any of the
following:

- some PDPs are more successful in finding capable regionally based staff
  versus others
- some PDPs define full time equivalent staff differently than other PDPs
- the labour market for staff with the requisite skills differs according to different
countries where PDPs are present
- Some PDPs work with and fund partner staff (e.g. clinical research partners)
  and others through establishing employee teams at existing or new sites

These overview figures reveal the significant range and diversity of the PDPs funded
by the MOFA. They reveal why comparative evaluation between PDPs is so
challenging and, along some dimensions, not even appropriate. This challenge has
informed the approach to this evaluation as well as the performance metrics used –
effectiveness, relevance, efficiency, impact - which are applicable across all PDPs.
7.2 Synthesis of Evaluation Results

**Effectiveness**

“Are we doing things right?”

Evidence of how the PDPs are performing in relation to their overall strategic objectives, and against the objectives of the MOFA grant. How well do the governance and organisational structure as well as management systems support the PDPs in achieving their objectives?

During the timeframe of the Dutch grant to the eight PDPs, the MOFA-funded PDPs developed four new neglected disease treatments and four diagnostic products. Clinical trials were started and concluded, some products were dropped from portfolios, and a substantial amount of discovery work, focused on breakthrough technologies, was undertaken.

With the exception of the FIND molecular diagnostic test for identifying MDR TB, products launched on the market were primarily incremental innovations, or “low-hanging fruit”. More substantial innovations, especially in the drug and vaccine field, will take more time. Recognising the risk and expense of new technology development, several PDPs have deliberately built a portfolio with a mixed level of innovation, aiming to get some incremental improvements to patients quickly while working on the higher risk, but potentially higher reward, technologies longer term.

Clinical research partnerships and significant trial capacity were built during the years of the Dutch grant, as well as health system capacity, including new approaches to robust and ethical trial design and management, treatment and care delivery, and substantial laboratory capability.

Partnerships were formed with biotechs, multi-national corporations, academic and other not for profit organisations, developing country research centres, and contract manufacturers. Independent experts assert that new partners entered into the R&D space based on PDP’s activities. Collaboration between PDPs was strengthened and assets and expertise were shared.

It would be fair to say that progress has been slower than expected on the objectives set out in the grant applications to MOFA for some of the PDPs. However, it would be inaccurate to conclude that this is a failure of effectiveness. Rather, it is a result of the fact that MoFA was willing to fund relatively higher risk (but potentially higher reward) discovery work, where uncertainty makes objective-setting and prediction of risks challenging.

Over the past few years, many of the PDPs made substantial progress in developing their management systems, adopting industry style approaches to portfolio and project management, organisational structure and governance mechanisms. However this review and previous evaluations (e.g. IPM, IAVI) also find a need for further work on strategic or business plans.

PDPs have developed explicit criteria for selecting partnerships and for advancing projects within the pipeline, or terminating them. PDPs which had earlier operated without strict criteria for project selection acknowledge that this cost them time and
money, for instance EMVI’s example of time wasted with an antigen that turned out to be impossible to produce.

The role of PDPs as product developers versus convenors or co-ordinators is important to understand. Some stakeholders perceive PDPs, such as IPM, Aeras, the TB Alliance and IAVI, which have their “own” products within their portfolio, as having a conflict of interest. Observers question whether it is appropriate for these PDPs to take on an independent convening function within the field. They question to what degree these PDPs can independently assess partner or external technologies, given their allegiance to their “own” technology. An assessment of whether these concerns are warranted requires an understanding of the supply and demand situation of the technology sector, the power balance within the sector, including the potential for alternative pathways of funding and partnership, and the transparency and rigour of the governance systems and portfolio selection and advancement criteria. The risk to be avoided is that these concerns and perceptions stifle incentives for innovation or (if the concerns are warranted) options for further development of viable candidates are actually closed off.

It may be helpful to clarify PDP roles, especially as these must be flexible and responsive to wider scientific developments, and communicate these clearly to stakeholders. IPM’s evaluation found it appropriate that, as “IPM made a deliberate decision to add value to the field by developing a pipeline of microbicide products”, “IPM has not viewed its role as a co-ordinator or gatekeeper vis a vis the global pipeline of compounds.” IAVI’s evaluation for the period 2003-2007, commented that as IAVI shifts more effort upstream to product design and develops more in-house capability, it also needs to better communicate its role in R&D. The evaluation recommended that IAVI “re-examine its identity in the R&D space”, and improve its communication about R&D lessons learned.

A key contributor for PDP effectiveness is the degree of success the PDP has had in engaging industry (pharma, biotech and manufacturers) to work as partners. The evaluations of IPM, IAVI and MMV all found robust industry partnerships. Some PDPs (Aeras) have attracted virtually all the private sector activity that exists in the sector. This may be a function of the PDP’s business-like approach and its superior negotiation skills, and/or a result of the economics of that technology sector and the PDP’s control over key assets on the pathway to market. Other PDPs (EMVI, TB Alliance) do not aspire to have partnerships with all developers in the sector, because they have a specific niche within the R&D pipeline; EMVI funds translational research and passes to others for development, whereas TB Alliance lets other do the earlier research and then shares costs during later stage clinical trials to take the product to licensure.

Other PDPs will inevitably have difficulty even finding a partner to try and negotiate with, and then more difficulty in convincing that partner that it is worth its while to “get up out of bed”. This seems especially true in tropical disease work, where there is a very small pool of expertise from which to draw and no dual market to eventually offset some of the costs.

Still other PDPs have a different sort of challenge: industry is already up out of bed, producing and making a profit, and the PDP needs to have superior negotiation skills to convince the partner to adapt or develop his product for neglected disease use, in a way that does not cannibalise the existing, profitable market. The latter scenario is what the TB Alliance has experienced with the development of moxifloxacin, which also has use as a general antibiotic. On the whole, PDPs have been successful in dealing with each of these partnering challenges.
We conclude the effectiveness section by summarising the major achievements of each PDP in the table below.

<table>
<thead>
<tr>
<th><strong>Aeras</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>In relation to Aeras’ three strategic objectives, Aeras’ major accomplishments during the period of the MOFA grant include:</td>
</tr>
<tr>
<td>- Further developing field site capacity in endemic countries, with local partners</td>
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<tr>
<td>- Obtaining regulatory permission to begin the first ever Phase IIb efficacy trials of two new TB vaccines – Aeras 402/Crucell Ad35 and MVA85A-Aeras-485 (Oxford). The Phase IIb trial for the Oxford candidate is currently underway and this is the first proof-of-concept trial of a new preventative TB vaccine in infants in more than 80 years.</td>
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<td>- Making some new scientific breakthroughs and discoveries related to molecules in the earlier stages of Aeras’ portfolio</td>
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<td>- Establishing a cGMP manufacturing facility for vaccine production, justified on economic as well as access grounds (i.e. minimising the time lag between licensure and distribution) and sharing this asset with other PDPs</td>
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The MoFA grant has been specifically funding the Aeras 402/Crucell candidate, development of field sites, and earlier basic research, including primate studies, with partners.

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<th><strong>DNDi</strong></th>
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<td>Of the 5 new treatments delivered worldwide for neglected diseases in the past five years, DNDi has delivered 3 of them:</td>
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<td>- Two fixed-dose ACTs for malaria: ASAQ in 2007 and ASMQ in 2008</td>
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<tr>
<td>- Nifurtimox Eflornithine Combination Therapy (NECT) for Human African Trypanosomiasis (HAT) in 2009</td>
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The Dutch funded DNDi’s malaria work, where progress has been substantial, but slower than expected according to the objectives set out at the initiation of the MOFA grant:

| - Negotiation and implementation of agreements with Sanofi and Farmaguintos for production of the two ACTs developed by DNDi: Agreements concluded, partners are producing. However, it turned out that FG did not have capacity to distribute ASMQ worldwide, so another partner had to be found. |
| - Identification of additional industry partners (2 for ASAQ and 2 for ASMQ) and negotiate agreements for industrial production: One additional partner (Cipla) for ASMQ identified: Cipla will produce and distribute for Asia. One additional partner for ASAQ identified but details still being negotiated. The challenge has been to find partners who are capable not only in terms of GMP but also in terms of having marketing channels within Africa to distribute. |
| - Transfer technology and scientific information for registration, production and distribution of the two ACTs: This process was delayed with ASMQ because the sole MQ supplier, Abbott, stopped producing MQ very suddenly. DNDi thus wasted 12-18 months identifying a new, capable supplier. |
| - Conduct clinical and product studies as necessary: Completed |
| - Submission for registration by industrial partners (Sanofi and Farmaguintos) FG submitted to PAHO Pre-qualification not to WHO pre-qualification. FG does not have relationships with NDRAs in endemic countries outside of Latin America, so another partner had to be found. Cipla will submit to WHO PQ and NDRAs of Asian endemic countries once their formulation is complete. |
| - Sanofi submitted to Moroccan NDRA and to WHO Pre-qualification, thinking this would be the option with greatest speed to market, but DNDi underestimated how much time it would take for the latter (DNDi thought 6 months but it took 16 months). |
**TB Alliance**

During the MOFA grant period, the portfolio of the TB Alliance grew from 9 to 22 projects (of which 3 are clinical). No new medicine has been developed for TB since 1960 - Rifabutin. The moxifloxacin trial is expected to result in a reduction of TB treatment from 6 to 4 months, enhancing compliance and reducing resistance. The trial is described as “one of the most advanced clinical development programmes for the treatment of active TB in over forty years……serving as a trailblazer for future TB drug development”. The TB Alliance has developed the largest single portfolio of ant-TB drug candidates in history. It is believed that 16 of the 41 TB projects worldwide involve the TB Alliance. Specifically, the MoFA-supported work on rimenophenazines has advanced quickly and reached an important milestone – the identification of lead compounds for preclinical development. MoFA also supported a major discovery project to inform the next generation of TB drug development – in vitro and in vivo clinical testing of various combinations of 3 drug regimens. As it would be too expensive to run clinical trials of multiple combinations, this project aims to choose which three drugs to combine in the pre-clinical stage. The FDA has agreed to the protocol, industry has agreed to allow their molecules to be tested in combination with others; the study was described as a “sea change” in how to enhance collaboration, which will result in a “leapfrog improvement”.

**EMVI**

During the course of the MOFA grant, EMVI successfully brought the MSP3 candidate through the pipeline and transferred it to the African Malaria Network Trust (AMANET), which is currently sponsoring its Phase IIb trial. EMVI also brought GMZ2 to Phase II. There have been some challenges in figuring out the process development with the AMA1 molecule, but it has shown some good results and there have been signs of MNC interest in taking it up after EMVI. EMVI is also working on adjuvants with MOFA support. Largely due to the challenges with the AMA1 molecule, work was delayed resulting in an underspend on the MOFA grant. However, the AMA1 issues have recently been resolved, MOFA granted a 12 month extension, and EMVI now projects that it will spend the entire MOFA grant and will in fact overspend, creating a deficit. Independent sources describe EMVI as “a good organisation that has made huge efforts to remove the conflict of interest that scared its earlier years and is now trying to make reasonable use of its limited funding”. EMVI has also refined its systems over recent years, becoming more transparent and criteria-based in grantee selection processes. EMVI is currently in the process of forming a European Economic Interest Group (EEIG) as its new legal status, and it will shift focus to take on vaccines for other poverty-related diseases.

**FIND**

The MoFA has been funding work focused on breakthrough technologies that would be focused on point of care diagnosis used at the most peripheral levels of the health system:

1. Development of an electronic (E-nose) consisting of a chemical sensor that could diagnose TB;
2. Development of a dipstick or agglutination immunoassay to diagnose malaria by detecting Plasmodium-specific antigens in a finger prick blood sample
3. First year of demonstration of an immunoassay to diagnose TB by detecting Mycobacterium-specific antigens in urine or sputum
4. Evaluation of a simple, instrument-free, test for detection of TB from a urine sample
5. Evaluation of a simple, instrument-free, test for detection of malaria from a finger prick whole blood sample
6. Evaluation of a hands-free test for determination of viral load at district hospitals or central TB-HIV clinics for clinical guidance during anti-retroviral treatment of HIV and AIDS.

Some of these technologies progressed to further research and will be tested in the field in coming months, others were dropped from the portfolio due to cost of production or lack of sufficient specificity, and still other projects were successful in terms of causing a mental shift in the research focus.

According to external experts, “What FIND has done, they have done well”. FIND initiated a study to investigate human resources and infrastructure available at different levels of the health system, in order to better understand the technologies that would be suitable for different levels of the health system. This study also revealed what percent of patients were seen at each level. FIND brought new products to disease endemic markets and labs where they did not exist previously, negotiated better prices, got acceptance and implementation. FIND demonstrated that a liquid culture system could be used in resource-poor setting; this reduces TB diagnosis time period from 45/60 days to 15 days. FIND engaged in co-development of LED microscopy, which can be used to diagnose multiple diseases and can lead to reduced lab workload and possibly better quality microscopy. The one “disruptive” technology FIND has so far developed is the molecular diagnostic test for identifying MDR TB. This test reduces the diagnosis time from 60 days to 2 days.

IPM

IPM was founded in 2002 as a new PDP with the mission of preventing HIV transmission by accelerating the development and availability of safe and effective microbicides for use by women in developing countries. The 2007/08 evaluation found that, as the largest player in the field (20% of funds), IPM is now placing greater emphasis on its role as product developer for the so called ‘next generation’ compounds., and less on co-ordinating the efforts of other researchers. IPM has:
- Engaged major pharmaceutical companies, obtaining royalty-free licenses for eight compounds to develop promising antiretrovirals (ARVs) as microbicide candidates, significantly expanding the microbicide pipeline (Gilead, Tibotec, Bristol-Myers Squibb, Merck & Co.)
- Developed new drug delivery models for microbicides (rings, gels, films, etc.) and analytic systems (ways to study the performance of microbicides)
- Established in house clinical trial material manufacturing facility to ensure gel and ring availability during clinical studies (given lack of outsourcing capacity)
- Made good progress on developing clinical research infrastructure in developing countries to prepare for clinical trials in 2009-2011; including supporting or planning to support 8 HIV incidence studies in 6 countries and establishing new clinical research centers (of 18 research centres, 11 are new, with 3 set as new teams within existing organisations with experience). The donor-led five-year evaluation of IPM completed in 2008 recommended that IPM review its product development timelines to ensure adequate preparations for IPM’s initial Phase III efficacy trial. IPM now plans to initiate its first pivotal efficacy trial in 2011.
- Worked with WHO and the European Medicines Agency (EMEA), including review under Article 58 for its dapivirine product; hosted yearly meetings with representatives of African regulatory and ethics bodies to update them on microbicide development and discuss pathways to licensure
- Integrated access issues across its portfolio, including a strategy under development for planning for regulatory activities, manufacture, scale-up and distribution in parallel to designing and carrying out efficacy trials; given IPM’s expertise, organizational setup and focus, IPM does not currently see itself as the major force in microbicide “commercialization.”
- In collaboration with other PDPs, advocacy organisations and high profile
champions, placed microbicides on the global agenda, including at the United Nations General Assembly Special Session on HIV/AIDS (UNGASS), MDG Review, and G8 as well as on the national agendas in many donor countries.

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<th>IAVI</th>
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<td>IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI is the only organisation solely focused on the development of an HIV vaccine and the second largest global programme in HIV vaccine R&amp;D, with over 40 active R&amp;D relationships. While IAVI’s search is for a single vaccine (ie effective against all strains), its effort focuses on HIV strains mainly prevalent in developing countries. In collaboration with its partners IAVI has advanced seven vaccine candidates forward to testing in human trials in Asia, Africa, North America, and Europe and hosted the evaluation of two additional vaccines developed by the US National Institutes of Health Vaccine Research Centre. IAVI has also tested three vaccine products to the point of failure and terminated those lines of inquiry in an evidence-based manner. A recent important breakthrough for the field is a new target for vaccine design: the identification and isolation of two new broadly neutralizing antibodies of significant potency and breadth. To date, only such 4 other such antibodies have been found in the last 25 years and these are the first to have been identified since 1996. Further accomplishments include many “firsts” for the field, such as the first AIDS vaccine targeting HIV subtypes circulating in Africa; the first AIDS vaccine trials conducted in Germany, India, Kenya, Rwanda, and Zambia; and, with the recent Dutch support, new scientific consortia to address key challenges impeding AIDS vaccine R&amp;D (the Neutralising Antibody, Live Attenuated and T-cell consortia). IAVI has conducted 19 Phase 1 and 2 Phase 2 trials in 11 countries (inc. 6 low and medium income countries). IAVI together with its partnering research centres has built a strong clinical and laboratory network throughout Eastern and Southern Africa as well as India. The IAVI Human Core Immunology Laboratory hosted by Imperial College, London and the Uganda Virus Research Institute (UVRI), were the first laboratories in the world to receive Good Clinical Laboratory Practice (GCLP) accreditation. A network of 30 laboratories are now enrolled in IAVI’s External Quality Assurance (EQA) programme, including 13 IAVI supported R&amp;D labs in Africa and India. The World Bank evaluation report also found significant contribution of IAVI to political commitment globally and across countries (UNGASS, G8, USG budget earmark), to resource mobilisation and to policy formulation are significant (through advocacy, policy research and publications)</td>
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<td>With respect to its overall R&amp;D goal and objectives, over the past 9 years, MMV has built and developed the largest-ever managed portfolio of around 50 antimalarial drug R&amp;D projects (from 35 by end 2006), and taken appropriate steps in replenishing the pipeline in line with evaluation recommendations, emphasising new chemical entities. MMV has redesigned its portfolio to focus on the next generation of innovative combination therapies and to address the challenge of the elimination/eradication agenda. With the Dutch grant to the MMV/GSK miniportfolio, one compound with good resistance profile (pyridine) the has entered Phase I on target at the beginning of 2009. MMV’s original objective was to register one new drug by 2010; this will be reached and exceeded. Three late stage clinical development projects have/are progressing successfully through the pipeline: Coartem® Dispersible was developed in partnership with Novartis and has been approved by Swissmedic, Switzerland’s stringent regulatory authority (SRA). Eurartesim® is in regulatory submission at SRAs and plans for its launch are underway, while the regulatory dossier for Pyramax® is currently being collated.</td>
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Artemisia extraction and benchmarking objectives in the Dutch grant have been met: to gather and disseminate information at conferences and meetings (MMV/WHO joint conference in China in November 2008; a technical meeting in Cranfield University UK in February 2008; the creation and ongoing update of an artemisinin section on the MMV website; and the drafting of an MMV Growers’ Handbook).

MMV’s access and delivery programme (supported in part by the Netherlands) was greatly expanded following the recommendations of the 2005 evaluation (including setting up the new Access and Delivery Advisory Committee). Since then MMV has further developed its strategy, logframe and partnerships, with WHO, RBM and GFATM, in particular through activities linked to the new AMFm scheme. Access activities funded by the Dutch include market intelligence gathering (eg pricing surveys in Ghana and Mozambique) and the pilot project in Uganda’s sub premium private sector (Ministry of Health Uganda and MMV).
Relevance

“Are we doing the right things?”

Evidence that the PDP’s objectives are consistent with beneficiaries requirements, country needs, global priorities and partners and donor’s policies.

The “low hanging fruits” mentioned previously, which have so far been the principal fruits of PDPs’ efforts, are relevant to the health needs of “niche” patient populations and health service levels where fewer patients are seen. MMV focused early efforts on accelerating “nearly there” products to market, such as Co-artem Dispersible for paediatric malaria treatment and other artemisinin based fixed dose combination treatments. Coartem D is a formulation change making an existing treatment more relevant to the needs of the paediatric segment, addressing a key gap in the attributes of currently available therapies. FIND has demonstrated impact, relevance and has contributed to scale up of relatively higher tech TB diagnostics, improving TB diagnosis at more sophisticated levels of the health system, where fewer TB patients are seen. DNDi has developed ACT combinations – artesunate amodiaquine (ASAQ) and artesunate mefloquine (ASMQ) - which are suitable for certain pockets of Africa, Asia and Latin America which have not yet developed resistance to AQ and MQ.

Obviously, selected patient populations do benefit from technologies with less relevance in terms of maximum suitability and access and/or which are incremental improvements over existing therapies. And in cost/DALY terms, a product requiring incremental investment and made available for early uptake to a relatively smaller group of patients can be comparable to a breakthrough technology requiring more investment and longer development times, benefiting a larger patient group. There must also surely be a motivating element to these early "wins"; PDP management are able to announce these successes and the PDP field overall benefits from this demonstration of results.

However, it is good to see that PDPs are also focusing their efforts on breakthrough technologies, of relevance to larger patient populations and with significant advantages over existing therapies. Seventy percent of FIND’s budget is allocated to development of point of care diagnostics, which would be used at peripheral health system levels where the majority of patients are seen. DNDi’s malaria focus was intended from the outset to be only temporary, in order to pick up the ASAQ and ASMQ opportunities. DNDi’s portfolio will now graduate to a sole focus on neglected tropical diseases including some substantial innovations, which will have maximum relevance to very poor, marginalised populations, who are currently subjected to sub-standard treatments such as malarsoprol for sleeping sickness.

Most of the PDPs have pipelines with mixed levels of innovation – incremental as well as “breakthrough” technologies. MMV has greatly expanded its upstream pipeline, focusing on identifying and developing products based on one or two new chemical entities, necessary as malaria parasite resistance to artemisinin based medicines increases.
Although IAVI is a comparatively small player in the HIV vaccine field, its effort is the only one focusing on HIV strains mainly prevalent in developing countries. The 2009 evaluation found that IAVI had acted “nimble” to shift more resources upstream to alternative approaches, in anticipation of the failure of vaccine approaches that rely on cell-mediated immunity.

IPM is developing “first in class” products, safe and effective microbicides for use by women in developing countries. The 2007/08 evaluation found that, as few researchers were focused on so called ‘next generation’ compounds, IPM recognised and sought to address this gap, to evaluate and in-license eight potentially effective compounds from pharma, and develop a product development pipeline. IPM is also making a significant contribution to formulation development for new delivery mechanisms (vaginal rings, tablets and films) to ensure product acceptability.

EMVI’s work has the potential to be highly relevant to developing country’s expressed needs. The other PDP developing malaria vaccine candidates, The Malaria Vaccine Initiative, has the malaria vaccine candidate which is closest to market, but it is only showing 30% to 50% efficacy (latter for severe malaria). Developing countries have expressed the view that they are only interested in taking up a vaccine with at least 80% efficacy, thus it is important to continue development of second and third generation malaria vaccines. The lead candidates in EMVI’s portfolio are showing immunogenicity results comparable to the level of antibodies induced by natural exposure to the wild parasite, which is believed to be a very promising sign of efficacy.

FIND’s molecular diagnostic test for identifying MDR TB will reduce the diagnostic time from 60 days to 2 days; this responds to the difficulty patients have affording to stay in capital cities during diagnosis and reduces health system overload. FIND is working on a technology that will allow diagnosis in 90 minutes, which would be even more relevant to patient and provider needs.

DNDi’s Nifurtimox-Eflornithine (NECT) combination for sleeping sickness replaces melarsoprol, a toxic drug that kills 5% of patients and requires administration 3 to 4 times a day for three to four months. In contrast, DNDi’s NECT therapy requires one week of therapy, with 2 infusions per day, which addresses needs of patients, and reduces burden on healthcare workers and overall system capacity.

Some PDPs (especially DNDi) seek to maximise relevance to local needs as well as eventual technology uptake by involving stakeholders within endemic countries in the entire research chain, including at the early priority setting stage. Specifically, DNDi relies heavily on feedback from the field in order to guide decisions about portfolio prioritisation. A key strategic advantage is DNDi’s links with Medicines Sans Frontieres (MSF); MSF can provide important information on the disease, identify where patients are located, and explain the shortcomings of current therapies. Another example is the TB Alliance’s community engagement initiative to engage communities and civil society around clinical trial sites used in the moxifloxacin programme. The programme aims to establish channels of communication between researchers and local community members to improve local understanding of TB disease, treatment and research; to facilitate trial implementation in consideration of local cultural normal and expectations; and to minimise the risk of community rejection of the trial through transparency and community empowerment. Another way PDPs work to maximise relevance is by involving senior developing country scientists and other experts on their Boards, and in scientific and access advisory committees; all of the MoFA-funded PDPs have been successful in engaging such involvement.
One of the objectives of the MOFA grant is to mitigate the effects of failing free market mechanisms. So in the absence of the MOFA-funded PDPs, would the private sector initiated activity be less? The answer is most certainly yes, but attribution is difficult. There have been large increases in development assistance for health, from $5.6 billion in 1990 to $21.8 billion in 2007.\(^3\) Health technology purchase for neglected diseases is largely channelled via global health institutions such as GAVI, the Global Fund for AIDS, TB and Malaria and PEPFAR. Two-thirds of GAVI grants and between 40 and 50% of Global Fund grants are used for health technology purchase. Although UNITAID’s funding is smaller than the previous examples, it is targeted entirely to commodity purchase, so it is having an impact as well. The Affordable Medicines Facility for Malaria may decrease the opportunity for premium private sector sales of ACTs but it will increase the overall volume of ACT sales. The G8 has agreed to support an Advanced Market Commitment (AMC) for the pneumococcal vaccine and has reviewed possible additional AMCs to “pull” a malaria, TB or AIDS vaccine through the pipeline. These funds and initiatives send “pull” signals to industry that an increasingly credible market exists so they must be at least partly responsible for increased industry presence in neglected disease work. Similarly, other mechanisms have emerged during recent years, which may help offset costs and therefore be partly responsible for increased R&D activity. The United States FDA priority review voucher is one example; Article 58 of the EMEA is another.

It would also be true to say that the severity and nature of the market failure PDPs are addressing is different for different technology and disease sectors. For example, manufacturers have developed point-of-care malaria diagnostic tests without PDP intervention, however the market failure in this case is information asymmetry, with many poor quality tests on the market and given lack of quality regulation, not much incentive for producers to improve their quality. FIND has rightly focused its efforts on assessing quality, providing an incentive for manufacturers to improve their quality control.

Moxifloxacin (TB drug) is a general antibiotic that already exists on the market to serve the profitable global antimicrobial market. But the product originator, Bayer, would have little incentive to make the incremental investment required to gain a TB indication, and then make the product available at concessionary prices to the public sector, potentially cannibalising otherwise healthy private sector sales. The TB Alliance has managed to attract Bayer to work together, despite these challenges. The market failure in the case of TB drug development is not the absolute lack of research activity, but the failure to deliver products at the rate needed. TB Alliance’s role then is appropriately focused on the increasing the speed of research and new product development.

In the NTD product sector, we can be even more confident than usual that the private sector will not invest in R&D on its own. There is no dual market (either wealthy/poor countries or private/public within developing countries) with which to offset some of the development costs. And the trials need to be conducted in very remote locations; some involving a five-day trek and some in conflict locations. When conducting trials for Human African Trypanosomiasis (sleeping sickness) trials, the trial site even has to follow the Foci of the disease. Industry is not set up to do these sorts of trials and

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does not have the links with, for example, Medicines Sans Frontieres and local chiefs, to help enrol patients and to follow up with them.

MMV has certainly facilitated and accelerated pharma research on malaria, such as the paediatric formulation for Coartem. Without MMV, it is unlikely that some partner companies would have taken forward malaria focused portfolios.

Currently, given the limited size of the dual market and the scientific challenges of HIV research, investing in HIV vaccines or microbicides is unlikely for R&D companies, unless and until the PDPs or others make significant progress. However, IAVI's new Innovations Fund is acting to stimulate new biotech activity and partnerships with IAVI, contributing to recent successes such as identifying new neutralising antibodies.

When it comes to malaria medicines and TB medicines, it is clear that some firms, especially smaller ones, do find these niche markets commercially interesting, as long as the activity does not get in the way of more profit-maximising activities. However, there is evidence that PDPs bring momentum to the field, make sure the opportunities do not get shelved when a more profitable project presents itself, and provide the mechanism and incentives for a greater range of firms to get involved in the R&D.

Almost all PDPs face a situation where there is uncertainty about the prospect for a commercially interesting market. BioVentures for Global Health conducted a study which estimated that TB vaccine manufacturers could generate a return from the market in developed countries and the developing world market could generate manufacturing efficiencies. However, studies conducted by Aeras and others have found the BVGH estimates to be overly optimistic. Part of the problem is certainly the difficulty in projecting demand in the context of uncertain product uptake and donor financing. Another part of the confusion arises from differences amongst what companies view as an interesting commercial opportunity. A 100 million dollar market opportunity is a distraction to a MNC, but it a sizeable opportunity for smaller companies.

Another secondary objective of the MoFA grant is to expand knowledge and achieve increased capacity. PDPs have built substantial capacity for evaluating new technologies, notably in the form of clinical trials capacity in developing countries. This is highly relevant to their goals, not only ensuring product efficacy for target populations, but also enabling important national level advocacy and capacity building, for example to address the regulatory challenges of new products and gain early insights about potential policy, programming and health system delivery implications. Mainly this has been in partnership with existing clinical research centres (e.g IAVI, MMV, IPM) but also in developing new sites (e.g. IPM, Aeras, TB Alliance, DNDi, EMVI), where existing centres are overburdened, inappropriate or where this has been required by government (see also comments below under Global Impact).

PDPs have also built health delivery capacity, including training and physical upgrading of facilities, and in the case of FIND, laboratory capacity has been built, to prepare the ground for new diagnostic technologies as they become available. EMVI's Phase IIb trial of GMZ2 in Gabon has strengthened the laboratory and data management as well as GCP capacities, in collaboration with AMANET. IAVI, IPM, MMV, TB Alliance, and Aeras have also contributed to supporting laboratories to achieve global standards. Although most of the PDP capacity development activity is undertaken as a means to an end of developing product and ensuring uptake, DNDi's
A final point on relevance relates to interpretation of the terms “public sector”, “developing or endemic countries” and “affordable pricing” in PDP/industry access agreements and how these terms are defined in practice. Where a dual market exists (such as for HIV related products and diagnostics and to a lesser extent malaria and TB products), the industrial partner is usually able to pursue commercial value in wealthy markets or in the private sector of developing country markets. How this is defined in practice varies across PDPs and often within each PDP, according to what has been negotiated with each partner. Some difficult issues for access may be how public private mix situations are handled (for example in Bangladesh, the government contracts with the private sector to deliver TB control) and whether endemic countries like India and China (which contain 33% of the world’s TB burden) are included as eligible countries for concessionary prices.

A large portion of TB (~50%) and malaria (~50 to 80%) treatment is accessed via the private sector in endemic countries, yet the majority of the PDPs evaluated have confined their access agreements to the public and non-profit sector. Some PDPs have been able to negotiate inclusion of the “non-premium” private sector, or private sector which operates under a government public-private mix contract. Some access agreements do not include any version of private sector as eligible for concessionary pricing and the “premium” private sector is left entirely out of access agreements. (The single exception may be a pilot study in two countries with DNDi/Sanofi’s ASAQ, prior to the arrival of AMFm.) MMV’s agreements seek to achieve affordable prices in both non premium private as well as public sectors. For example, MMV contracts stipulate an ex-factory target price of $1.00 for an adult course of treatment and $0.50 for a paediatric formulation. Partners have the right to market and distribute the drugs at a price suitable to them in the premium private sector.

These differential pricing experiments are lacking in a fundamental pre-condition required for tiered pricing success: separable markets. Low priced or free product available within the same geographic location as premium priced products, and within an environment where regulation is lacking and distribution channels not especially discrete, sets up an obvious incentive for arbitrage across markets. It is difficult to see how the tiered pricing structures present in some PDP-industry agreements can be successfully implemented in practice, without creating an obvious incentive for diversion from public to private sector.

This role in ‘price contracting’ with industry partners is a new and challenging area for PDP expertise, and unfortunately it is a bit of an afterthought where access agreements were already concluded many years ago. Time will tell whether the tiered pricing arrangements achieve the right balance between incentivising industrial participation, versus achieving affordability and access. The AMFm (Affordable

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4 For example, it is well known that local production in developing countries can raise costs, and prices, above those which are available on the competitive market. See for example Guimier et al, paper for the UK Department for International Development. http://www.dfidhealthrc.org/publications/atm/Guimier.pdf

5 Public vaccine distribution channels are more discrete from private, so these arguments apply more to drugs and diagnostics
Medicines facility for Malaria) initiative may help solve this problem in malaria, but the challenge will remain for TB focused PDPs.

However, it should also be noted that increased PDP leverage in access negotiations may come at a cost. Across the PDPs, a common observation was that the earlier the PDP becomes involved with a candidate and/or the higher the PDP’s investment into the candidate in cash or technical terms, the more leverage the PDP has to negotiate access-favourable definitions of eligible sectors, countries and prices.
Efficiency

Evidence of how economically resources/inputs (funds, expertise, time, etc) are converted into results

The economic downturn has caused several PDPs to look hard at doing more with the same money or doing the same with less money. Some have shifted work from higher to lower labour cost countries. Some report that they have succeeded in capping partner budgets, with no impact on activities, so essentially costs are transferred to private sector, saving public funds. Still other PDPs report that reduced budgets have resulted in a slow down in work, in order to use less cash, e.g. enrolling patients more slowly in clinical trials or delaying the start of a new trial. This is not a greater efficiency because it is not doing more with the same money, or doing the same with less money; it is doing less with less money, which essentially means the PDP becomes less able to reach its objectives. This is a point for donors to take on board – that there may be a limit to the efficiencies PDP’s can achieve in times of tight purse strings and reduced effectiveness in reaching goals may be an inevitable result of reduced funds available.

There is little hard data on efficiency of PDPs and limited understanding about what would be an appropriate efficiency benchmark, or comparable examples. The LSE study referenced previously (Mary Moran, March 2005) provides some empirical evidence. Nonetheless, some PDPs have made attempts to document their efficiency, for example, Aeras conducted a study and found it was 60% cheaper than industry partners in its per patient clinical trials costs.

Vaccine clinical trials are extremely expensive, so it will be important for vaccine PDPs to have rigorous processes for selecting only the best candidates within their portfolio to take to the field, and also to look for other, validated ways (e.g. human challenge studies, if appropriate) to assess the vaccine’s potential prior to commencing expensive field trials. Neither Aeras nor EMVI have the benefit of validated challenge studies, though there is progress in that direction with blood stage malaria vaccines. This means that, for the time being, field trials are the only way to assess efficacy.

Several PDPs have begun to build up large workforces and infrastructure requiring substantial capital investment. This can be risky for the PDP, as this reduces their flexibility to adapt to a donor finance downturn or to a major setback in a research programme. Donors reportedly prefer PDPs which have critical mass, but the risk is the incentive this creates for building critical mass for its own sake and not because it is essential.

When deciding whether to invest in fixed assets, PDPs should analyse what it costs to invest in the asset versus what it costs to contract-in for the service or expertise. All costs should be included - capital and variable - as well as an opportunity cost of capital, which should be commensurate with the risk of the investment regardless of the source of funds. There may be strategic considerations to account for as well, for example the availability of expertise required on a contract basis, or the balance sought between direct control (which may mean greater speed) and building capacity or maintaining maximum flexibility to scale up or scale down in response to volume of work or availability of funds. It appears that donors are requiring PDPs to conduct such “make versus buy” analyses, in which case the investment decisions should be evidence-based. It is encouraging that PDPs which are making such capital
investments, such as Aeras, IAVI and IPM, are making spare capacity available to other PDPs; which ensures there is better utilisation of the capacity created. For example, other PDPs have used Aeras’ manufacturing facility to manufacture vaccines, for which Aeras charges them a price to cover costs. The plant is reportedly making enough revenues from contract manufacturing for others to cover its variable costs.

There is a tendency to look at management costs as a percentage of annual expenditure as an indicator of efficiency, but when organisations are less mature (as many of the PDPs are) this percentage will usually be higher. Once the PDPs have reached their full maturity, this percentage should come down. However there may still be variance due to the peculiarities of each PDP with such different technologies and strategies. There is also likely to be variation in cost accounting policies across PDPs, so different interpretations about what constitutes an overhead makes it difficult to get a comparable figure. That said, where the information was available on PDP administrative costs, they were within acceptable limits of about 10%. With pressure on budgets, several are also making efforts at administration savings.

Some PDPs have decided to keep their organisation relatively lean and rely substantially on external expertise. The advantage of this may be a lower wage cost base and greater flexibility to upscale and downscale the external inputs according to business needs and available finance. If number of staff as a percentage of expenditure is used as an indicator, these PDPs will appear to be more efficient. However, the potential disadvantage may be that they end up paying more for the contracted-in expertise and possibly have less control over it, so this may be a false economy.

Decades of inactivity in neglected disease technology development result in the need for substantial investment to build up a robust portfolio. There are also gaps in the what might be called the “enabling environment” that need to be addressed - clinical trial infrastructure, research tools, availability of biomarkers, and defining the regulatory framework. The result may be the appearance of high investment in relation to little end output, but the reality is that addressing these issues now will ultimately accelerate technology development in the longer term.

Efficiency can also be assessed in terms of money it takes to get a product to launch stage. MMV’s World Bank evaluation found that its spending on bringing a new drug to market so far has been ‘modest, relatively speaking’, at about $150m including costs of failure. This is attributed to in kind support from pharma, in-sourcing extant intellectual property, the lower cost of clinical trials for malaria than for some other products, and skilled management.

However, it is very hard to make this sort of analysis comparable. It is difficult to ensure that full costs, including out-of-pocket, costs of failure and opportunity costs of capital have been included. And the starting playing field for different technologies is unequal. As noted previously, some technologies are “low-hanging fruit” requiring minimal incremental investment. Other technologies (e.g. neglected tropical diseases) are entering a space where there has been little historical R&D investment, so it may take more money to build up a portfolio. It also takes significantly less money and time to get a new diagnostic to market as compared with a drug and especially a vaccine.

DNDi has required their industrial partner to pay 3% royalties on its sales to the private sector, and it uses this revenue to fund its R&D work. Other PDPs are also looking at similar royalty payments on sales to developed country markets, though
this obviously would need to be agreed with the industry partner initially, so would not be possible for agreements already concluded. Although attracting revenues as a means of funding continued R&D may not be defined as an efficiency gain per se, it does represent the transfer of R&D costs from public to private sector, and it is therefore an interesting option where dual markets exist and where the PDP has contributed sufficient added value to warrant a royalty payment.

Partnering with firms in India and China for manufacturing as well as R&D expertise is increasingly pursued as an efficiency-enhancing strategy. Research work in India tends to be one-third the European costs and it increasingly comes without sacrifice to quality or timelines. Working with producers in endemic countries may bring the additional benefit of capacity development: some PDPs see pharmaceutical production and research capacity development as an important end in itself, while others see it as a happy by-product of a relationship chosen on commercial grounds.

Efficiency of the PDP’s operation is important but so also is the greater efficiency that the PDP can create in the health system. Superior technologies can allow laboratories to perform more tests with increased accuracy. Easier to administer tropical disease technologies may eventually allow these vertical treatment systems to be integrated into the transversal health system, and so on.

Efficiency of the entire PDP system should also be an objective. When observers see more than one PDP operating in a single disease or technology space, such as there is within the malaria vaccine sector, there are questions about whether it is a good use of donor funds to support the overheads of multiple PDPs. Certainly having more than one PDP operating in a single sector raises co-ordination issues for the PDPs themselves as well as the donors who fund them. However, there are also arguments in favour of having multiple PDPs within one space:

- Neglected disease R&D is so severely under funded that, as long as there is a large candidate pool from which to draw, the increased activity supported by multiple PDPs may be a good thing for speed and quality of products developed
- It provides multiple avenues for inventors to get to market, which may increase incentives for innovation
- PDPs may divide up within the single disease or single technology spaces so that there is no overlap, increasing the focus of each
- PDPs may have different funding sources for which they are eligible, and groups to which they advocate for increased funding may similarly differ, so that the result may be an overall increase in funding available to the sector

Similar tensions existed when push versus pull incentives were being analysed in relation to Advanced Market Commitments. Stakeholders questioned whether having both “push” funding via PDPs as well as “pull” funding via AMCs would result in overpaying, creating windfall profits for industry, and be a poor use of donor funds. In theory, if more money is available, you will simply get more investment and get more producers of more products more quickly. In this virtuous competitive rent-seeking model, one would expect firms to swarm in to exploit the combined opportunity so as, at least on average, to incur costs that virtually exhaust the rents available through PDP funding. However, this theory only holds true if there is a reasonable pool of capable firms able and willing to “swarm”. There definitely seems to be a reasonable pool within malaria vaccine research – over 100 candidates exist worldwide at present. The result of the PDP/AMC discussion was the conclusion that, it may cost more to have multiple avenues to market, but given the huge health need and the cost-effectiveness of these technologies, it will likely still be cost-effective.
Impact

Impact on poverty and health for patients in developing countries.
Impact on the global access architecture.

It is difficult to isolate and attribute the effect of a PDP specifically on health impact, in an environment where there are so many contextual influences and drivers of health impact. Therefore, the focus in this section is on indicators of impact – primarily uptake – and also on PDP actions/interventions which are likely to bring about uptake and resultant health impact.

Bringing products to market is an essential precursor to uptake, and the projections made in 2004 by the Pharmaceutical R&D Policy Project – that PDPs would bring 8 to 9 new products to market between 2004 and 2009 – have been realised. Eleven PDP products have received regulatory approval, and eight of these come from MoFA-funded PDPs:

<table>
<thead>
<tr>
<th>PDP</th>
<th>Product with regulatory approval</th>
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<tr>
<td>Coartem D</td>
<td>MMV</td>
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<tr>
<td>Paromomycin</td>
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<td>JE Vaccine India</td>
<td>PATH</td>
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<td>Inactivated oral cholera vaccine</td>
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<td>Liquid culture DST</td>
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<td>Rapid MTB ID</td>
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<td>LPA line probe assay</td>
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<td>Minicolumns (mAECT)</td>
<td>FIND</td>
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<td>ASAQ</td>
<td>DNDi</td>
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<tr>
<td>ASMQ</td>
<td>DNDi</td>
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<tr>
<td>Nifurtimox Eflornithine Combination Therapy (NECT) for human African trypanosomiasis</td>
<td>DNDi</td>
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This reveals that PDPs have been effective in delivering new neglected disease products. But have they been effective in delivering health impact? Most of the products so far developed by PDPs are incremental innovations - “low-hanging fruit”. While we remain hopeful, we do not yet have sufficient evidence that PDPs can deliver breakthrough innovations. Also, while receiving regulatory approval shows potential for impact, product uptake is a better indicator of actual health impact.

Currently, concrete uptake data is only available for DNDI’s products. The total market for ASAQ (Fixed Dose Combination or co-blisters) is estimated at a maximum of 100 million for both the public and private sectors. Initial uptake of DNDI’s ASAQ was delayed and low, in comparison with health need – 5.3 million treatments for 2008. DNDI attributes this to the lengthy WHO prequalification process (obtained in October 2008) and the slow policy change at each individual national level and within international organizations. The slow policy change at each national level should not have been surprising, as the same challenges with Coartem ACT uptake have been well documented. Uptake has been incrementally improving – 20 million to 25 million treatments by end of 2009 (20 million confirmed as of September 2009), and a goal

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of 50 million by 2010. As DNDi signed a non exclusive agreement with Sanofi-Aventis, other generic producers can start penetrating the market and this is expected to happen in 2010 and 2011.

With ASMQ, more than 25,000 ASMQ treatments were used in Brazil in 2007-2008 and in 2009, the Brazilian government ordered 100,000 ASMQ treatments. This compares to an estimated market size of approximately 250,000 (the majority of P. falciparum cases in Latin America are in Brazil). The estimated market size for Asia is 1.5 million. DNDi has recently concluded a transfer of technology and partner agreement with Cipla India to address this need.

In the case of “FIND’s” diagnostic tools, the situation is a bit different. Some of the technologies already existed on the market, and FIND’s role has been to immediately move to evaluation and demonstration of appropriateness for low-income endemic country settings. FIND has facilitated a change in national policies in many countries, a precursor to implementing new tools. In Uganda, national policy was changed recently to incorporate liquid culture assay. In Ethiopia, Lesotho, India and Uganda, FIND tools of liquid culture, line probe assay, and the rapid TB diagnostic test were incorporated, but uptake figures were not available within the timeframe of this report.

MMV has assessed “structured demand” (i.e. public tenders as opposed to the premium and non premium private sector) for its first product to be registered and introduced (with Novartis) Coartem Dispersible. This will be the main channel through which new ACTs are delivered at least to 2011, before the AMFm pilots start to show impact. This estimate is based on 2008-09 demand for Coartem products, forecasts for global ACTs and an estimated 60% switch to Coartem D for children. Current and future Coartem countries could take up to between 50-60million Coartem D treatments per year by 2011.

Other PDPs are engaging in market-proximate activities, bringing the technology on the verge of uptake and impact, for example:
- Some PDPs have produced evidence propelling WHO to change its guidelines or recommendations to countries; this is an important step in catalysing the pathway to market, encouraging country demand, and in encouraging rationale use (where the product already exists and the PDPs role has been to assess the efficacy, quality or appropriateness of the technology)
- Funding has been secured from UNITAID or Global Fund which allows introduction of the technologies over the next few years
- Prices negotiated by PDPs with partners may be an indicator of potential impact. For example, with FIND’s liquid culture project, FIND negotiated prices down from 15 to 20 euros per tube to 1.95 per tube.

In other cases, the technology is so far from market that it may only be possible to infer eventual impact by looking at the burden of disease and/or in combination with reviewing the weaknesses of the existing therapies that will be replaced. A few examples:
- Neglected tropical diseases collectively comprise the world’s 6th leading cause of DALYs; their burden is well known but not well documented as

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7 DNDi’s manufacturing partner, Sanofi-Aventis, through the plant in Morocco (Maphar) will have a production capacity of 70M by the end of 2009. This plant produces the fixed dose combination ASAQ and most treatments are for the public sector.
underreporting is widely acknowledged. The equity rationale for combating these diseases may be the most compelling reason to invest in this sector: these diseases affect the poorest, most marginalised individuals and communities in the world. Of the world’s poorest 2.7 billion living on less than $2 per day, an estimated 1.2 billion are affected by NTDs. Examples of economic toll: The cost to each household following a Human African Trypanosomiasis outbreak is equivalent to 5 months income; Chagas disease in Brazil alone causes losses of over $1.3 billion in lost wages and industrial productivity.

- TB accounts for more deaths among women than all causes of maternal mortality combined. TB is also the leading killer of HIV positive patients. TB primarily affects adults of working age where the disease exacts a vast economic toll in treatment costs and in lost productivity. The BCG vaccine for TB was developed in 1921; it is not relevant to the needs of developing countries. A 50-90% effective TB vaccine could eliminate about one-third of the world’s TB disease and fatalities, while vaccination of children will prevent childhood TB. A new TB vaccine would save USD 25 billion per year in health care costs and restore USD 16 billion per year in lost productivity in high-burden countries. Cost per DALY averted in Sub-Saharan Africa estimated to be $6 to $10 for the BCG-replacement vaccine and $21 to $26 for the booster vaccine.

- Malaria is the third largest contributor to the global disease burden. Other interventions such as indoor residual spraying, insecticide treated bednets, case management with currently available drugs and intermittent presumptive treatment with SP in pregnancy have low cost per DALYs, however none of these interventions is able to stop the transmission, i.e. such interventions need to be repeated regularly. A malaria vaccine with 90% efficacy could avert 1,432 deaths per 100,000 infants. The cost per DALY saved would be $12.

- Women account for half of all people living with HIV worldwide, and nearly 60% of HIV infections in sub-Saharan Africa. Many prevention approaches are not working effectively for the most vulnerable. The cost per DALY saved of microbicides was estimated in the IPM-commissioned study by the London School of Hygiene and Tropical Medicine. The estimated cost per HIV infection averted by a microbicide in the base case, minimum cost scenario in a rural area of India (Karnataka) would be US$788 or US$29/DALY averted, assuming that an HIV infection averted saves 27 DALYs in India. In South Africa in an area of high HIV prevalence, the cost per HIV infection averted in the lowest-cost scenario of microbicide introduction would be US$1,678 per HIV infection averted or US$67/DALY averted, where one HIV infection averted saves 25 DALYs in South Africa. These are both cost-effective interventions according to World Bank threshold of $1,425 per infection averted in India and $3,005 in South Africa. By comparison, the cost of preventing mother to child transmission of HIV in India costs $81-$189 per DALY saved.

- HIV vaccines are expected to be cost-effective, in comparison with ART for example. IAVI has sponsored demand and impact modelling and although the actual cost of future vaccines is unknown, the maximum price at which a vaccine would be considered cost-effective can be calculated. Given the high lifetime costs of treatment, analysis found that a price as high as US $800 per vaccination would still be cost-effective when compared to the treatment costs avoided. A vaccine would have to cost no more than US $25 per vaccination to be cost-saving. These models predict, for instance, that an AIDS vaccine with 50% efficacy given to 30% of the population would avert 5-28 million new infections in low and middle income countries between 2015 and 2030.
(roughly 24% of the infections that would otherwise occur) and US$132 billion in treatment costs.

PDPs are also engaging in activities that have an impact on the global access architecture, that is, actions which may facilitate product development and delivery even beyond the PDP’s own disease or product sphere. For example, most of the PDPs are producing evidence that makes developing country markets less opaque, and when this information is made public, it may encourage industry activity even independently of the PDP. Examples include burden of disease studies (all PDPs), demand studies (almost all PDPs), including projection of future financing (IPM and others), studies that characterise the needs of the product user at different levels of the health system (FIND).

There are also PDP activities which help catalyse the path to market for any product developer, whether within or outside a PDP. FIND negotiated a concessionary price with one LED microscope manufacturer, but shared the protocol with all of industry. The concessionary price creates a price ceiling, but any manufacturer can enter the market with a price below that ceiling. Similarly, many PDPs (e.g. TB Alliance) are working with regulators to agree the data and the process needed for registration, for example, and this is paving the way for the entire field, beyond simply the technologies being funded by the PDP. DNDi has commissioned a study to critically assess the various options for getting products registered in Africa; this will be shared widely and if regulators agree to the recommendations, it may lead to some efficiency gains in the registration processes which would be of benefit to all PDPs. Both MMV and IPM are exploring new registration channels with EMEA, using Article 58, as well as working with other stringent regulatory authorities.

Another example of investment, which may benefit the field as a whole as long as others have access, is the development of field capacity for clinical trials. The sums required for this can be substantial, for example, one PDP spent 20 million dollars to develop one site. Clearly, this raises sustainability challenges. It also raises questions about ownership and control of the sites. Many PDPs refer to sites in which they have invested substantial sums as “their” sites. While this may be an issue of inappropriate semantics in some cases, in other cases the PDPs may actually have negotiated contractual restrictions with the site, which limit its autonomy. For example, there is one case where the site is required to seek permission from the PDP if it wants to conduct a trial with more than a certain number of participants. This restriction has been placed to prevent the scenario that a commercial developer would wish to use the site to trial a technology which has not been assessed by the PDP’s Scientific Advisory Committee as being appropriate for developing countries, i.e. to ensure that the PDP’s SAC-approved technologies get first priority. Such arrangements carry two potential risks: that the site’s autonomy and capacity may be restricted and that other legitimate developers (whose technology has not been recognised by the PDP’s SAC) are left without an avenue for bringing a technology to market. The latter risk is lessened if there are other sites appropriate for the competing developer to use, but in the case of very specialised sites, alternative sites may not be available.

Other PDPs have the explicit goal to develop trial capacity as a public good, from which others can benefit. The platforms DNDi helped develop for Human African Trypanosomiasis and Visceral Leishmaniasis trials have country-level decision makers at the helm, who are free to choose which clinical trials they undertake; FIND is about to start work with these platforms. EMVI contributed to capacity development of a trial site in Burkina Faso, which has now become a reference
centre in Africa and is receiving funds from several organisations, including the US National Institutes of Health.

The TB Alliance has contributed to global knowledge by conducting the first-ever comprehensive assessment of global capacity to conduct registration-standard Phase II and Phase III TB drug trials. To date, 88 sites in 41 countries have been assessed and ten more sites are currently being evaluated. The 88 sites already reviewed have been provided with direct feedback on areas of strength and deficiency. The results of the global mapping exercise have been uploaded on to a database, which is accessible to all via the TB Alliance website. This tool can serve as an important tool for all developers, inside or outside TB Alliance. Another example of benefiting the wider community comes from TB Alliance’s plans to use the moxifloxacin trial to build up a biological specimen bank for use in identification or validation of TB biomarkers. The goal is to enable ability to predict efficacy based on surrogate markers, which has relevance to future TB drug research as well as TB diagnostic research.

Several PDPs (eg IAVI, IPM, Aeras, DNDi) are working with their partners and other PDPs to ensure that capacity built is effectively shared and deployed. However, it is also the case that, while there have been some successes in sharing, more remains to be done to maximise the benefits. The IPM evaluation notes that, given PDP incentives to maintain capacity for their own research, it may be up to donors to stimulate or require more collaboration. The Gates funded Malaria Clinical Trials Alliance, led by the African research partners helps to co-ordinate efforts with malaria PDPs and research groups. EMVI is of the view that no other disease sector works as collaboratively as the malaria vaccine field. All of the funders work together, culminating in the malaria vaccine technology roadmap (MVTR), approved by all the partners – e.g. MVI, EMVI, BMGF, WHO, EC, NIH etc. Stakeholders meet every six months to co-ordinate and agree priorities.
### 8 Impact of the Dutch grant on the PDPs

The figure below shows the total size of the MoFA grant over the 4 years. The MoFA provides a significant portion of overall funding for some PDPs (EMVI and to some extent, Aeras) and a small proportion of overall funding for other PDPs albeit a significant portion of a specific project (DNDi, FIND).

![Dutch grant over 4 years](image)

**Source:** MOFA Program Appraisal documents

Dutch funding was valued by all grantees not only for its financial value but also for the signals it sends, particularly to other European donors and to the European community. As a ‘public’ source of funding, the MoFA support, along with other governmental and international agencies, helps alleviate potential ‘tipping’ issues to do with rules of the US Internal Revenue Service concerning private US foundations such as BMGF\(^8\).

Some PDPs seemed to be more comfortable than others with the earmarked quality of the grant process, though all acknowledged that, in practice, the support had been very flexibly employed. Better accordance with the Paris principles for enhancing aid effectiveness may be sought in future rounds through linking into the PDPs ongoing reporting cycle and co-ordinating with other donors on report frequency and formats.

The following were the specific observations made about the impact of the MOFA funds:

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\(^8\) This issue is fast becoming a major problem for PDPs and their US private foundation donors due to the need to demonstrate the 33% ‘public support’ principle.
- FIND: The MoFA contribution represented 55% of the overall budget for the discovery programme. Other funders to the same project were USAID and EU. MOFA support was reported to be fundamental to ensuring that these projects were fully funded and able to proceed according to timetable. MOFA funding was also attributed with attracting other partners – UNITAID, CDC, JHU and local partners for infrastructure. A challenge with funding that is attached to specific project lines relates to the fluidity of the pipeline in diagnostics. Products come and go from the development pipeline much faster than for drugs; this makes flexibility in funding and reporting more appropriate and valuable.

- EMVI: Earmarked funding separates the MoFA grant from other grants in terms of the selection process required, monitoring and management of the portfolio. This has created some problems in the past, however EMVI is planning to adopt another process, involving the SAC, for applying for future MoFA grants. MoFA funding represents a large portion of the overall budget of EMVI (e.g. about half of the 2008 expenditure was funded by MoFA).

- DNDi: MoFA has financed 40% of the “FACT” malaria project, making a significant contribution to support the launch of ASAQ and ASMQ and the deployment if the products in endemic countries. Donor funding of a specific project is an exception for DNDi, as most donors participate in joint funding of the whole trajectory of the R&D process, allowing DNDi to provide one consolidated report to the donors.

- Aeras: The MoFA funding has been important to Aeras not only in terms of its financial volume (MoFA provides 13% of Aeras’ funding) but also in terms of the leverage it generates amongst the international donor community. Unfortunately the decreased funding from BMGF and MoFA for 2009/2010 has led to the need to delay the start of clinical trials for some of the candidates in the Aeras portfolio and/or slow down patient enrolment into the trial to rates supported by funds available. Aeras had planned to give Crucell 14 to 16 million dollars in 2010, 6 million of which would have come from the MoFA. More precisely, the lack of MoFA funds will slow down the manufacturing process development at Crucell.

- IPM: Funding from the Netherlands makes up 11% of total funding received to date. IPM has not experienced any challenges with the management of the Dutch grant. The Dutch government is supportive of IPM’s work and provided budget neutral extensions to the grants as needed. The Ministry of Foreign Affairs can play a significant role in advocating for microbicide research in addition to providing funding for the research, especially among other European donors.

- IAVI: Over time the Dutch have contributed around 12% to IAVI’s total budget since 2000. Dutch funding in part supported the NAC’s achievements, and hence has contributed to important steps for the field. Sustained and multi-year commitment for R&D has meant that IAVI can direct funds to the early science programme. A specific reporting challenge was the required forward looking activity plan for the yearly budget request. The timing of this report did not match IAVI’s own budget cycle, whereby Board approval of the annual budget happens late in the year and the resulting programme workplans are not finalised until after. The flexibility of the Dutch in managing the programme made up for the restrictions imposed by the award. IAVI is facing the challenge of increasingly restricted funds (from 0% in 1996 to 58% in 2009) due to an increase in sponsored research funds, as well as more restrictive funding by some of its public sector donors. This could risk IAVI’s ability to be flexible and ‘nimble’ in its scientific programmes.

- MMV: Dutch grants constitute just over 5% of MMV’s total funds received and pledged since 1999. The current MoFA grant has helped in particular to fund
Artemisinin related activities and to begin essential Access & Delivery activities. However, the programme is reported by MMV to be complex to manage and account for, a project management exercise in itself. Another challenge was the necessity to pay all expenditures out of an individual Netherlands account at the bank, whatever the currency. Finally, the grant-specific audit by KPMG as stipulated in the grant agreement for each year cost around CHF 6,000 per annum.

- TB Alliance: MoFA contributed substantially to the portfolio growth with the support of several new projects, including riminophenazines, NDH-2, bifunctional molecules, malate synthase inhibitors, protease inhibitors, and phenotypic (whole-cell) screening. MoFA has led the way in supporting strategic initiatives that will accelerate the field overall, including clinical site assessment, new combination testing, and biomarker research. The MOFA support is important financially to TB Alliance, supporting almost half the projects in the discovery portfolio. It is also important in terms of diversity of funding; TB Alliance only has four other active funding partners. MoFA was also critical in that it financed projects that did not fit into some of TB Alliance’s other, more restrictive, grant frameworks. Specifically, MoFA willingness to finance work that accelerated the field overall and work to ensure accessibility and access was valuable because it did not fall into the traditional discovery or clinical challenges that other donors favour. The MoFA grant had significant strategic importance to TB Alliance. As other donors hold in esteem the support of MoFA, it helped to raise TB Alliance’s profile and supported the credibility of TB Alliance as a reliable and efficiently run operation. Finally, MoFA funding helped increase the overall investment in TB; with MoFA support, TB ALLIANCE was able to advance the riminophenazine project through lead optimisation, at which time it generated substantial support from the Chinese government to help further the development of a novel riminophenazine compound for drug-sensitive and drug-resistant TB. The TB Alliance expressed its gratitude for the flexibility and understanding that MoFA demonstrated over the course of the grant in allowing new projects to be added when exciting new opportunities arose that required additional funding, and when existing projects were delayed. However, TB Alliance noted some general points about project funding. “The uncertainty in drug development has serious implications when funding that is time limited is also tied to a specific project. In the event that a project is delayed, there is a real risk that funds allocated to that project may be lost, if they cannot be reallocated to other projects or the timeframe for the use of the funds cannot be extended.” As suggested by several PDPs, core funding was recommended as a more suitable method of funding in this sector, where scientific risk is high.
## Annex One: Interviews

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<th>Name</th>
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<td>Jerry Sadoff</td>
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<td>Adrian Hill</td>
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<td>Helen McShane</td>
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<td>29</td>
<td>Jaya Banerji</td>
<td>MMV</td>
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<tr>
<td>30</td>
<td>Claude Oeuvray</td>
<td>MMV</td>
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<td>31</td>
<td>Ian Bathurst</td>
<td>MMV</td>
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<tr>
<td>32</td>
<td>Pamela Norick</td>
<td>IPM</td>
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<td>33</td>
<td>Nick Davies</td>
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<td>34</td>
<td>Joe Romano</td>
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<td>35</td>
<td>David Friend</td>
<td>CONRAD (IPM)</td>
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<tr>
<td>36</td>
<td>Eric Adam</td>
<td>FIND</td>
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Annex Two: Questionnaire

1) Short description of what the PDP does, including the following information.

   a. Please list all the disease areas within which you are working to develop product(s)

   b. Please complete the table below to indicate where each product is located within the R&D pipeline (or if product is already on the market). Please also indicate the type of technology (e.g. drug, diagnostic, vaccine)

<table>
<thead>
<tr>
<th>Planning stage/not yet started</th>
<th>Early product development</th>
<th>Process development</th>
<th>Clinical trials</th>
<th>Licensing/regulatory</th>
<th>Production, sales and marketing</th>
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<td></td>
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<td>I</td>
<td>II</td>
<td>III</td>
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<tr>
<td>Product A</td>
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<td>Product B</td>
<td>Product C</td>
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   c. Please indicate your annual expenditure for 2008 and your average annual expenditure for the past 5 years.

   d. Please indicate number of full-time employees and their geographic location

2) Effectiveness

   a. Table with accompanying text summarising how the PDP is doing against its key current strategic objectives in its strategic or business plan

   b. Table with accompanying text summarising how the PDP is doing against the objectives of the Dutch grant. Did the PDP meet the objectives? If not, why not? Was there over/under spend? Was the PDP able to negotiate grant reprogramming (if necessary) with the Dutch? What did the grant deliver – i.e. outcomes?

   Further effectiveness Indicators:

   c. Governance mechanism of the partnership

      i. Evidence of appropriate representation on Board and scientific committees (independent, of global standing, relevant range of expertise)

      ii. Please provide information on: Legal status of the PDP, partner selection mechanisms, mechanisms in place to safeguard the PDP’s mission from capture by commercial interests e.g. Conflict of Interest policy

   d. Scientific review process - Is there a documented policy on how decisions made? e.g. criteria for gating? Who assesses the projects against the criteria?

   e. Organisational effectiveness

      i. Capable mgmt team, with appropriate public/private sector skills mix, e.g. including industrial technology development experience

      ii. Existence of business plan with steps to be taken by whom and when, risks identified and actions to mitigate

      iii. Engagement of developing countries (+representatives of) along the different stages of the R&D process?

      iv. What M&E mechanisms exist? What are processes for managing performance?
3) **Efficiency**: (Evidence of how economically resources/inputs (funds, expertise, time, etc) are converted into results). Indicators:

   a. How does the PDP make decisions about the relative priority of projects in a resource-constrained environment? What are the criteria for dropping projects and what is the process? Have any ever been dropped? What lessons learned?
   b. What is the plan for getting products to market? E.g. develop up to registration and seek industrial partners (for commercialisation) after proof of principle Phase II clinical trials?
   c. What are the projected future funding needs for the PDP, next 5 years?

4) **Relevance**: (Evidence that the PDP’s objectives are consistent with beneficiaries requirements, country needs, global priorities and partners and donor’s policies)

   a. Estimated cost/DALY of the new technology (the one(s) supported with the Dutch grant) versus other existing, comparable treatments
   b. Evidence that candidate (the one(s) supported by the Dutch grant) has superior safety, efficacy, suitability, and affordability profile versus existing options.
   c. Evidence of capacity building in the broad sense (building scientific capacity e.g. in protocol development, laboratory capacity, quality assurance programmes and ethics) Not only transfer of infrastructural resources and training but also social technology – the institutional and organisational capacity needed to conduct successful clinical trial level product development activities in low-income countries.
   d. Evidence of work at local level with / through existing health system and in compliance with local rules and regulations
   e. PDP participation in (international) discussions, e.g. on Global Health Research or Public Health, Innovation and Intellectual Property
   f. Does the human resources policy include targets for employment of staff from low or middle-income countries?

5) **Impact** on poverty and health for patients in developing countries

   a. What policies and actions have been taken to facilitate uptake/public health impact? Please explain if the PDP has engaged in any of the following:

      i. Market segmentation agreements with industry – esp. division of rights in “mixed payer” markets such as Brazil and India.
      ii. Tiered pricing agreements with industry. What is the plan to minimise risk of arbitrage (leakage between pricing segments)?
      iii. Policy on data sharing (e.g. so generics can rely on the dossier for bioequivalence testing)
      iv. Agreements on licensing, royalties
      v. Consideration of regulatory pathways in relation to speed and safety/quality?, e.g. looking for regulatory pathways that would speed up availability of product.
      vi. Analysis of burden of disease
      vii. Demand analysis, incl. analysis of future, anticipated financing
      viii. Analysis of potential distribution strategies and partners

10 e.g. registration in country of manufacture + WHO re-qualification as alternative to registration on SRA - DNDi did with ASAQ in Morocco
ix. Analysis of potential manufacturing strategies and partners: considered manufacturing in e.g. India or China to reduce costs?

x. Analysis of government decision making processes at country level for new technology introduction

  b. Impact on the global “access” architecture (longer term impacts)

  i. Policy for or evidence of sharing scarce assets (e.g. clinical trials infrastructure) with global community/amongst PDPs. Evidence of creating synergies with other PDPs.

  ii. How involved in regulatory issues – improving national approval processes – clinical trials, licensing. How capturing synergies across PDPs in this area?

  iii. Evidence/policy of access to intermediates, to drug libraries? Are these available to the global community?

  iv. Evidence that the PDP increased the absolute volume of resources (financial and human) dedicated to the discovery and introduction of new drugs and vaccines for neglected diseases?

  v. Has the PDP contributed to global knowledge to “ease/speed the pathway” to market for others?

6) Please provide 5 strengths and 5 weaknesses of the PDP.

7) Please explain the principle challenges of the PDP, going forward.

How does MoFA’s funding impact the PDP?

  a. financially (% of total funding - did it make a difference)

  b. strategically (did it attract other partners or open doors)

  c. managerially (was the programme funding manageable, reports requested)

  d. What were the challenges with the Dutch grant?

  e. How was the relationship between the PDP and the Dutch managed?

  f. Was the interaction between the MoFA and the PDP effective?

  g. How else beyond funding can donors provide PDPs with support? E.g. Advocacy or policy advice, management or technical advice, finance application and reporting, etc
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