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**Product Development Partnerships
(PDPs): Lessons from PDPs
established to develop new health
technologies for neglected diseases**

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Executive Summary

There has been little historic research and development (R&D) investment in technologies to address developing country health needs. The reasons for this are numerous and include:

- High capital costs to undertake the R&D and the long time between R&D investment and “commercialisation” of the resulting technology
- R&D investment not appropriate (in this case, insufficient commercial returns)
- High technical risk associated with the underlying R&D
- Development and/or success/uptake of the technology depends on actors from different sectors

In the past decade, Product Development Partnerships (PDPs) have been established to overcome these barriers. PDPs knit together partners from academia, industry, the public sector and international agencies into long term partnerships, building trust and leveraging each partner’s strengths towards a common goal. Each PDP is focused on a specific technological goal, for example the development of a malaria vaccine appropriate for use in developing countries. The field of actors involved, or with potential for involvement, in the R&D for such neglected diseases is relatively small, and can be fairly easily identified. Evidence has been emerging that these partnerships result in quicker, less costly development of the technologies with superior public health benefits relative to existing technologies. They also improve the overall enabling environment for other actors to do the same.

This paper discusses the nature of the investment barriers (mentioned above) in the neglected disease field and how the PDP model overcomes them. Those interested in applying the PDP model to overcome barriers in another technology sector can consider to what degree the same investment barriers are relevant and whether this model may be one way of addressing them.

Introduction

Background

Over the past decade, Product Development Partnerships (PDPs) have been established, focusing on developing new technologies to address priority health needs in developing countries. Questions are being raised within the UK government about the applicability of the PDP model to other technology sectors, such as clean energy technologies to address climate change. This short briefing paper was commissioned to give a brief overview of PDPs and to consider characteristics of need that are well suited to the PDP approach. This paper will form the starting point for discussion on the appropriateness of this approach to other sectors/areas.

Description and Scope of PDPs

Product Development Partnerships are one variant of public private partnerships focused on improving health in developing countries. PDPs are focused on product discovery and development, as opposed to partnerships focused exclusively on delivery of existing technologies (so called “access” partnerships) or health service delivery.

PDPs knit together public sector funding with private sector in-kind funding, and manage the contributions of public sector, NGOs, academics and private sector towards a common objective of developing a new health technology targeted to the needs of developing countries. The majority of PDPs work as virtual non-profit R&D organisations, whereby activities are outsourced to academic or private sector partners, with the PDP linking together expertise, and providing public funding, technical oversight and portfolio management. Each PDP focuses on specific types of technologies (e.g. drugs, vaccines, diagnostics) and some PDPs limit themselves to a specific disease area. (See Figure 1, Annex 2 for a map of PDP partners).

Most PDPs actively manage a portfolio of projects. Like private pharmaceutical companies, PDPs pursue multiple innovation avenues as an effective way to spread risks and increase the chance of success. PDPs engaging in portfolio approaches have independent scientific-advisory boards, responsible for selection of projects and partners based on scientific merit/technical feasibility of developing the technology. The degree to which the priority health needs of developing countries are addressed is also taken into consideration. Such a selection process is seen as a key advantage, cushioning donors from picking the funding winners/losers and placing that responsibility with those who have better information and expertise with which to make those decisions.

PDPs leverage additional investment from private partners, often in the form of “in-kind” inputs such as pro-bono human resource inputs and access to proprietary molecular libraries.

To support the equitable distribution of affordable products, PDPs negotiate terms with partners with regard to which countries, and which sectors within countries will have preferential access to the technology, and at what prices.

PDPs are not the sole means by which to incentivise product discovery and development within the neglected disease field. There are initiatives which make the market more credible – so called “pull” mechanisms - such as the first Advanced Market Commitment and increased funding for health technology purchase through The Global Fund to fight AIDS, TB and Malaria, PEPFAR, UNITAID and GAVI. There are other initiatives which, like the PDP model, are focused on reducing the costs and risks of R&D – “push” mechanisms. These include the United States Food and Drug Administration (FDA) priority review voucher, Article 58 of the EMEA, and “Enterprise” type initiatives to promote greater scientific collaboration in HIV and AIDS research. The WHO Expert Working Group on R&D Financing reviewed an even wider list of possible incentive mechanisms, e.g. Prizes, platform technologies, and direct support to small and medium size enterprises in emerging markets.

History of PDPs

A relatively recent addition to the international architecture, PDPs have arisen to address the mismatch between the need for health technologies to specifically address developing country health problems and the commercial sector’s traditional lack of willingness to meet that need, due to the costs and risks of such research and development (R&D) traditionally being too high relative to the market potential.

The model was based, explicitly, on private virtual drug development business models, and was additionally, seen as a tool for advocacy (more money and attention to neglected diseases overall), and as a tool to get the public and private sector to trust each other more, to work together in more productive ways. Funding soon emerged from the Bill and Melinda Gates Foundation, and the model flourished.

Other donors came on board, attracted by the possibility to move beyond the more linear model of support to individual technologies through academic institutions towards supporting a portfolio of projects, selected by scientific experts. Sixteen PDPs were founded between 1999 - 2003.¹ (Please see Annex 1 for a full listing of PDPs, their area of focus and their funders).

High R&D costs and long time to market

Drug and vaccine development may take up to 20 years and may entail several unsuccessful efforts before the successful technology is brought to market. The highly regulated clinical development process makes medical research highly risky and capital-intensive. Vaccine development costs are estimated to range between several hundred million dollars and US\$1.5 billion. Similarly, the cost to develop a drug new chemical entity is estimated to be between US\$600 million to US\$800 million, including out-of-pocket costs, costs of failure and costs of capital. The incremental innovations produced by PDPs to date have costed less to develop,² however the more innovative technologies further back in the PDP pipelines will require higher investment perhaps approaching the figures cited above.

R&D investment not appropriable

A few PDPs face a situation where there may be the prospect of a mildly interesting commercially opportunity, however the demand projections are hampered by uncertainty around product uptake and donor financing. Most PDPs are developing products for which there is non-existent, or at least, insufficient market potential to off-set the very high risks and costs of development mentioned above. There may be absence of a commercial segment (either wealthy countries or wealthy private market within poor countries) from which to gain some revenues and/or the absence of a dependable supply of donor finance to purchase for the public sector.

Although lack of ability to protect or enforce intellectual property (IP) may lead to reduced ability to appropriate investment in technology R&D generally, thereby further reducing incentives for investment, this is not so much the case in the neglected disease technology sector. In line with World Trade Organisation (WTO) TRIPS (Trade-Related Aspects Of Intellectual Property Rights) requirements, major generic-producing countries are now honouring patents registered after 1995. Thus the intellectual property on the more innovative technologies developed through PDPs will be enforced internationally and generic versions will not be available. This strengthened IP environment supports R&D incentives for the products with some limited commercial attractiveness, but it has little impact on the R&D incentives for technologies targeting the most neglected diseases.

High technical risk associated with the underlying R&D

To add to the above-mentioned mismatch between costs of R&D and market potential, the technical risk is also very high in developing neglected disease technologies. Many of the technologies under development lack animal models, lack agreed standards for registration of new technologies, and lack biomarkers with which to predict efficacy. PDPs may consequently work with regulators to agree the data and process needed for registration; this paves the way for the entire field, not just the PDP-developed products. A TB drug development PDP is working on

¹ Combating Diseases Associated with Poverty, FSG, Nov 2004, Health Partnership Review, Global Forum for Health Research, May 2008

² Mahmoud, A., Danzon, P., Barton, J., and Mugerwa, R., *Product Development Priorities*, Disease Control Priorities Project, The World Bank, 2004.

building up a biological specimen bank to use in identification or validation of TB biomarkers. This should enable ability to predict efficacy based on surrogate markers and is of relevance to TB drug developers as well as TB diagnostic research.

Many 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, whereas PDPs facilitate links with local NGO health service providers and communities, to help enrol patients and to follow up with them.

Prior to PDPs, the neglected disease R&D pipelines were noticeably empty; one study estimated there were only 20 neglected disease drug projects in development between 1975-2000.³ Because there has been so little investment historically in neglected disease R&D, only 16 of 1,393 medicines developed between 1975 and 2000 were for LDC-specific diseases.

The situation has changed significantly with the emergence of PDPs. Ten new technologies have been brought to market⁴ already by PDPs, and there are currently 122 candidates in the development pipelines of the PDPs collectively. This includes 90 biopharmaceutical candidates (up from 5 projects in 1990) and 32 diagnostic / vector control candidates. (See Figure 2, Annex 2 for overview of the stages of PDP technologies in development).

Development and/or uptake of the technology depends on actors from different sectors

Wellcome Trust funded research⁵ demonstrated the comparative advantage of public/private approaches to neglected disease development. This research revealed that, within the drug sector, PDPs have been responsible for increased neglected disease R&D activity and are proving superior in terms of time to market, cost-efficiency, health value and innovative level of the products, when compared with industry working alone and public groups working alone in neglected disease technology development. As an example of the way these groups may come together: academic groups and biotechs may bring valuable scientific ideas, larger pharmaceutical multinationals bring clinical trial expertise and PDPs bring their knowledge of the global health architecture, helping private companies to navigate the developing country regulatory environment and liaise with other actors in the public health space. PDP management knits together all these different partners towards a common objective.

Once the technologies are developed, success is defined by their uptake and health impact. There are two principle components to this - is there financing to facilitate this uptake and are there health systems to do the same?

On the financing side, there have been large increases in development assistance for health, from US\$5.6 billion in 1990 to US\$21.8 billion in 2007.⁶ Health technology

³ Source: PRPP (2005a). New EU approaches to funding R&D for neglected diseases. London: Pharmaceutical R&D Policy Project. Presentation by Mary Moran, March 2005

⁴ Products through regulatory approval: Coartem D (MMV), Paromomycin (India) (iOWH), JE Vaccine India (PATH), Inactivated oral cholera vaccine (IVI), Liquid culture DST (FIND), Rapid MTB ID (FIND), LPA line probe assay (FIND), Minicolumns (mAECT) (FIND), ASAQ (DNDi), ASMQ (DNDi)

⁵ Source: PRPP (2005a). New EU approaches to funding R&D for neglected diseases. London: Pharmaceutical R&D Policy Project. Presentation by Mary Moran, March 2005

⁶ Ravishankar, N., Gubbins, P., Cooley, R., Leach-Kemon, K., Michaud, C., Jamison, D., Murray, C.. Financing of Global Health: tracking development assistance for health from 1990 to 2007. The Lancet Volume 373, June 20, 2009. pages 2113 - 2124.

purchase for neglected diseases is largely channelled via global health institutions such as the Global Alliance for Vaccines and Immunisation (GAVI), the Global Fund for AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief (PEPFAR). The financing picture is looking more positive than it ever has in the past and this financing can easily transition from inferior, older products, to new PDP products, once developed. PDPs help negotiate the funding landscape, even to the extent of working with global funds on demand projections.

PDPs also negotiate the delivery side. Early on, PDPs factor in total delivery costs and ease of technology delivery into their "target product profiles" and these form part of the basis of project selection at the scientific advisory council portfolio selection stage. As the R&D pipelines for PDPs mature, they have become increasingly involved in developing "access" strategies. In this transition, the scope of their partners has widened to encompass not only partners needed to develop the product, but also those responsible for financing and delivering the product.

In other technology sectors, it may be important to think not only about how to incentivise R&D, but also how to facilitate uptake - how the purchase decisions are made, who finances purchase, how the technology fits in with complementary technologies and how the technology delivery is supported at country level.

Successes

PDPs are achieving tangible results – notably rich pipelines of technologies in development and ten product launches since their start – and there are signs that they are stimulating "ripple effects" which are more difficult to quantify but equally as important. One of these ripple effects is capacity strengthening of clinical trial infrastructure for neglected disease research in developing countries. This is one example of PDP's impact on the global access architecture, which may facilitate product development and delivery even beyond the PDP's own disease or product sphere. Another example is the evidence PDPs produce to make developing country markets less opaque. When this information is made public, it may encourage industry activity even independently of the PDP. Examples include burden of disease studies, demand studies including projection of future financing, and studies that characterise the needs of the product user at different levels of the health system.

Weaknesses

PDPs have demonstrated that they can deliver products to market, but can they deliver health impact? While receiving regulatory approval shows *potential* for health impact, product uptake is a better indicator of *actual* impact and it is too early to have robust data on uptake.

A second concern is that most of the products so far developed by PDPs are incremental innovations - "low-hanging fruit". We do not yet have sufficient evidence that PDPs can deliver breakthrough innovations. A portfolio of more innovative, earlier stage products may mean less short term progress, but with greater health impact longer term.

A third concern is cost linked to the two challenges below – funding shortfalls and proving impact. Some PDPs are pursuing a model of conducting more activities in-house, implying a higher degree of control over IP and inputs, but a higher level of

costs. Not surprisingly, PDPs with business models on the “in-house” end of the continuum are more expensive than PDPs with the “outsource” models, and they absorb a disproportionate amount of funds allocated to the PDP sector overall.

A fourth area of concern arises when a PDP pursues a strategy of developing “own” products. Researchers who are not chosen as partners by these PDP’s scientific advisory committees complain that the PDP’s alliance to its own technology has a negative effect on overall innovation in the sector. If true, this situation would be exacerbated when the PDP dominates funding available for the sector or controls key assets (e.g. clinical trial infrastructure) needed to create an alternative path to market. It is especially important that PDPs in such situations have independent review mechanisms. It is important regardless, but even more so in these situations, that there are alternative paths for innovation to flourish, i.e. that the PDP is only one of several methods of supporting technology development in the relevant sector.

Challenges

Sustainability and Funding. With products moving into the more expensive phases of the R&D pipeline, PDP funding needs are growing. Sustained and increased funding will become critical if earlier investments are to result in the launch and use of new products.

Attribution/proving impact. 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. PDPs have achieved tangible results (e.g. launched products) and are having ripple effects as well. There are signs that PDPs are correcting market failures, causing more R&D activity to take place in the neglected disease space than would otherwise be the case. However, it is still quite difficult to attribute changes specifically to the PDP and to know what would have happened in the counterfactual case - absence of the PDP.

The PDP model is suitable when:

1. The costs and/or risks of technology development are too high in relation to the anticipated market return, such that there is likely to be underinvestment by the private sector in the technology’s development
2. There are market failures such that the private sector’s contribution to R&D in the sector is absent or is not socially optimal (e.g. investment does not account for the “externality”/public good created by vaccines or the public good arising from pollution control or stemmed climate change)
3. Existing technologies are sub-optimal, e.g. on grounds of cost effectiveness and the new technology developed would be in demand, being a substantial improvement upon existing technologies in terms of quality, safety, effectiveness, etc, allowing higher uptake at lower cost.
4. Funding for existing technologies is readily available (or can be constructed through a deliberate “pull” incentive mechanism, created to increase market attractiveness) and can transition easily from existing, inferior products to newly developed products, thereby easing market access and technology uptake.
5. PDPs would seem to work best to address a specific technological goal or gap (drug or vaccine or diagnostic for a specific disease). Other models may be considered if the goal is to support for technological innovation more broadly in a particular field.

6. The PDP model (as a form of “push” incentive) essentially pays for effort, whereas “pull” incentive mechanisms only pay upon success. Push may be preferable over pull when effort is easy to monitor and measure and/or when the funder has a higher tolerance for risk. Pull mechanisms may be a superior incentive mechanism when it is easy to specify the desired outcome, when agents are not capital constrained, and when the funder is risk-averse.
7. PDPs, or other push mechanisms, may be more suited to situations where pockets of expertise are relatively concentrated and easy to identify. Conversely, a key advantage of pull mechanisms is that the funder can draw on the expertise of a large and diffuse set of researchers, rather than identifying and funding a handful with the greatest potential, as with “push”. This advantage is especially important in cases where knowledge is spread throughout the world or experts are hard to identify.
8. Push funding, including via PDPs, may be well suited to situations where the desired innovation is likely to come from smaller or capital constrained firms. Indeed, many of the organisations and firms from whom innovation might be expected in the neglected disease field – such as biotechs – are relatively capital-constrained.

Key questions include:

- What type of innovation is required? Is there a specific technological goal, or is the goal innovation more broadly in a sector?
- Which actors need to be involved in developing the innovation, and how easy is it to identify them?
- Are small grants needed for short inputs or deeper, longer term partnerships?
- How easy is it for donors (or their agents) to monitor the R&D effort/progress made?
- What balance between cooperation and competition is optimal?
- Which mechanism would be best to leverage additional private or public investment?
- How would the technologies developed via the PDP model be linked with provision of market access and commercialisation assistance?
- How would developing countries be involved in defining the target product profiles or selection of projects to support? Presumably the technologies to be developed should be based on criteria they define based on priority needs of their countries.
- What types of incentive mechanisms exist already for the sector, and how does the PDP model address a gap and fit into the mix? For example, how is the PDP linked to “pull” mechanisms and other means to ensure deployment and diffusion, once the product is developed?
- Who are the decision makers with regard to deployment of the new technologies and will they support the deployment of those technologies?
- How easily can existing funding transition from old to new technologies? Is there potential to construct new targeted “pull” funds to help accelerate uptake of the technology, once developed?

Annex 1

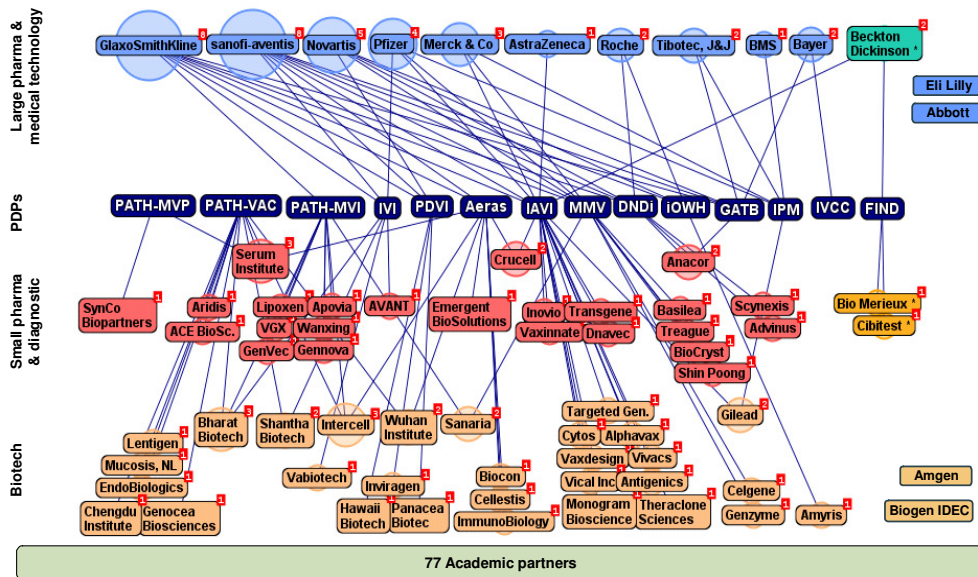
DISEASE/PRODUCT	PD PPPs																
	HIV/AIDS Vaccines		HIV/AIDS Microbicides			Malaria Drugs	Malaria Vaccines		TB Drugs	TB Vaccines	TB/Other Diagnostics	Other "Neglected Diseases"					
FUNDERS	IAVI	SAAVI	IPM	GMP	MDP	MMV	MMI	EMVI	TB Alliance	AERAS	FIND	DNDi	IOWH	PDM	HHVI	Rota ADIP	Pneumo ADIP
FOUNDATIONS																	
Bill and Melinda Gates Foundation	+		+	+		+	+		+	+	+		+	+	+	+	+
Elison Medical Foundation																+	
Rockefeller Foundation	+		+			+			+						+		
The Wellcome Trust						+											
Others	+																
GOVERNMENT BILATERAL AID AGENCIES																	
Canadian Government (CIDA)	+																
Government of Denmark (DANIDA)	+		+														
Government of the Netherlands	+		+			+											
Government of Norway	+		+														
Ireland Aid	+	+	+														
Swiss Government (DEZA/SDC)						+											
Swedish Government (SIDA)	+																
U.K. Government (DFID)	+		+		+	+											
USAID	+					(+)*	(+)*										
OTHER GOVERNMENT FUNDING																	
Government of South Africa			+														
National Institute of Health (NIH), USA			+														
MULTILATERAL AGENCIES																	
European Union	+	+						+									
UNDP																	
UNAIDS	+																
UNFPA			+														
WHO						+			+				+				
The World Bank	+					+											
NGO																	
Médecins Sans Frontières (MSF)													+				
BUSINESS																	
Pharma	+							+									
Others	+	+				+											

Source: DFID Central Research Department Strategy Paper: Investing in new tools for HIV, malaria and tuberculosis through Public Private Partnerships; Alastair Ager, Joanna McGowan, Val Shewin and Saul Walker, October 2005 and adapted from page 110 of Annex 9b of 2004 IPPPH report. Sander and Widdus, The emerging landscape of public-private partnerships for product development.

Annex 2: Figures

PDPs are working with a constellation of biopharmaceutical and academic partners

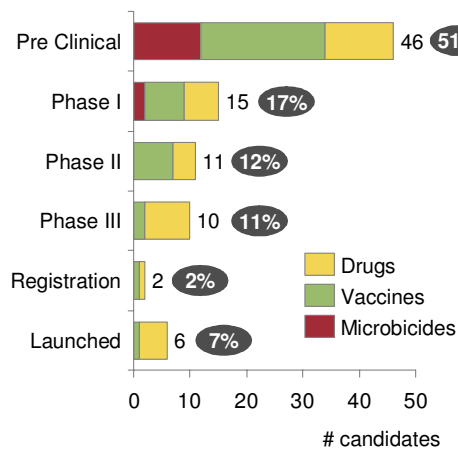
Snapshot of network map of PDP R&D partners based on data provided by PDPs, July 2009



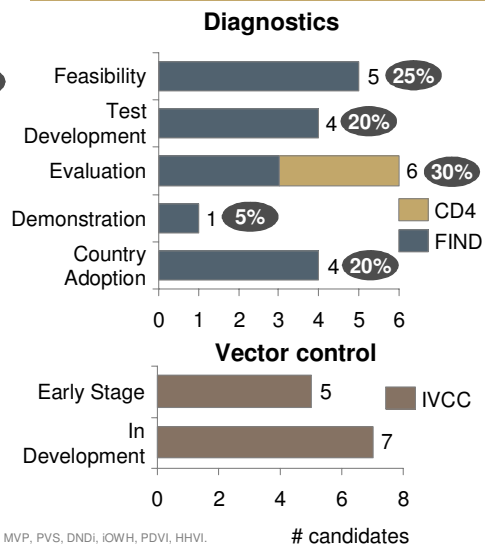
Note: Size of halo and number in red represent number of partner's connection to PDPs.
 * Becton Dickinson is a medical device company, and Bio merieux and Cibtest are diagnostic companies.
 Source: BCG analysis presented at PDP Forum, PDPs in 2009: State of the Art, July 2009

Combined PDP pipeline today includes 122 candidates

90 biopharmaceutical candidates in development...



... and 32 diagnostic & vector control candidates



Notes: Includes products not funded by Gates Foundation.
 Biopharmaceutical candidates in development include: IAVI, IPM, IVI, GATB, Aeras, MMV, MVI, MVP, PVS, DNDI, iOWH, PDVI, HHVI.
 Source: PDPs

⁷ Boston Consulting group analysis presented at PDP Forum, PDPs in 2009: State of the Art July 2009.

