V. Works produced

In the following section, we report in the form of chapters 1-3, the papers that were produced as result of our project. Chapter 4 concludes with the report of the closing workshop that was held in Geneva, Switzerland, on April 3 2014, to present and diffuse the results to the community of experts and policy-makers.

Chapter 1:

Can medical products be developed on a non-profit basis? Exploring Product Development Partnerships for Neglected Diseases

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Abstract

Reliance on market forces can lead to underinvestment in social welfare enhancing innovation. The lack of new medical products in the area of neglected diseases is a case in point. R&D for neglected diseases has increased with new funding and collaborations taking place mainly through Product Development Partnerships (PDPs). PDPs are self-governing, private non-profit R&D organizations. In contrast to push and pull instruments designed to address private sector R&D underinvestment, PDPs have voluntarily emerged to address the public health challenge. In this study we examine how non-profit R&D collaboration for neglected diseases takes place through PDPs. We find that PDPs act as "system integrators" that leverage the resources and capabilities of a diverse network of public, philanthropic and private sector partnerships. This paper contributes to the understanding of R&D in a non-profit context and highlights the importance of collaboration and non-market institutions for promoting innovation where market failures are present.

1. Introduction

Over a billion people are affected by diseases that have a large burden in developing countries but no or small burden in the developed world (WHO 2010). Historically, government public health programs and the pharmaceutical industry have neglected these poverty-related diseases. Very few new medical products (drugs, vaccines and other biological products, diagnostics and vector control products) are developed for their prevention and treatment. Pharmaceutical firms, absent market incentives to spur their commercial interest, are reluctant to independently engage in this endeavour. As a result, they pass up opportunities for socially valuable innovation.

Economists have proposed a range of economic instruments to incentivize firm-level R&D in neglected diseases. Push mechanisms that aim to bring down firms' costs of R&D, such as grants, tax credits and loans are the more broadly used by policy-makers. Pull mechanisms, on the other hand, such as milestone or end prizes, secured quantities or price, aim to increase market attractiveness by lowering risk of R&D and assuring revenue for the outputs.

Meanwhile, a rising number of self-governing private non-profit organizations have emerged to catalyze R&D for neglected diseases. Product Development Partnerships (PDPs) have produced various new diagnostics and therapies in the form of reformulated or repurposed versions of existing drugs, vaccines and biological products. They have also built significant R&D project portfolios with several novel vaccines and drug candidates in the pipeline, including new chemical entities (NCEs). Most of PDPs do not undertake any in-house R&D activities but rather operate through external collaboration. PDPs mobilize funding from philanthropic and public entities and partner with a number of public and private institutions to implement R&D projects, including academia and public research institutes, pharmaceutical, biotechnology and other private for-profit firms such as contract research organizations.

The PDP openness to external R&D collaboration can appear to mirror a similar trend in the pharmaceutical and biotechnology industry (Juliano 2013). However, the motivation for PDPs to pursue R&D collaboration is distinctly associated to their non-profit mission. Large pharmaceutical firms are increasingly sourcing their R&D portfolios by in-licensing external R&D projects and through mergers and acquisitions (M&A) to raise growth and revenue prospects (Schuhmacher et al. 2013). In contrast, the common goal of PDPs is to build R&D portfolios to develop products that address unmet health needs. This entails that the final product must be affordable and accessible to patients. In this context, partners involved in PDP-led R&D projects have to operate within the confines of the PDP mission. The concept of "partnership" implies a commitment to a common goal through the joint provision of complementary resources and expertise, and the joint sharing of the risks involved (Ridley 2001).

The research is informed by literature review and in depth interviews with staff of PDPs. Previous literature has described the role of PDPs in the neglected disease landscape (Moran 2005, Grace 2006, Chataway et al. 2007, Grace 2010, Moral et al 2010, Chataway et al 2010). While building on this literature, we further explain the operation of PDPs, identify their core capabilities, provide an update of PDP outputs, and analyze the variety among PDPs and the constraints of the PDP approach.

The study is divided in seven sections. Following the introduction, the second section presents the problem of insufficient innovation for neglected diseases. The third section then describes the economic instruments that are designed to stimulate innovation in neglected diseases. The forth section explores how PDPs are accessing and leveraging external resources and capabilities through R&D collaborations. The fifth section explains the variety within the PDP landscape. The sixth section discusses the limitations of the PDP organizational form. The seventh section concludes.

2. The shortfall of innovation for neglected diseases

The "neglected disease" expression points out a problem of insufficient new medical products developed to address diseases that have a large burden in developing countries but no or little burden in the developed world. There is no single definition of "neglected disease". The WHO defines "neglected diseases" as a group of 17 diseases that affect more than 1 billion people worldwide that persist under conditions of poverty and are concentrated almost exclusively in impoverished populations in developing countries (WHO 2010).[2] Infectious diseases in particular account for 10 million deaths each year, of which more than 90 percent occur in developing countries (WHO Health Statistics 2010). For purposes of our study, we consider the WHO listed diseases and also include three communicable diseases: tuberculosis, malaria and HIV/AIDS.[3] These are diseases prevalent in developing countries and often co-exist with other neglected diseases. However, they differ from other "neglected" diseases in that they may be found also in developed countries (tuberculosis and HIV/AIDS) and generally receive more financing for R&D and delivery.

New medical products are essential to the prevention, control and elimination of disease. The current level of R&D for new medical products targeting neglected diseases is negligible relative to the health burden of the diseases. The unbalance is evident if we consider (i) the amount of R&D investment for neglected diseases compared to the global R&D investment for all diseases and the health burden of neglected diseases, and (ii) the number of new medical products developed for neglected diseases compared to other diseases.

One study has found that global R&D investments by public, philanthropic and private sector in neglected disease research in 2010 (approximately 2.4 US$ billion) accounted for only 1% of overall health R&D investments (240 US$ billion) (Røttingen et al 2013). Funding for neglected diseases has slightly increased from an estimated US$ 2.8 billion in 2005 (Global Forum for Health Research 2008) to 3.045 US$ billion in 2011 (G-Finder 2012). The largest funders are public donors with a total US$ 1.9 billion in 2011, followed by philanthropic donors with a total US$525.1 million in 2011 (G-Finder 2012).

[2] The diseases concerned are: Buruli ulcer; Chagas disease; cysticercosis; dengue; dracunculiasis; echinococcosis; endemic treponematoses; foodborne trematode infections; human African trypanosomiasis; leishmaniasis; leprosy; lymphatic filariasis, onchocerciasis; rabies; schistosomiasis; soil-transmitted helminthiases; and trachoma.

[3] The inclusion of these diseases is consistent with other studies, i.e. Trouiller et al 2002 and the G-FINDER Report on Neglected disease R&D, 2012.

The small number of new medical products for neglected diseases as compared to other diseases is an indication of the persistent gap in innovation in this area. One landmark study found that between 1975 and 1999, 1,393 new drugs (excluding vaccines) were made available to the public, but only 16 of these were meant for neglected diseases (Troullier et al. 2002). A recent study finds that of the 850 new therapeutic products, NCEs, new indications, new formulations, fixed-dose combinations, and vaccines and biologicals) registered in the period 2000 to 2011, only 37 (4%) were indicated for neglected diseases, comprising 25 products with a new indication or formulation and eight vaccines or biological products. Of those 25 products, only 4 were NCEs. Only 1% of all registered clinical trials were for neglected diseases (Pedrique et al. 2013).

Generally firms invest in R&D with the expectation that revenues generated from the sale of new medical products will increase as a result. They finance R&D from their own resources (from profits), as well as from public support instruments such as tax breaks and grants. Nonetheless, firms generally tend to invest less than the socially optimal level of R & D. The reasons include high risks and costs, problems of R&D financing and incomplete appropriability of returns to R&D (Nelson 1959, Hall 2010). To address the appropriability problem, firms can seek legal protection for the invention through government-granted patents that give the firm a time-limited monopoly control (i.e. manufacture, use, and sale) over the product. Patents support the firm's pricing strategy, aimed at setting a price as profitable as the buyer (there can be several possible buyers, such as government health authorities, insurers, prescribers/pharmacists, patients out-of-pocket) is willing to pay.

The pharmaceutical industry historically has invested very little in R&D for new medical products in the area of neglected diseases. This is to be expected as the market for neglected diseases does not offer firms many opportunities for profit, despite the gross unmet needs for treatment. Accordingly, the economic barriers to R&D in neglected diseases by private firms can be described as follows (Webber and Kremer 2001):

- Commercial markets are small
- Individual purchasing power is limited, even though the number of patients may be very large
- High R&D costs (estimated to be the same as for new medical products for other diseases) and inherent risk in R&D will not be covered by returns on investments.

Moreover, patents as an incentive for appropriability of R&D returns are not an effective mechanism to stimulate R&D in neglected diseases given the absence of a profitable market. and rather affect the availability of affordable medical products (WHO 2006).

It can be assumed that the risks and costs of new product development for neglected disease R&D may be the same as for other diseases.[4] Medical product development is generally very costly with high risk of failure. However, precise data

[4] There can be ample variance depending on the disease (the extent of research and development gaps, market attractiveness), the type of product and means of undertaking clinical trials.

on R&D costs of pharmaceutical firms is generally unavailable or undisclosed. This is a critical constrain for the adequate design of economic instruments and their employment to incentivize R&D in neglected diseases as well as in others. When firms do provide cost data, it is not specified how the R&D costs is calculated or what is included in the cost (Morgan et al. 2010). It is estimated that a drug in the form of a NCE may take between 13 –15 years, from discovery to when it is available in the market. For vaccines, the full R&D process may take 12 years. The levels of attrition (likelihood of failure of projects) can be close to 60% of projects, higher in the discovery stage. Published estimates of the R&D cost diverge widely, with existing studies varying in methodologies, data sources, samples and time periods. For example, one recent study by health economists calculate that the net median R&D cost may be in the range of 13 million to $204 million US$, while existing estimates range from 161 million US$ to 1.8 billion US$ (Light and Warburton 2011).

There is also no concrete data on the extent of R&D investment overall in medical products by pharmaceutical firms. While R&D costs have risen in the past two decades, revenues for pharmaceutical firms have increased six times faster, with net profits after taxes substantially higher than profits for all other Fortune 500 companies (Light and Lexchin 2012). At the same time, the overall rate of innovation in the pharmaceutical industry has been in decline. The number of total innovative new medical products approved has fallen since the 1990s, while many of those are "me too" drugs, rather than new chemical (or molecular) entities, and without significant therapeutic value.

3. Economic instruments to stimulate innovation in neglected diseases

In the last decades, various instruments have been designed and some implemented to address the underinvestment problem above illustrated. With the aim of filling the gap between private and social returns to R&D in the field of neglected diseases, ''push'' and ''pull'' instruments have been explored by public and philanthropic sectors for financing and increasing R&D efforts.

"Push" instruments aim at stimulating R&D by reducing the costs of R&D for industry. These include instruments that pay for inputs to R&D, such as providing direct funding to research, particularly basic research but may also extend to applied research (grants to universities, government public research laboratories, or for projects jointly with industry), R&D tax breaks, direct grants for small firms, funding for clinical trials in developing countries, open innovation platforms, patent pools and related initiatives, fast track regulatory review (approvals), pre-competitive research platforms for sharing R&D costs and regulatory harmonization. Some of the problems that are associated to pull instruments are that they may not provide sufficient incentive for R&D by themselves. Incentives between grantees and funders may be imperfectly aligned, and the instruments are vulnerable to politization/lobbying (Sampath and Hedge 2011).

"Pull" instruments pay for the outputs of R&D. The main barrier considered is insufficient market attractiveness, rather than high cost of R&D. Pull instruments aim to address the problem of lack of commercial markets. They are designed to create demand for yet-to-be-developed products and effectively enlarge the market for medical products in neglected diseases. Pull instruments reward the output (new

medical products developed) rather than pay for inputs to R&D. There is limited practical experience with pull instruments for neglected diseases.[5] One attractive feature of pull instruments is that they are less costly than other instruments as they do not entail up-front payments. Money is spent only if milestones are reached or new medical products are developed in accordance to pre-defined criteria. The specified criteria would be pre-set by the purchaser (i.e. government, philanthropic organization or international organization). The firm or other entity could then decide on the R&D strategy to deploy to meet the criteria. Once the milestone is reached or the product is developed, the disbursement of the committed money would be made, and the purchaser could make the product available to patients at low or no cost. Examples of pull instruments include prizes, funds for end-payments (such as the Health Impact Fund), funds that would allocate resources to any research organization,[6] and advance market commitments (AMC).

A critical condition of the pull instrument is that payment has to be attractive enough to provide incentive to the participant in the scheme. In theory, the adequate size of the incentive may vary among participants. For private firms, it requires increasing the likelihood of return of their R&D investments (at best, bring profits, at minimum, no loss). For other types of organizations, such as non-profit product development partnerships (PDPs), the size of the incentive required may be lower. In the design of pull instruments, a crucial element is the amount of the commitments (including specifications such as doses to be purchased and purchase price) that would be required to provide a strong enough incentive to create a market that would surpass the barrier to R&D investment. The economist Michael Kremer foresaw that substantial industrial investment in neglected disease R&D would occur only if expected rates of return are broadly equivalent to those anticipated from R&D in conventional areas. However, without proper information on actual costs of R&D, public resources may be wasted. Robust data on the cost of R&D for new medical product development should inform these decisions. However, as discussed earlier, the existing estimates for medical product innovation are unreliable.

[5] An AMC program has yet to be tried for incentivizing new medical products. The first experience of the design of large-scale pull instrument is the AMC GAVI Alliance initiative since 2009 to make available existing pneumococcal vaccines. It was designed by a group of economists (Levine, Kremer et al. 2005). Governments and the Gates Foundation made a binding commitments of 1.5 US$ billion to fund the pilot AMC for which vaccine manufacturers could bid. In 2010, GlaxoSmithKline and Pfizer committed to supply 30 million doses of their pneumococcal vaccines for 10 years that had recently been approved in Europe and the US (Synflorix and Prevenar-13) at a maximum price of 3.50 US$ a dose. The two vaccines were selling for average 40 Euros in Europe and 90 US$ per injection in the United States. Each manufacturer's share of AMC funds is disbursed as a subsidy per dose, in additional to the tail price of 3.50 US$, thus the total price up to 7 US$ for approximately the first 20% of vaccine doses procured from each manufacturer (Cernuschi et al. 2011). The aim is to enable firms to quickly recover incremental investment costs incurred to allow scaling up of supply capacity to serve GAVI-eligible countries faster through the WHO and UNICEF as procurement agents. The expectation is that the vaccines will be distributed to 40 developing countries that will pay 15 cents of the 3.50 US$, with the remaining cost covered by the AMC. The estimate cost per child receiving the vaccine is 4,722 US$ (Scudellari 2011). Some concerns that have been raised are the costs of the system, transparency by firms on vaccine manufacturing costs and profit margins, geographical scope, eligible purchasing agents, and entry of developing country producers that can lower vaccine costs (MSF 2013).

[6] Some of these proposals include the Product Development Partnership Financing Facility (PDP-FF), the industry R&D Facilitation Fund (IRFF), the Fund for Research in Neglected Diseases (FRIND), and a Fund within a global framework on health research and development. These proposals are reviewed in the 2012 report of the WHO CEWG, pg. 176-179. See WHO 2012b.

A different means to spur medical innovation is via open models based on collaboration. In the discovery phase, open models of innovation rely on collaboration, sharing of information among volunteers and open access to data. Two examples of these projects that have been studied are CSIR Team India Consortium's Open Source Drug Discovery project (CSIR OSDD) and The Synaptic Leap's Schistosomiasis project (TSLS) (Ardan and Rottingen 2012).

4. Organizations to drive innovation in neglected diseases: Product Development Partnerships

Evidence suggests that collaboration in R&D for neglected diseases is increasing. One study has found that there are around 348 organizations from private and public sector (academic/research institutions, biotechnology companies and other medium and small firms such as contract research organizations, and large pharmaceutical companies) participating alone or in partnership with each other in the development of a combined pipeline of 374 drugs and vaccines for 23 neglected diseases (BVGH 2012). The majority of collaborations are reported to be taking place through PDPs, with a 40% share of participation in the total number of projects (BVGH 2012). Another study has found that for the 123 new medical products in development in the period of 2000 to 2011, public organizations were involved in 66 products (54%), private industry in 28 products (23%), and private non-profit organizations (including PDPs, charities, foundations, and philanthropic institutions) in 19 products (15%), with the remaining 10 products (8%) involving a mix of sponsors. All three NCEs for neglected diseases were being sponsored by private non-profit organizations (Pedrique et al. 2013). It also appears that large pharmaceutical firms are increasingly interested in joining PDP projects more than undertaking their own. The annual report by IFPMA for 2012, lists 132 R&D projects for new medicines and vaccines (excluding HIV/AIDS) involving IFPMA member companies of which 112 are projects with PDPs and only 20 (15%) projects are firm-only undertakings.

PDPs in the past 15 years have become part of the puzzle of how to close the innovation gap for neglected diseases. One study found that the PDP pipeline included 63 neglected disease drug projects (excluding vaccines, diagnostics and microbiocides) under way at the end of 2004, including two new drugs at the registration stage and 18 new products in clinical trials, half of which had already reached Phase III (Moran 2005). But new projects have been launched since the end of 2004, amplifying this trend (BVGH 2012). A full list and description of new products developed by PDPs is found in the Appendix to this paper.

Since the 1990s the number of PDPs has grown from one to 23 PDPs in 2014 that we have identified in our study.[7] We define for purposes of our study PDPs as self-

[7] Our complete list of PDPs includes, in alphabetical order: AERAS, Contraceptive Research and Development (CONRAD), Consortium for Parasitic Drug Development (CPDD), Dengue Vaccine Initiative (DVI), Drugs for Neglected Diseases (DNDi), European Vaccine Initiative (EVI), Foundation for Innovative New Diagnostics (FIND), Global Alliance for TB Drug Development (TB Alliance), HIV Vaccines Trials Network (HVTN), Infectious Disease Research Institute (IDRI), Innovative Vector Control Consortium (IVCC), International AIDS Vaccine Initiative (IAVI), International Partnership for Microbiocides (IPM), International Vaccine Institute (IVI), Medicine for Malaria Venture (MMV), Microbiocides Development Programme (MDP), One World Heath (IOWH), Malaria Vaccine Initiative (MVI), Meningitis Vaccine Project (MVP), Pediatric Dengue Vaccines Initiative

governing[8], private, non-profit organizations that aim to develop new medical products in the area of neglected diseases. They do so by leveraging sources of knowledge, capabilities and assets of external public, philanthropic and private sector organizations.

PDPs are not push or pull instruments for R&D. As discussed in Section 3, push and pull instruments are policy instruments designed mainly to promote private investment in R&D[9]. In contrast, PDPs are R&D organizations that have emerged to bring about innovations in an area where neither the private or public non-market institutions can or are willing to do the task alone (Chataway et al. 2010). The private sector lacks interest in undertaking alone the range of R&D activities for medical product development on neglected diseases. Yet in the PDP framework, it appears that private sector can be induced into collaboration if costs and risks are reduced and there are other drivers, such as a boost to public relations. Academia and other public research institutions generally do not have the full range of necessary resources, capabilities or assets to undertake medical product R&D, even though there is resolve to address unmet health needs. Public sector institutions involved in R&D are usually focused on discovery and creating knowledge (upstream), but not for product manufacturing (downstream). They stop where the practicalities of product development come up.

Members of the global public health community (such as the World Health Organization, civil society organizations and doctors) initiated PDPs as a practical mean to increase R&D for neglected diseases. However, it is not evident why a new organizational innovation in the form of PDPs was needed in the context of existing organizations in global public health governance. These include public research institutions, firms (biotechnology, big pharmaceutical firms), government, international organizations such as the WHO, World Bank, UNDP, UNESCO, UNICEF and UNITAID, civil society organizations and existing networks of research collaborations. We trace the origins of PDPs and identify gaps in existing organizational structures that PDPs are responding to.

Some of the early PDPs were catalysed at the WHO through the Special Programme for Research and Training in Tropical Diseases (TDR) and the experience with partnerships it progressively forged in the 1980s-90s.[10] Before the TDR, there

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(PDVI), Sabin PDP, South African AIDS Vaccine Initiative (SAAVI), and Turberculosis Vaccine Initiative (TVI). To date we have interviewed several representatives from four PDPs, two producing drugs (DNDI, MMV), one producing vaccines (MVP) and one producing diagnostics (FIND).

[8] We include PDPs that are part of a larger PDP organization, (i.e. MVP and MVI are part of PATH, Sabin PDP is part of the Sabin Vaccine Institute).

[9] Instruments such as direct grants to small and medium firms and for clinical trials in developing countries, milestone or end-prizes, purchase or procurement agreements, and others, can be complementary to the role of PDPs, and PDPs themselves can use them.

[10] The WHO is the leading directing and coordinating authority for health within the United Nations system. The WHO TDR program, in existence since 1975, is cosponsored by UNICEF, UNDP and the World Bank. The aim of the program was to intensify research on major tropical parasitic diseases, taking into consideration that such activities should be carried out mainly in endemic countries, define the research priorities, extend cooperation with national institutions and other governmental and non-governmental organizations in regard to the coordination of research in this field, and mobilize extra-budgetary resources for scaling up these objectives (WHA 27.52). The TDR was set up mainly as partnership between public donors, co-sponsors and endemic country governments represented in an independent board-type structure. Its research priorities are defined by a scientific committee of experts

was no international framework focused on coordinating research to support infectious disease control, particularly in the developing world (UNICEF et al. 2007). The role of TDR evolved in time, from focus on strengthening research capability building in endemic countries to promoting international collaboration to increase R&D for neglected diseases. Scientists engaged in the private sector had been participating in TDR committees, but private sector was not engaged formally in the work of TDR. In time, opportunities did arise for product development in collaboration with industry. However, it appeared to be too costly and complex to manage and implement by TDR and outside its mandate. With this in mind, the idea of creating independent, disease focused organizations appeared as an avenue to speed up R&D and delivery of new medical products to meet health needs.

The TDR assisted in the creation various PDPs since 1999[11] while other PDPs were created independently.[12] Non-profit philanthropic foundations such as the Rockefeller Foundation have played an active role in cultivating PDPs. The establishment of the Gates Foundation by Bill and Melinda Gates in 2000 gave a big push to PDPs as new funding sources that became available to them. PDPs also have surged in the context of the process of "vertical dis-integration" in the pharmaceutical industry (Cockburn 2004).

The characteristics of PDP organizational design that differentiate them from collaborative bilateral or multilateral networks on R&D for neglected diseases, public institutions and pharmaceutical firms with R&D capacity include the following:

(i) They are established as non – profit entities that guarantee them independence and no shareholder expectations of growth and revenue maximization motives

(ii) Their objective is to develop new medical products that can have a public health impact (specialized, access core to their mission)

(iii) Their focus on developing "system integration" capabilities to engage and leverage diverse resources and capabilities of various actors in the R&D chain

(iv) They have in-house capabilities on managing a portfolio of R&D projects. External partners often undertake the R&D activities, though some have in-house R&D capacity.

As example of product development through PDPs, in Figure 1 we report the case of the development of a new anti-malaria drug. The project was led by DNDi with the collaboration of TDR.

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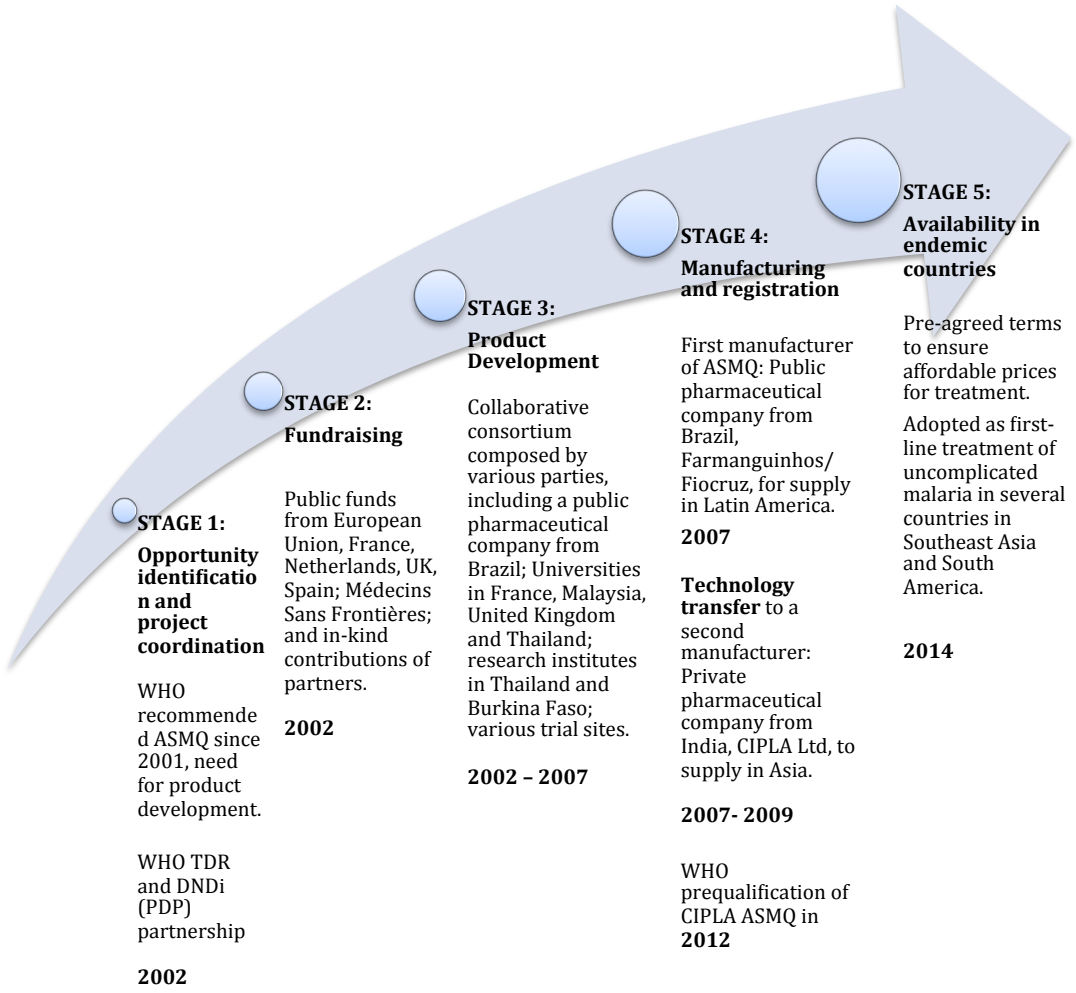
and oversee the selection of research projects for funding and evaluated progress of various scientific working groups and technical staff, with representation of endemic-countries (UNICEF et al. 2007).

[11] In 1999, the Malaria for Vaccines Venture (MMV) was created. In 2000, the Global Alliance for TB Drug Development (TB Alliance). In 2003, the Drugs for Neglected Diseases initiative (DNDi) was created as a joint initiative of Médecins Sans Frontiers, TDR and representatives of disease endemic countries. In 2003 the Foundation for Innovative New Diagnostics (FIND) as also created.

[12] In 1993, the Infectious Disease Research Institute (IDRI) was created as a non-profit research institute.

Figure 1. An example of how PDPs work: The case of development of a fixed – dose combination of existing antimalaria drugs, artesunate (AS) and mefloquine (MQ), for Latin America and Southeast Asia.



Sources: http://dndi.org/treatments/asmq/partnership.html and Wells et al. 2013 (our elaboration).

PDPs are able to operate on a non-profit model provided that they can receive sufficient funding for their R&D projects and operations. A fundamental element of the PDP is thus to attract funds for donors. For public and philanthropic donors, return to investment is measured differently than in the case of shareholders in the pharmaceutical industry R&D model. As such, philanthropic and public donors do not exert the same pressure as shareholders and venture capitalists do on for-profit firms. Donors are interested in the end result of PDPs in terms of medical products developed to address unmet health needs. In contrast, shareholders interest in the pharmaceutical industry is to maximize profit on their initial investment.

Funding is also a central enabling factor for R&D collaboration through PDPs. It allows PDPs to make propositions attractive to partners and reduce their risk (cost) of engagement. PDP financing is channelled to pay for services (i.e. academia, contract

research organizations in clinical trials), and reduces the costs of product development for industry involved in R&D, with clinical trials, manufacturing and registration, being the largest cost factors.

The core objective of PDPs is to develop new products that meet public health needs. A number of PDPs have agreed to a common definition of "access" as referring to a coordinated set of activities needed to ensure that the products developed will ultimately have an equitable public health impact (Brooks et al. 2010). An expert commission under auspices of the World Health Assembly has noted that a framework to guide new medical production should contain the following principles (WHO 2006):

1) *Availability:* new product development and adequate supply (quantity) of product.

2) *Acceptability:* usability and appropriateness of the product tailored to specific needs.

3) *Quality:* product effectiveness, standards for carrying out testing and clinical trials.

4) *Affordability:* ensuring financing of product development and procurement, affordable prices.

For a PDP the measure of success is not only product development. The new medical product must be effective, high quality, acceptable to the target group, and available at an affordable price. In this regard, many PDPs establish "access" policies. A PDP access policy may include defining upfront the contours of a technology appropriate and affordable resource-limited settings. Generally the target product profile for each R&D project is developed taking into account the unmet need, the disease profile, the local environment (including regulatory framework, purchasing power) in which the product would be delivered. They may also define a product design and set benchmarks for product manufacturing cost and final price. The PDP product profiling helps clarify expectations for all partners and subcontractors in R&D projects. Nonetheless, some PDPs adopt a more flexible approach to determine product profiles, for example opting to define the pricing strategy for the new medical product at a later stage. An access policy also serve in some PDPs to inform their strategy for the management of intellectual property rights (IPRs), in particular to ensure that IPRs do not create obstacles for the PDP to access know-how and assets, affordability of new products, and follow-on R&D. Some PDPs have specific, publicly - disclosed IPR policy (Munoz 2014).

Most PDPs pick up opportunities for projects based on dormant or discontinued research elsewhere that can be applied to neglected diseases. PDPs producing drugs have generally focused on developing repurposed products rather than NCEs (Pedrique 2013). In the area of vaccines this is also the case. The most clinically advanced malaria vaccine candidate to date, the RTSS is being developed by the pharmaceutical firm GlaxoSmithKline (GZK), the PDP Malaria Vaccines Initiative (MVI) and PATH.[13] The RTSS is not a new vaccine candidate. Scientists in GSK in

[13] The results of phase III trials of the vaccine's capacity have shown approximately a 50% percent success rate.

collaboration with a US Department of Defence biomedical research laboratory created the vaccine in 1987. The pricing arrangement announced for the RTS,S vaccine for young infant and children in Sub-Saharan Africa is that GSK will be paid to cover the costs of the vaccine manufacture and receive a 5% return (MVI 2013).

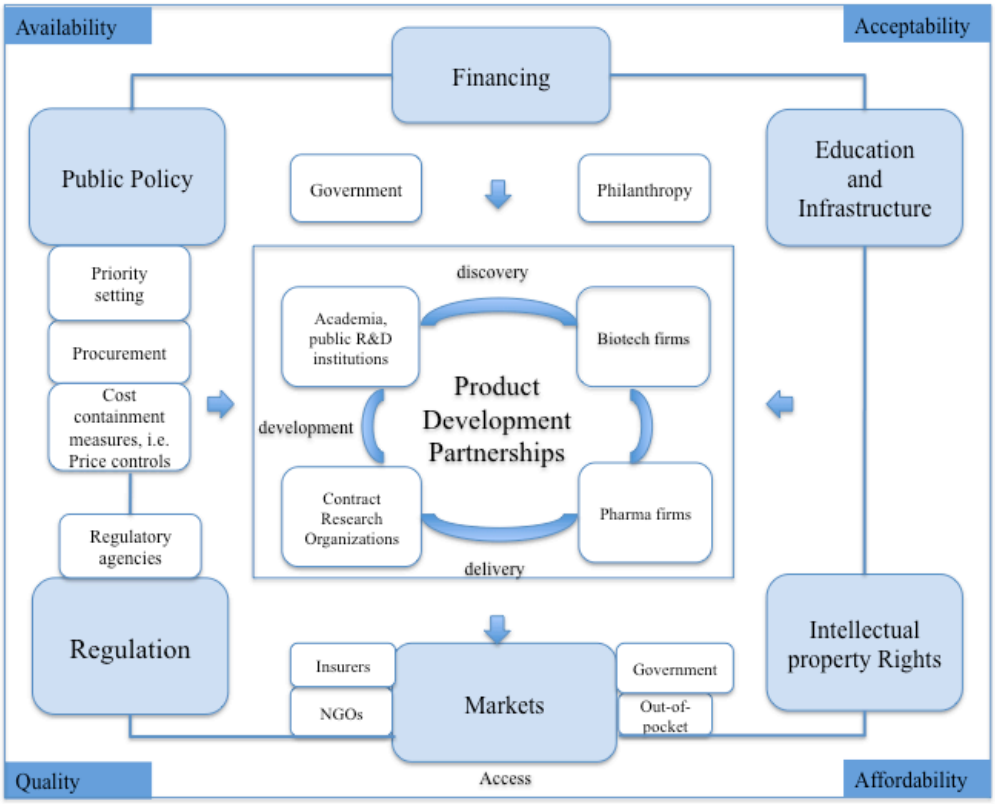
PDPs generally also aim to keep down costs of R&D. While PDPs have to cover the costs of the product development and take into account costs of product delivery (including registration costs), PDPs are aware that they need to stay as near as possible to the marginal costs of production to meet the access goal. PDPs are able to channel most of their resources to pure R&D activities (in addition to R&D portfolio management and advocacy for funding) as compared to marketing (to promote sales) which now commands a larger budget that research in most pharmaceutical firms.

PDPs can be understood to function in the context of health innovation ecosystems (Papaioannou et al. 2009) that reach beyond national boundaries. The PDPs structure is shaped, and in turn can shape, the ecosystem they operate in. Our context for analysis is therefore the broader ecosystem (rather than the industry) that includes the community of organizations (i.e. suppliers, sources of knowledge), institutions (i.e. regulatory authorities, government bodies), and individuals (i.e. managers, policy-makers in disease endemic countries, patients) that influence PDPs. The ecosystem is composed of multiple players involved in the production and dissemination of drug, vaccine and diagnostics for neglected diseases, and influenced by external factors relating to public policy, financing, regulation, intellectual property, human resources and infrastructure, and markets.

Figure 2 depicts the innovation ecosystem that PDPs operate and the principles that we consider should guide medical product development.

As described by Chataway et al. 2007, PDPs can play both a role of integrator and broker among various private and public sector actors. In the innovation ecosystem, PDP play the role of “system integrator” that can involve actors in any stage of the R&D chain, from discovery all the way to implementation and delivery. These can involve universities and public research institutions, pharmaceutical companies, biotechnology firms, contract research organizations, governments of endemic countries and regulatory agencies.

Figure 2. PDPs in the Medical Product Innovation Ecosystem*



Sources: Morel 2005, WHO 2006 (our elaboration)

PDPs undertake R&D mainly via collaboration, rather than alone. For most PDPs, the capabilities/assets for R&D (such as financial resources, vaccine/drug discovery, development, manufacturing, distribution) do not reside with the PDP itself. Accordingly, the main avenue by which PDPs create a R&D resource base is via alliances. The PDP search, select and draw in these capabilities/assets from external sources, including academia, pharmaceutical firms, biotech, contract research organizations, public and philanthropic organizations. This search, selection and decision-making process is an organizational process, but it may also be the source of a dynamic capability. These are 'routines' or operational processes in PDPs that need to be understood to be able to identify their dynamic capabilities.

Traditionally large pharmaceutical companies are rarely inclined to share knowledge outside the firm, although outsourcing of research activities, mergers and acquisitions and in licensing of compounds from biotechnology firms are increasing trends (Schuhmacher et al. 2013). It appears paradoxical that pharmaceutical firms are willing to engage in PDP-led R&D projects when they are usually when they are usually locked in searching for the next blockbuster product (Cockburn, 2006). Partnership of large pharmaceutical firms with PDPs in the form of sharing resources for R&D for neglected diseases by for-profit companies that are constrained by shareholders' values should not take place, according to economic theory, but through PDPs it does. By working with PDPs, pharmaceutical firms can still protect shareholder value while sharing access to research tools and technology, and

undertaking manufacturing and distributing final products with reduced risks and most costs covered.

For projects in the discovery phase, PDPs tap into skills in academia, biotech and large pharmaceutical firms as knowledge sources, negotiating access for compound libraries[14], know-how and compound screening capabilities. PDPs often engage pharmaceutical firms for manufacturing, where the latter provide in-kind contributions, such as infrastructure and personnel time, that aid in low cost production.

In negotiating the terms of engagement with partners in the developed stage, PDPs need to carefully evaluate access considerations in negotiating price of manufacturing and distribution by a partner, as well as what price is acceptable in order to incentivize a partner to manufacture and distribute in disease-endemic countries with long term sustainability, at an "at cost" or "no profit, no loss" basis. PDPs need project managers with good market knowledge and negotiation skills. PDPs can leverage the fact that commercial incentives do exist for certain neglected diseases such as HIV/AIDS, malaria and tuberculosis (TB) that are prevalent in both developed and developing countries.

PDPs also can identify target products that can have potential commercial markets in the private sector in disease endemic countries, where manufacturers can have a margin on sales, and leverage this incentive to get better terms (i.e. lower production cost and final sale price) in the public sector in disease endemic countries.[15] PDPs can assist in bringing overall costs down by leading and financing of registration processes or finding other partners for this purpose.

PDPs have governance independence as self-established entities, though they depend on external financing. Management of R&D projects involves partners that are vertically disintegrated, and the internal management structure brings flexibility to PDPs in decision-making. There is little pressure for PDPs to expand, as is the case with pharmaceutical firms that often face pressure to undertake mergers and acquisitions as a manner to keep up growth expectations of shareholders. Pressure to contract in size is more likely in case of reduced funds.

In the PDP analysis it makes sense to give attention to the role of R&D managers and managerial processes (Technical Advisory Body -Board- Managers), as PDPs main job is to build and manage R&D project portfolios. Managers play the critical

[14] Access to chemical compound collections of pharmaceutical firms is very important. However, they themselves caution that the existing chemical diversity in pharmaceutical firms for the search of new drugs is limited (Payne et al. Nature Reviews Drug Discovery, 2007). The portfolio of several PDPs include proejcts for radical innovations (i.e. the discovery of new chemical entities).

[15] A case example is the combination drug ASAQ developed by DNDi in partnership with Sanofi. It is now registered in over 30 sub-Saharan countries and India, and prequalified by WHO. DNDi developed ASAQ in collaboration with Sanofi and other partners, it claimed a patent and then licenced it out to Sanofi for African and other developing countries. Under the DNDi/Sanofi agreement, Sanofi has committed to supply the public sector in endemic countries at a no - profit -no loss maximum price of US$ 1. In the private sector, Sanofi is free to sell at market price and is paying a royalty back to DNDi, which is reinvested in additional studies. DNDI and Sanofi agreed not to file any new patent, which can therefore be freely produced and distributed by any other pharmaceutical company in the world. DNDi is currently facilitating technology transfer to ensure production of ASAQ by an African manufacturer.

role of coordinating and overseeing partners' separate tasks and building synergies, as in most PDPs R&D activities are carried out outside the PDP. The leadership in terms of decision-making remains within PDPs, while in most PDPs the R&D activities are outsourced to partners, which has been described as "virtual" R&D organizations (Grace 2006, 2010). PDPs build specialized capabilities in project portfolio management by focusing on a single type of medical product and a single disease or a core set of diseases. Such framework endows PDPs with disease type experience that biotechnology or pharmaceutical firms rarely have.

The entrepreneurial aspect of PDPs deserves to be highlighted. PDPs are built by individuals or groups of individuals with an idea (purpose to drive R&D into neglected diseases), who identify opportunities within the ecosystem (new sources of philanthropic financing, growing openness to R&D collaboration in the pharmaceutical sector) and design an organizational form under which it may be possible to assemble the resources/capabilities needed to carry out R&D taking into account the specificities of the market for new products for neglected diseases. The organizational and managerial processes in PDPs include selecting targets for R&D projects and management of the portfolio of projects, including the various alliances/contractors. Managers, advised by boards and technical bodies, have a central role in making operational and strategic decisions to identify complementarities and select and align internal and external assets for developing target products, and then engaging external partners where necessary to access the necessary assets and capabilities. This 'asset orchestration' (Teece 2012) is a core capability that PDPs need to build and continuously strengthen.

Experienced project managers are core assets of PDPs. Once disease and target product profiles are set by the PDP (taking into account science, financing and access considerations), project managers source, negotiate, and manage partnerships with public and private sector participants. They drive discovery projects, select which promising candidates to advance to trials or products to advance through the pipeline or projects to terminate. In managing risk, the considerations for PDPs are similar as in pharmaceutical firms.

The overall measure of success in advancing the R&D portfolio is the number of product approvals that meet the target product profile, with few project terminations. PDPs work on the basis of attrition rates and pre-established milestones and timelines. Evaluation of the PDP effectiveness is made through the project portfolio management based on the initial plan. This is same overall process as in a pharmaceutical or biotech company. PDPs have generally adopted "private sector" managerial methods for their work. They are non-for profit but aim to operate efficiently. Donors/funders also monitor PDP performance and may require measures of cost-effectiveness and public health impact, although donor requirements are not harmonized nor are the processes or measures harmonized among PDPs.

PDPs generally have a small, core team of staff with public health and industry experience, whose work is overseen by a Board. PDPs try to compensate for their limited internal capacity in terms of own staff (limited experience in project management from discovery up to development, and delivery) by engaging outside expertise in advisory manner (similar to WHO TDR model). External expert advisory bodies provide additional technical and scientific expertise. Boards are influential in the PDP overall strategy and portfolio design but project management tends to be an

activity left to the project managers that are the core PDP staff. The technical staff in PDPs also receives advise from technical advisory committees that are composed of experts in medical product development and related areas. The Board membership mixes skill and experience from public and private sector. The incentives for members of the Board are not monetary.

We identify several types of capabilities that PDPs need to build and maintain, in additional to the core "systems integration" capability. These include the capability of the PDP to detect and negotiate with target partners for contracting services and building alliances, the capability to reshape resources within the target partners (i.e. reconditioning the manufacturing infrastructure or costing structure of a pharmaceutical/vaccine/diagnostic maker firm to develop the product according to the PDP product target), and to identify when acquisition (or bringing in-house a certain R&D activity) is the appropriate mode for obtaining new resources and capabilities, as well as the capability to build relationships with partners, endemic country governments and partners. PDPs also build knowledge capability, in terms of knowledge of the diseases and demand, medical product R&D, regulatory processes and requirements for product approval.

5. PDPs: variety within the landscape

While PDPs share common characteristics, there are important variances among PDPs. PDPs differ in their legal form, scope, internal structure and how they make strategic choices.

Table 1. PDP Common Characteristics and Differences

PDP Common Characteristics	*PDP Differences*
Non-profit institutions	Legal form: stand alone versus part of another organization, permanent versus temporary
Objective is product development of medicines, diagnostics, vaccines and biologicals for neglected diseases	Scope: disease and geographical coverage, type of medical products developed, involvement in implementation phase
Priority setting driven by medical needs: products developed need to be affordable and adequate to the local context to facilitate uptake. Define target product profile. Requires low cost of product manufacturing and selling price	Internal structure: size of staff and roles, outsourced versus in-house R&D capacity, governance model, external advisory support
The public health goal and R&D objective of PDPs drive their strategic choices (i.e. priority setting, governance and sources of financing)	Strategic choices: IP policy, partners selection and type of relationship, transfer of technology to developing countries, capacity building for developing countries
Collaborative R&D model: most PDPs have little or no in-house R&D activities, work with diversity of partners from the public and private sector. Managing the collaborations is the key task of a small core number of in-house staff in PDPs.	
Internal structure: core staff, Board, advisory committee	
Funding from philanthropic and public sources	

5.1 *Legal form*

While PDPs are all non-profit institutions, they vary in their specific legal form. Most PDPs are stand-alone entities yet a few are part of a larger organization (i.e. MVP and MVI are part of PATH, Sabin PDP is part of the Sabin Vaccine Institute). Likewise, most PDPs are registered as non-governmental organizations (i.e. IAVI, TB Alliance), while some are recognized as international organizations (i.e. DNDi, FIND, MMV in Switzerland). PDPs are generally created as a permanent institution, but some PDPs, particularly those that are a project of a larger institution, can be of a temporary nature, to complete a particular goal (i.e. develop a medical product for a specific disease target) and is discontinued thereafter (i.e. MDP has terminated its activities since 2009 although the founding organizations continue to carry out similar work).

5.2 *Scope*

PDPs vary in scope, including in terms of their disease coverage, geographical area for which they target their medical products, the type of medical product to develop (medicine, micro-biocide, vaccine or diagnostic), and the level of involvement of the PDP in activities in the implementation phase**.**

In Table 2, PDPs are classified in accordance to the type of medical product they aim to develop. We identified 15 PDPs for vaccines, 4 PDPs for new medicines, 4 PDPs for microbiocidies, and 2 PDPs for diagnostics.

Table 2. Type of Medical Product by PDP

	Drug	Vaccine	Vector control	Microb	Diagn
AREAS		X			
MMV	X				
DVI		X			
EVI		X			
IVCC			X		
IAVI		X			
OWH	X	X			X
IVI		X			
MVI		X			
MVP		X			
PDVI		X			
Sabin		X			
SAAVI		X			
TBVI		X			
DNDi	X				
CPDD	X				
TB	X				
IDRI	X	X			X
CONRA				X	
HVTN		X			
IPM				X	
MDP				X	
FIND					X
Total	6	14	1	3	3

The variance in the disease coverage of PDPs is presented in Appendix 1. Most PDPs focus on a single disease, although some PDPs cover up to 6 diseases. Malaria is the disease most covered. The profile of each disease presents specific challenges for medical product development through the PDP model. For example, while most neglected diseases affect particular geographical regions or countries, some diseases such as HIV/AIDS, Malaria and TB have a broader geographical reach in terms of disease burden. This in turn creates to some extent market incentives for private partners (i.e. population in developed countries travelling to endemic ridden areas in developing countries for tourism or military mission).

Disease profiles also vary in their mortality rates and incidence. Moreover, the science and knowledge challenges vary among diseases. (i.e. whether any products are currently available for prevention/treatment or cure).

PDPs also vary in the level of involvement in the late stage development process. While all PDPs work from the point of discovery to product development, some PDPs stop at the point where the product is developed, while others continue to follow up

implementation activities, including assisting in product pre-qualification by WHO, national registration and uptake and delivery in endemic countries.

5.3 *Internal structure*

The size of core staff of PDPs varies largely in respect to the size of the PDP R&D portfolio and disease coverage. Some PDPs that have a large portfolio have operations in more than one country or location. We also find some variance in specific roles that staff, Board and advisory committees and their relationships with each other and partners involved in R&D projects.

5.4 *Strategic choices*

There is a significant variance in the strategic choices of PDPs in terms of the way R&D is undertaken and the portfolio is managed, and in particular the selection and agreements with partners. Most PDPs do not carry out R&D activities in-house. These are undertaken by various partners for each of the various stages of medical product development, i.e. early research, translational and implementation. Nonetheless, some PDPs do undertake their own research, as in the case of IDRI and Areas. PDPs also vary significantly in the way they manage their R&D project portfolio.

For some PDPs, negotiations for the establishment of partnerships are undertaken on a case-by-case basis. Most PDPs have some basic principles on ensuring access that guide negotiations for access to knowledge (compounds for screening), low cost of production from industry partners and royalty-free licenses at least for endemic countries. In some PDPs, negotiations and relationships with partners are guided by broader policies, in areas such as intellectual property (IP) (i.e. some PDPs define at the outset that IP should generally not be sought for any product developed, while others define that the partner can claim or share with the PDP the IP from a potential product), licensing terms (i.e. non-exclusive or exclusive terms of licenses for pre-existing IP or new products developed). PDPs may also have particular policies concerning the level of control of the PDP, partner or funder may have of the R&D project (decision making). PDPs generally are face greater pressure from partners to have a stake in decision-making when the financial input of the partner is substantial. PDPs may also have particular policies concerning funding sources.

PDPs also vary in the extent to which they consider capacity building and transfer of technology to developing countries a part of their mission. For example, DNDi includes these activities as part of its mandate. In South Africa, SAAVI is linked to the national Medical Research Council and its work includes programs to support community involvement and education interventions in relation to HIV issues.

There are numerous projects that include transfer of technology to developing countries, such as the involvement of Zenufa, based in Tanzania, as a second manufacturer of ASAQ, a DNDi product, and the meningitis vaccine manufactured by Serum Institute of India (SILL) Ltd, Pune, India, an MVP product. The decision on whether to go with a manufacturer in a developed country, or a clinical research organization from a developing country is also a strategic one. Considerations include

cost of production and knowledge of the disease and local context to promote the affordability and uptake of the medical product in endemic countries.

6. Discussion

We have shown so far that PDPs are contributing to increase R&D to address the lack of new medical products for neglected diseases. We have also explained how PDPs function within the broader context of health innovation ecosystems and how PDPs are able to bring about R&D collaboration. We have also identified the core capabilities that PDPs need to build and strengthen to play the role of "system integrator" to stimulate R&D in neglected diseases. Furthermore, we analyzed the variety among the PDP landscape. In this section we discuss potential shortcomings of the PDP organizational form and current operation.

6.1 *Constraints on determinants of R&D productivity*

PDPs still appear to have limited R&D capabilities. They have yet to prove whether they can develop NCEs, though there are a number of NCE projects in late stage clinical trials. NCEs are riskier to invent than finding new uses for existing drugs or new formulations, and the latter can be developed in a shorter time frame, and thus delivered to those in need, in shorter time frame. But discovery of new NCEs will be needed to reach substantial improvements in terms of therapeutic benefits over existing drugs. Transaction costs and costs of coordination are higher and more complex. To date PDPs have focused to a substantial extent on "low-hanging fruits": existing drugs being evaluated for new indications, new formulations of existing drugs, novel fixed-dose combinations. Not new chemical entities (NCEs).

Project managers in PDPs need to be highly skilled to do the range of activities they may be entrusted to do, or if these activities are separated among project managers (by R&D phase or activity) they will need to be highly coordinated among them, i.e. scientific expertise, evaluating licensing opportunities, designing appropriate clinical trials.

PDPs are small organizations. The empirical evidence on the relationship between firm size and innovation is inconsistent (Cohen 2010). Some empirical literature finds that in the pharmaceutical industry size confers an advantage. Henderson and Cockburn found that discovery in larger pharmaceutical firms is more productive deriving from economies of scope and scale (Henderson and Cockburn 1996), yet in drug development large firms have the advantage of scope, rather than returns to scale (Cockburn and Henderson 2001). However, small firms, such as biotechnology firms can be highly innovative. The share of NCEs that are attributable to small biotechnology and pharmaceutical firms has increased to nearly 70% since 1980 (Munos 2009). Moreover, the large scale of R&D portfolios in large pharmaceutical firms and trends in growth via mergers and acquisitions has not lead to its increased innovativeness in terms of newly approved NCEs.

PDPs with small project portfolios may also have a perverse incentive to cling onto projects that should otherwise be terminated. There is evidence that single-product early stage firms are more reluctant to abandon development of their only viable drug

candidates in contrast to firms with multiple products in development (Guedj and Scharfstein 2004).

6.2 *Constraints on financing and priority setting*

Governments of disease endemic countries, global health organizations particularly the WHO, public and philanthropic donors should have more coordinated R&D priority agendas and funding efforts based on the global burden of disease. Currently activities are highly disjoined.[16]

PDPs, as has been pointed out with respect to other multi-stakeholder institutions in global health, derive their legitimacy from their effectiveness in improving specifically defined health outputs and outcomes in contrast to traditional multilateral agencies, that derive legitimacy from multi-government representation and deliberation (Sridhar, 2012). In PDPs donors decide on priority areas for funding, the conditions attached to fund disbursements, instruments for control, transparency requirements, etc. These requirements are not harmonized among PDPs and are not made public. The risk is that the priorities of governments, particularly from endemic disease countries, do not match the donor priorities and therefore the PDP R&D efforts may deliver products that will not find entry in disease endemic countries. Currently there is no assurance that the current portfolio of PDP R&D projects matches the expectations of disease endemic countries.

PDPs maintain close relationships with partners in collaborative R&D schemes. The interests and priorities of various partners, public and private, can be in tension. The PDP has the role of neutrally managing these tensions, but it is not exempt from influence. Hence, the PDP access and other related policies are critically important. Not all PDPs openly disclose their policies for the establishment of partnerships. None disclose the details of the deals made. While this is standard practice in the pharmaceutical industry, in pursuing public health objectives of PDPs in the non-profit framework, greater transparency should be expected.

PDPs as independent entities could use added oversight from the global public health community. Currently some level of oversight is exerted only by privately by funders. The WHO could provide additional leadership in establishing priority areas for R&D in neglected diseases and coordinate with other new multi-stakeholder institutions that assist in the purchasing and disbursement of new medical products such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance. However, the ability of countries to align their priorities for programs with the budget in WHO is currently restricted. Member States approve and decide on the use of only the portion of the budget that is financed by Member State contributions (about 25% of total funding) while donors decide on the use of extra-budgetary (voluntary) funding (over 80% of total funding) from State and non-state actors.[17]

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[16] A WHO expert working group (CEWG) proposed a binding R&D treaty to improve priority-setting based on public health needs, promote increased government financing for R&D and coordination among public and private R&D (CEWG 2012). There are proposals by governments and civil society, PDPs, for the establishment a global R&D framework that monitors, coordinates, and finances medical innovation for neglected populations, in the form of a new R&D treaty ((DNDi and MSF 2012). to establish a Global Health R&D Observatory within the WHO.

[17] See WHO document A66/48, WHO Reform, Financing of WHO, Sixty-Sixth World Health Assembly, Provisional Agenda Item 11, 13 May 2013.

Donors, especially philanthropic foundations, are also not responsive to any broader global health community. Their legitimacy as in the case of PDPs rests in their effectiveness of their interventions but delinked from any accountability to governments. With their amount of resources, they are able to exert enormous influence global health policies. The interviews we conducted point that PDPs are not always clear who is setting the priorities for the PDP and various interests are aligned; whether it is the funder, (i.e. Bill and Melinda Gates Foundation being the largest philanthropic donor), the Board, the pharmaceutical industry partner, or the government of endemic-disease countries. When a representative of a PDP was interviewed, we were told, "When Gates says that we should increase efforts for vaccines, we know that the risk for PDPs not in the vaccine field is real". There could be potential conflicts of interests in the Board, for example when an active pharmaceutical company representative or funder (i.e. Gates Foundation, Médecins Sans Frontiers) is on the Board. PDP do not seem to have a clear strategy on how to tackle the issue. Some PDPs want to keep independence and give assurance of being a neutral catalyser for R&D, while others consider of great importance to have key partners represented in the Board.

PDP financing is also not assured on a long-time horizon. PDPs are highly vulnerable to fluctuations in financing, especially at times of financial downturn affecting governments and donors. Public and donor financing to PDPs are reported to have decrease in light of the recent economic downturn since 2008, down US$128.7 million. (G-Finder 2012). PDPs also must invest considerable resources must be used in fund raising and public relations. They have to undertake marketing and advocacy activities to attract new funding. PDP R&D portfolios are mostly in early stages (development, early clinical stages) with important exceptions. As projects progress to larger clinical trials, the costs will likely increase significant together with total funding needs. There may not be adequate cost estimations of total funds needed for completion. Already some PDPs are struggling to ensure funding estimated is needed for their phase III projects (i.e. case with DNDi projections).

Some PDPs have been experimenting with alternative means to raise financing in addition to advocating for increased resource allocations from the global health community. For example, IDRI created three for-profit start-ups (biotechnology companies) as a means to continue financing for the non-profit arm, including by licensing vaccine adjuvants to pharmaceutical firms for developed country markets that were originally developed for neglected diseases (Nature Biotechnology, 2009). A problem identified is that PDPs cannot attract venture capital or some types of grants (i.e. small business grants in the US) that are available to small innovative firms but not to non-profits. However, the relationship between non-profit and for-profit arms of the PDP is likely to increase the tensions on the public interest mission of the PDP.

6.3 *Constraints of access and delivery*

The PDP set up creates a tension between incentives to R&D and access goals. In practice, managing an agenda of R&D plus access is complex. A case example is defining the product price and IPR policy. In cases where the market is too small to stimulate competition, products will need to be supplied at cost, or at a price corresponding to a small margin above the lowest manufacturing costs to ensure sustainability of production. Yet due to asymmetric information the PDPs can be

paying higher than "at cost" to partners. Partners may also seek IPR protection for the new medical product, in particular for diseases that have some commercial market (i.e. HIV/AIDS, malaria, tuberculosis, meningitis).

PDPs also face challenges of ensuring that end users can access products once developed. Introduction of new tools for various indications has often been associated with a significant delay between global availability and local adoption. Donors are funding product development but not product delivery. The capacity to conduct research to support and sustain public health initiatives in developing countries remains weak, which is a barrier to long-term availability of existing products.

6.4 *Constraints of contracting and coordination problems*

The disintegrated R&D structure of the majority of PDPs raises contracting problems and transaction costs, as compared to centralized vertically integrated R&D within a single organization (Cockburn 2005).

Problems of asymmetric information exist in contracting with partners. Academic researcher may be better aware of the true value of their research, contract research organizations (CROs) about the costs of clinical trials, and pharmaceutical firms about the cost of manufacturing and distribution. Moral hazard may occur, in particular in manufacturing, given that the PDP is covering most of the costs, therefore the firm involved is more likely to take risks. Contractual terms of PDP collaborations are not disclosed. Non-disclosure of contractual terms makes it more difficult for PDPs to share information, learn from each other's experience and share it with outside R&D projects. In particular, IPR terms can limit the freedom of PDPs to coordinate R&D, grant sublicenses for manufacturing and other activities with third parties.

We observe that PDPs tend to select those that they have previously worked with. A possible explanation is incomplete information on potential partners. In doing so, opportunities for collaboration may be missed, for example with partners from disease endemic countries.

PDPs operate independently with no overall coordinating entity or priority-setting public policy guidance, other than the own PDP governance structure and pursuit of their mission. The only coordinating entity to some extent is the Gates Foundation. As a funder of several PDPs, the Foundation sees the broader picture of PDP R&D projects, yet analysis of PDP portfolios or other initiatives to coordinate at a broader level are disclosed to the public. PDPs may be subject to the problems that pharmaceutical firms face in pursuing the same leads to dead ends, making unnecessary efforts to replicate screening, studies, that others have already undertaken.

There can also be a lack of coordination and collaboration among PDPs leading to unnecessary duplication of efforts, though we do not have sufficient evidence to explore the extent to which this may be affecting R&D outcomes. Competition in a non-profit economy is a topic not often explored. In the case of PDPs, it is evident that PDPs can be competing with each other for the same select sources of funding to capture resources. The overlapping of R&D portfolios in terms of disease or leads may not constitute a problem in itself, given the high levels of failure that can be

expected in medical product development, particularly vaccines and new drugs. However, resources may be wasted and spill overs foregone by the potential lack of cooperation and sharing of information and resources among PDPs. If the sources of financing for PDPs are not assured or policies implemented by governments and funders to regulate the PDP behaviour in another direction, this competitive environment can be expected to continue. However, there are indications that PDPs are working to increase coordination and collaboration amongst themselves. For example, the TB Alliance granted DNDi a royalty-free license to develop anti-TB compounds for use against other neglected diseases in the R&D portfolio of DNDi.

Sharing information among PDPs can also serve to build collective bargaining power to achieve better deals and strengthen their future negotiating positions with partners, particularly with pharmaceutical firms. PDPs could share with each other their experiences in negotiating with partners, the terms of deals, including a better understanding of how firms define terms such as what "at cost", "no loss", "fully burdened manufacturing cost" and "cost plus" that may significantly vary the cost of a PDP R&D project, and strategies for IPR management. PDPs could also work more closely in their common operations in areas such as advocacy to donors and technology platforms to bring down costs and increase effectiveness.

6.5 *Constraints of insufficient transparency*

As independent non-profit organizations, PDPs face demands for accountability from various sources, including donors, endemic country governments, partners and the end-users of the medical products that they aim to treat. They are legally accountable in terms of compliance with the health regulatory standards for new medical products in general. However, PDPs could improve their transparency and disclosure, as well as performance assessment mechanisms. PDPs and partners are not systemically disclosing publicly all relevant scientific and clinical data that could be useful, for example cases when clinical trials fail to avoid making the same mistakes or following the same leads. PDPs need to make the terms of their deals with partners, financial allocations and costs of their R&D projects more transparent to allow proper evaluation. PDPs could increase credibility and legitimacy by establishing governance instruments and institutional policies to reduce the risk of capture or undue influence by donors and other actors and avoid conflict of interests in managing their R&D portfolios. Some PDPs have established policies, for example with respect to ensuring multiple sources of financing to avoid donor capture, policies on access and management of IPR, but these are isolated initiatives. There is also a lack of systemic assessment of PDPs based on commonly agreed methodology or metrics. Despite the growing amount of resources being challenged for neglected disease R&D to PDPs, there are no reliable methods or regular assessment reviews of PDP performance as compared to other alternatives (Ridley 2004).

6.6 *Constraints of insufficient use of capabilities in disease-endemic countries*

Not all PDPs see their mission as seeking to build up the capacity of developing countries themselves and technology transfer to undertake R&D on treatments for those diseases that particularly affect disease endemic countries. Greater R&D capacity in developing countries has many benefits, such as lower R&D costs, price of manufacturing and distribution, and increasing market competition to drive down long term prices for medical products. In the case of the meningitis vaccine developed

by the PATH Meningitis Vaccine Project (MVI), the India Serum vaccine institute was able to offer to manufacture the vaccine at the target price set by MVI that would allow endemic-country governments to procure the vaccine (0.50 USD a dose). No other big vaccine manufacturer was willing to produce at this price. PDPs should seek greater collaboration with emerging economies that are increasing their role in the neglected diseases landscape.[18]

7. Conclusions

We have described an interesting phenomenon under the lens of economics of innovation. PDPs are a new form of pharmaceutical R&D in the area of neglected diseases. We have found evidence that PDPs are able to bring about new medical products. We did not consider the efficiency of the PDP organizational form as compared to others. Reasons for having not carried out any efficiency analysis are various. In particular, the needed data for undertaking such analysis were not available and even if the data had been obtained, the absence of counterfactual cases would have strongly limited the scope of the analysis. Moreover, the various PDPs investigated in the paper are not readily comparable because they deal with different diseases and medical products, thus the scientific and technological problems they try to solve are of different levels of complexity.

In this study we analyse exclusively the experience of PDPs in the area of neglected diseases. Nonetheless, there is increasing academic and policy interest in exploring the potential of PDPs in other areas, such as antibiotics[19]. There is also growing interest in promoting greater collaboration and information sharing to advance drug development, particularly in the pre-competitive stage of discovery.[20]

We find that PDPs act as "system integrators" that leverage the resources and capabilities of a diverse network of public, philanthropic and private sector partnerships.

PDPs are able to mobilize private firms to join R&D projects and provide in-kind contributions. By binding together and coordinating the activities of the various firms and other organizations, the PDP integrator role is beneficial to all involved. PDPs facilitate access to financing and exchange of knowledge, and they diffuse knowledge among the group that in turn may also be internalized by individual participants. Public policy should encourage PDP type of activities and R&D collaboration.

Some of the constrains we found associated to PDPs are coordination problems, insufficient transparency in contractual terms with partners and the mismatch between the financing horizons of donors and the time frame of medical product development.

[18] So and Ruiz-Esparza 2013.
[19] World Health Organization 2012a.
[20] See Ekins et al 2013. In the case of neglected diseases, openness is facilitated by the particularity that funding comes from public sources and potential profits are nil or low. For other diseases, intellectual property and profit margins are central components of the business strategy of firms, and may be the case too for academia. In this context, the incentive for openness and knowledge sharing in product development is weaker, although on the whole it would beneficial to speed up medical product development.

According to Weder and Grubel (1993), private agents have found many ways to internalize R&D externalities and to solve coordination problems that arise from the public good nature of knowledge and research. They call these solutions "Coasean institutions" according to the principle developed by Ronald Coase that knowledge externalities induce the creation of private institutions capable of internalizing them. The institution analysed and documented in this paper –the PDPs – clearly represent a new Coasean solution to this broad class of problems including R&D and knowledge externalities as well as coordination failures on decentralized markets for knowledge and new products.[21]

A limitation of this paper is the lack of information available concerning the contractual terms of PDP collaborations with partners and processes for determining how funds are allocated to partners. This information is not publicly available and it was not possible to collect comparable data. If such information were available, future research could evaluate the performance of PDPs including resource allocation, selection and termination of R&D projects and the appropriateness, affordability and health impact of new medical products produced by PDPs as compared to other sources, or alternatives to promote R&D in neglected diseases.

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References

Årdal, C. Røttingen, J.A. (2012) 'Open Source Drug Discovery in Practice: A Case Study', PLoS Neglected Tropical Diseases, 6/9: e1827.

[21] However, as Weder and Grubel cautioned, policy has to limit the natural rent-seeking activities of private agents by establishing constraints on the cooperative agreements that are taking place with firms within the collaborative R&D structure (Weder and Gruber 1993). In the case where public moneys are being channelled to PDPs, policy can play a role in defining conditions for disbursement such as that all partners work to fulfil the PDP mission and avoid potential rent-seeking, and promote greater transparency.

Bio Ventures for Global Health (2012), *Developing New Drugs and Vaccines for Neglected Diseases of the Poor: The Product Developer Landscape.* San Francisco: Bio Ventures for Global Health.

Brooks, A.D. Wells, W.A. McLean, T.D. Khanna, W.A. et al. (2010) 'Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships', Innovation Strategy Today, 3:1-5.

Cernuschi, T. Furrer, E. Schwalbe, N. Jones, A. et al. (2011) 'Advance market commitment for pneumococcal vaccines: putting theory into practice', Bulletin of the World Health Organization, 89: 913-18.

Chataway, J. Brusoni, S., Cacciatori, E. Hanin, R. et al. (2007) 'The International AIDS Vaccine Initiative (IAVI) in changing landscape of vaccine development: a public private partnership as knowledge broker and integrator', European Journal of Development Research, 19/1: 100-17.

Chataway, J. Hanlin, R. Mugwagwa, J. Muraguri, J. (2010) 'Global health social technologies: Reflections on evolving theories and landscapes', Research Policy, 39: 1277-88.

Cockburn I. (2005), 'Blurred Boundaries: Tensions Between Open Scientific Resources and Commercial Exploitation of Knowledge in Biomedical Research'. Prepared for the Advancing Knowledge and the Knowledge Economy Conference, January 10-11, 2005, National Academy of Sciences, Washington, DC.

Cockburn, I. Henderson R. (2001) 'Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research', Journal of Health Economics 20: 1033–1057.

Cockburn, I. (2006) 'Is the pharmaceutical industry in a productivity crisis?', Innovation Policy and the Economy, 7.

DNDi, MSF (2012), *Medical Innovation for Neglected Patients* (Geneva, 2012; pubd online 2012) http://www.msfaccess.org/sites/default/files/MSF_assets/Innovation/Docs/MedInno_Report_MedInnforNegPatients_ENG_2012.pdf> accessed 24 June 2013.

DiMasi, J. Hansen, R. Grabowski, H. (2003) 'The Price of Innovation: New Estimates of Drug Development Costs', Journal of Health Economics, 22: 151-85.

Ekins S. , Waller C., Bradley M., Clark A., Williams A. (2013). 'Four Disruptive Strategies for Removing Drug Discovery Bottlenecks'. Drug Discovery Today.

Grace C. (2006), *Developing new technologies to address neglected diseases: The role of Product Development Partnerships and Advanced Market Commitments*, London: DFID Health Resource Centre.

Grace C. (2010), *Product Development Partnerships (PDPs): Lessons from PDPs established to develop new health technologies for neglected diseases*, London: DFID Human Development Resource Centre.

Hall, B. Lerner, J. (2010) 'The Financing of R&D and Innovation', in Handbook of Economics of Innovation, 1: 609-93.

Henderson R., Cockburn I. (1996), 'Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery', The Rand Journal of Economics 27/1: 32-59.

Hobday, M. Davies, A. Prencipe, A. (2005) 'Systems Integration: a core capability of the modern corporation', Industrial and Corporate Change, 14/6: 1109-143.

IFPMA (2012) *Status Report on Pharmaceutical R&D to address diseases that disproportionately affect people in low and middle income developing countries* (Geneva, 2012; pubd online 2012) <http://www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_R_D_Status_Report_Neglected_Conditions.pdf> accessed 24 June 2013.

Juliano, R.L (2013) 'Pharmaceutical Innovation and Public Policy: The Case for a New Strategy for Drug Discovery and Development', Science and Public Policy, 40: 393-405.

Kremer, M. (2001) 'Creating Markets for New Vaccines-Part I: Rationale'. In: Jaffe A, Lerner J. Stern S. (eds.) *Innovation Policy and the Economy*, pp.35-72. Cambridge, MA: MIT Press.

Levine, Ruth. Kremer, Michael. Albright, Alice. (2005), *Making markets for vaccines: Ideas to action. Report of the Center for Global Development Advance Market Commitment Working Group.* Washington D.C: Center for Global Development.

Light, D. Warburton, R. (2011) 'Demythologizing the high costs of pharmaceutical research', BioSocieties 6: 34–50.

Light, D. Lexchin, J. (2012) 'Pharmaceutical research and development: what do we get for all that money?', BMJ, 345:e4348.

Metcalfe and Ramlogan (2008) 'Knowledge, understanding and the dynamics of medical innovation,' MPRA Paper, 9112, University Library of Much, Germany.

Moran, M. (2005) 'A breakthrough in R&D for neglected diseases: new ways to get the drugs we need', PLoS medicine, 2/9: e302.

Moran, Mary (2005) *The New Landscape of Neglected Disease Drug Development*, London: LSE and Wellcome Trust.

Moran, M. Guzman, J. Ropars, A.L. Illmer, A. (2010) 'The role of product development partnership in research and development for neglected diseases', International Health, 2/2: 114-122.

Médecins Sans Frontières (2001), *Fatal imbalance: The crisis in research and development for drugs for neglected diseases* (Geneva; pubd online September 2001)

<http://www.doctorswithoutborders.org/publications/reports/2001/fatal_imbalance_short.pdf> Accessed 24 October 2012.

Médecins Sans Frontières (2013), *Global vaccines community must bring price of new vaccines down* (Geneva; pubd online April 2013) <http://www.msfaccess.org/our-work/vaccines/article/2040> accessed 5 July 2013.

Morel C., Morel C., Acharya T., Broun D., Dangi A., Elias C., Ganguly N.K, Gardner C., Gupta R.K, Haycock J., Heher A., Hotez P., Kettler H., Keusch G., Krattiger A., Kreutz F., Lall S., Lee K., Mahoney R., Martinez-Palomo A., Mashelkar R.A, Matlin S., Mzimba M., Oehler J., Ridley R., Senanayake P., Singer P., Yun M. (2005), Health Innovation Networks to Help Developing Countries Address Neglected Diseases, Science, 309.

Morgan, S. Grootendorst, P. Lexchin, J. Cunningham et al. (2011) 'The cost of drug development: A systematic review', Health Policy, 100/1: 4-17.

Munos B. (2005), 'Lessons from 60 years of drug discovery', Nature Reviews Drug Discovery, 8/12: 959-968.

Muñoz, T.V. (2014) 'Intellectual Property Management in Non-Profit Medical Product Development,' unpublished manuscript.

MVI, GSK (2013), *Fact Sheet: The RTS,S malaria vaccine candidate* (Geneva; pubd October 2013) <http://www.malariavaccine.org> accessed 25 October 2013.

Papaioannou T, Wield D, Chataway J. (2008), 'Knowledge ecologies and ecosystems? An empirically grounded reflection on recent developments in innovation systems theory' Environment and Planning C: Government and Policy 27:2 319 – 339.

Paul, S. Mytelka, D. Dunwiddie, C. Persinger, C. et al. (2010) 'How to Improve R&D productivity: the pharmaceutical industry's grand challenge', Nature Reviews Drug Discovery, 3/9: 203-14.

Pedrique, B. Strub-Wourgaft, N. Some, C. Olliaro, P. et al. (2013) 'The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment', The Lancet Global Health, Geneva, 2013; pubd online 24 October 2013) <http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(13)70078-0/abstract > accessed 28 October 2013.

Policy Cures (2012), *G-FINDER: Global Funding of Innovation for Neglected Diseases, Report for 2012*, Australia and UK: Policy Cures.

Ridley, R. (2001) 'Putting the Partnership into Public Private Partnerships', Bulletin of the World Health Organization, 79/8: 694-97.

Ridley, R. (2004) 'Product Development Public Private Partnerships for Diseases of Poverty: Are there more efficient alternatives? Are there limitations?', IPPPH Meeting, London, April 15 and 16, 2004.

Røttingen, J.A. Regmi, S. Eide, M. Young, A et al. (2013) 'Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?', The Lancet, 382/9900: 1286–307.

Sampat, B. Lichtenberg, F. (2011), 'What Are The Respective Roles Of The Public And Private Sectors In Pharmaceutical Innovation?' Health Affairs, 30/2: 332-39.

Scudellari, M. (2011) 'Are advance market commitments for drugs a real advance?', Nature Medicine, 17/2: 139-39.

So A. Ruiz-Esparza Q. (2012) 'Technology innovation for infectious diseases in the developing world', Infectious Diseases of Poverty. 1: 2.

Sridhar, D. (2012) 'Who Sets the Global Health Research Agenda? The Challenge of Multi-BiFinancing', PLoS Med, 9/9. e1001312.

Teece. D. (2012) 'Dynamic Capabilities: Routines versus Entrepeneurial Action,' Journal of Management Studies, 29/8.

The Boston Consulting Group (2010), *Path Vaccine Product Development Assessment: Summary of Findings*, (Boston; pubd July 2010) <http://www.path.org/files/OTP-bcg-vacc-dev-eval.pdf> accessed 14 May 2013.

Trouiller, P. Olliaro, P. Torreele, E. Orbinski, J. et al. (2002) 'Drug development for neglected diseases: A deficient market and a public health policy failure', The Lancet 359: 2188–94.

Toole, A. (2012) 'The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry', Research Policy, 41: 1-12.

UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (2007) *Making a Difference: 30 Years of Research and Capacity Building in Tropical Diseases*. Geneva: World Health Organization.

Webber, D. Kremer, M. (2001) 'Perspectives on stimulating industrial research and development for neglected infectious diseases', Bulletin of the World Health Organization, 79: 735–41.

Wells S., Diap G., Kiechel J. (2013). 'The story of artesunate–mefloquine (ASMQ), innovative partnerships in drug development: case study', Malaria Journal, 12:68

World Health Organization (2006) *Public Health-Innovation and Intellectual Property Rights: Report of the Commission on Intellectual Property Rights, Innovation and Public Health*. Geneva: World Health Organization.

World Health Organization (2010) *First WHO Report on Neglected Tropical Diseases: Working to overcome the global impact of neglected tropical diseases*. Geneva: World Health Organization.

World Health Organization (2012a). The Evolving Threat of Microbial Resistance, Options for Action. World Health Organization, Geneva.

World Health Organization (2012b*) Research and Development to Meet Health Needs in Developing Countries : Strengthening global Financing and Coordination. Report of the Consultative Expert Working Group on Research and Development: Finance and Coordination.* (Geneva; pubd April 2012) <http://www.who.int/phi/CEWG_Report_5_April_2012.pdf> accessed 3 July 2013.

Appendix

1. Disease Coverage by PDP

	AERAS	MMV	CONRAD	DVI	TB Al	HVTN	IAVI	IPM	MDP	MVI	MVP	PDVI	SAAVI	TBVI	CPDD	IVCC	FIND	IVI	OWH	Sabin PDP	IDRI	EVI	DNDi	# of PDPs covering the desease
Malaria		x								x						x	x		x		x	x	x	8
Leishmaniasis															x				x	x	x	x	x	6
Tuberculosis	x				x									x			x				x	x		6
HAT															x		x						x	3
Chagas																				x	x	x	x	4
Dengue				x								x				x						x		4
HIV			x			x	x	x	x				x									x	x	8
Helminths																			x	x			x	3
Typhoid																		x						1
Cholera/Diarrheal disease																		x	x					2
Leprosy																					x			1
Meningitis											x										x			1
Schistosomiasis																				x				1
Pneumonia/Influenza																		x			x			2
Shigellosis																								1
# of diseases covered by the PDP		1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	3	4	4	4	6	6	6	

Specialist PDP ⟷ Generalist PDP

2. Products developed by PDPs

PDP	Innovation type	ct Description	Disease	Region Target	Year	Partners
DNDi	Combination therapy	NECT - Nifurtimox-Eflornithine co-administration Reduces the number of eflornithine infusions needed, has a higher cure rate than eflornithine alone and fewer severe adverse events. Cost of treatment is lower, simpler to administer and more adapted to field conditions where it is used.	HAT	Africa	2009	Médecins Sans Frontières (MSF); Swiss Tropical and Public Health Institute (Swiss TPH); National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC) (WHO), with drugs donated by Sanofi and Bayer Schering Pharma AG.
DNDi	Combination therapy	SSG&PM co-administration Combination of sodium stibugluconate (SSG) and PM. As efficacious as single-dose SSG, with the advantage of being shorter course, therefore lessening the burden on health systems, and more cost-effective.	VL	East Africa	2010	Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; Addis Ababa University, Ethiopia; University of Makerere, Uganda; Ministries of Health of Sudan, Kenya, and Uganda; Médecins Sans Frontières (MSF); i+ solutions, IDA Foundation The Netherlands; GLAND Pharma and OneWorld Health (OWH), USA; LEAP (Leishmaniasis East Africa Platform) The London School of Hygiene and Tropical Medicine (LSHTM).

DNDi	Combination therapy	New VL Treatments Single dose AmBisome® 10mg/kg and three drug combination therapies based on AmBisome®, miltefosine, and paromomycin (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin) Currently effectiveness studies are being carried out in South Asia to demonstrate feasibility in implementing the new treatment modalities recommended by WHO (miltefosine-paromomycin, AmBisome®-miltefosine, AmBisome®-paromomycin, AmBisome® 10mg/kg) in primary healthcare settings in India with a view to extending their use in the region.	VL	South Asia	2011	INDIA: National Vector Borne Disease Control Programme (NVBDCP), Indian Medical Research Council (ICMR), Delhi; Rajendra Memorial Research Institute of Medical Sciences (RMRIMSI), Patna, Bihar State Health Society (BSHS); Médecins Sans Frontières (MSF), Spain. BANGLADESH: Ministry of Health, International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Dhaka; Community Based Medical College (CBMC), Mymensingh. USA: One World Health (OWH), San Francisco. University of Tokyo, Japan; Institute Tropical Medicine-Antwerp, Belgium; LSHTM, UK; WHO Special Programme for Research and Training in Tropical Diseases (TDR)
DNDi	Formulation	Paediatric dosage form of Benznidazole New paediatric dosage formulation and dosing regimen of Benznidazole.	Chagas	Latin America	2011	Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutierrez, Argentina; Instituto Nacional de Parasitología, Dr M Fatala Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministério de Salud, Província de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patologia Regional, Hopital Independencia, Santiago del Estero,

						Argentina: Centro de Chagas y Patologia Regional, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil
DNDi	Combination therapy	ASAQ – Fixed-Dose Artesunate/Amodiaquine fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ) Easy dosaging, based on four, optimized age-specific regimens. Less expensive than all other fixed-dose combinations containing artemisinin derivatives. No patent.	Malaria	Africa	2007	Sanofi, France; MMV, Switzerland; AEDES, Belgium; Zenufa, Tanzania; National Centre for Research and Development on Malaria, Burkina Faso; Universiti Sains Malaysia; University of Oxford, UK; Institute of Research for Development (IRD), Senegal; Université de Bordeaux, Faculté de Pharmacie, France; Mahidol University, Thailand; Bertin Pharma, France; Médecins Sans Frontières/Doctors without Borders (MSF); Epicentre, France; WHO-TDR; Kenya Medical Research Institute (KEMRI), Kenya ; Indian Council of Medical Research (ICMR), India; National Malaria Control Programme, Ministry of Health, Sierra Leone; Komfo Anyoke Teaching Horpital (KATHI), Ghana

DNDi	Combination therapy	ASMQ – Fixed-Dose Artesunate/Mefloquine Used in the field for many years, the combination of artesunate (AS) and mefloquine (MQ) is one of the five ACTs recommended by WHO for the treatment of uncomplicated P. falciparum malaria, preferably as a fixed dose combination. Easy-to-use treatment regimen with one single daily dose of one or two tablets to be taken over three days. 3 presentations of ASMQ are available for children; tablets are small and easily crushable. Developed in Brazil – Farmanguinos/Fiocruz.	Malaria	South East Asia, Latin America	2008	Industrial partners: Farmanguinhos, Brazil; Cipla, India. Other partners: Shoklo Malaria Research Unit, Thailand; Universiti Sains Malaysia; University of Oxford, UK; TDR; Indian Council of Medical Research (ICMR), India; Epicentre, France; National Institute of Medical Research, Tanzania; Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland; Kenya Medical Research Institute (KEMRI), Kenya; Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso; Medicines for Malaria Venture (MMV), Switzerland
MMV	Combination therapy	Coartem® Dispersible (artemether-lumefantrine) (Approved by regulatory authority (Swissmedic) and WHO Prequalified) The first high-quality artemisinin combination therapy (ACT) formulated especially for children. Coartem® *Dispersible* contains a fixed-dose combination of artemether (20mg) and lumefantrine (120mg) for the treatment of acute uncomplicated *P. falciparum* malaria.	Malaria	Endemic countries	2009	Novartis Pharma, Switzerland
MMV	Existing product	Artesunate injection (WHO prequalified)	Malaria	Endemic countries	2010	Guilin Pharmaceutical Co. Ltd., China

	received prequalification	Superiority of artesunate injection over quinine injection as first-line treatment for patients with severe malaria.				
MMV	Combination therapy	Eurartesim® (dihydroartemisinin-piperaquine DHA/PQP) (Approved by regulatory authority (EMA)) A fixed-dose combination of dihydroartemisinin-piperaquine (DHA/PQP) for the treatment of uncomplicated *P. falciparum* malaria.	Malaria	Endemic countries	2011	Sigma-Tau Industrie Farmaceutiche Riunite, Italy
MMV	Combination therapy	Pyramax® (pyronaridine-artesunate(Approved by regulatory authority (EMA) A fixed-dose combination of pyronaridine and artesunate.	Malaria	sub-Saharan Africa, Southeast Asia and India	2012	University of Iowa, IA, USA; Shin Poong Pharmaceuticals, South Korea
MMV	Combination therapy	Sulfadoxine-pyrimethamine + amodiaquine (SP+AQ) (Working towards WHO Prequalification) Sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) once a month for 4 months for children during the malaria season for prevention.	Malaria	Endemic countries	2012	Guilin Pharmaceutical Co. Ltd., China

FIND	Diagnostic	SD BIOLINE HAT First rapid test to screen for sleeping sickness This cheap and very simple-to-use test can be performed by health workers with minimal training, using fresh blood from a finger prick, and the results are obtained after only 15 minutes.	HAT	Angola, the DRC and the Central African Republic	2012	FIND and the Institute of Tropical Medicine (Belgium), MicroCoat Biotechnologie GmbH (Germany), the International Livestock Research Institute (Kenya), the Institute of Tropical Neurology (France), Médecins sans Frontières (Spain), the National HAT Control Programme of the DRC (PNLTHA, Democratic Republic of the Congo), the Centrafrican Institute of Agronomical Research (Central African Republic), the World Health Organization and Standard Diagnostics, Inc. (Republic of Korea).
FIND	Diagnostic	Liquid culture and drug susceptibility testing Mycobacterium Growth Indicator Tube (MGIT) and drug susceptibility testing (DST) A Mycobacterium Growth Indicator Tube (MGIT) and drug susceptibility testing (DST).	TB	Endemic countries	2007	Becton, Dickinson and Company (BD), United States
FIND	Diagnostic	Rapid Speciation for MDR / TB Capilia TB test A Capilia TB test. Simple, fast (15 minute) detection of TB.	TB	Endemic countries	2007	Tauns Co. Ltd, Japan
FIND	Diagnostic	GenoType MTBDRplus®/ Line Probe Assay (1st line drugs) A DNA strip test. Allows simultaneous molecular identification of tuberculosis and the most common genetic mutations causing resistance	TB	Endemic countries	2008	Hain Lifescience, Germany

		to rifampicin and isoniazid.				
FIND	Diagnostic	Primo Star iLED Light-emitting diode (LED) fluorescence microscopy. Improved TB case detection, durable, affordable, energy-efficient.	TB	Endemic countries	2009	Carl Zeiss MicroImaging GmbH, Germany
FIND	Diagnostic	Xpert® MTB/RIF/ Automated nucleic acid amplification test (NAAT) Self-contained and cartridge-based technological platform that integrates sputum processing, DNA extraction and amplification, TB and MDR-TB diagnosis.	TB	Endemic countries	2010	Cepheid, USA
IDRI	Diagnostic	KalazarDetect An in vitro diagnostic medical device designed for the qualitative detection of antibodies to members of L.donovani complex in human serum.	Leishmaniasis	Endemic countries	2009	InBios, International, USA
iOWH	Ingredient	Semisynthetic Artemisinin prequalified by the World Health Organization (WHO), A key ingredient in first line malaria treatments	Malaria	Endemic countries	2012	Sanofi-Aventis, USA University of California, Berkeley (UCB), USA Amyris Inc., USA
iOWH	Formulation	antibiotic Paromomycin Intramuscular Injection (PMIM) Alife-saving medicine for the treatment of visceral leishmaniasis. OWH resurrected PMIM, a drug	VL	South Asia, East Africa and South America	2011	Gland Pharma, India

		abandoned by for-profit pharmaceutical companies, and developed it into a safe, effective and low-cost treatment for Kala-Azar.				
IVI	Vaccine	Killed whole-cell oral cholera vaccine mORC-Vax™ (Vietnam), Shanchol™ (India) Reformulated a bivalent, killed whole-cell oral cholera vaccine, by replacing a high toxin-producing strain with a low toxin-producing strain and changing the antigen content of other strains.	Cholera	India, Vietnam	2011	Vabiotec, Vietnam Shantha Biotechnics, India Eubiologics, Korea
MVP	Vaccine	MenAfriVac™ Adapted existing Meningitis vaccines to make them suitable for Meningitis A	Meningitis A	Sub-Saharan Africa	2010	(PATH and WHO Partnership) Syncs Bio/Netherlands -Serum Institute of India Center for Biologics Evaluation and Research of the U.S FDA Serum Institute of India (SILL) Ltd, Pune, India UK National Institute for Biological Standards (NIBSC) Trial sites in India and Africa
CONRAD	Contraceptive	SILCS Diaphragm Safe, comfortable, and easy to use, expanding non-hormonal contraceptive options for women Launched in 6 European countries in June, 2013. Next step is regulatory submission to the United States Food	Contraception/ HIV	Europe	2013	Collaboration between PATH, a Seattle, Washington-based global health nonprofit; CONRAD, a reproductive health product development organization operated through the Eastern Virginia Medical School in Norfolk, Virginia; the United States Agency for International Development (USAID); and other partners. In 2010, PATH licensed the

		and Drug Administration for market approval in the United States. PATH and research partners in Uganda, India, and South Africa also aim to introduce SILCS in low-resource settings.				SILCS design to Kessel Marketing & Vertriebs GmbH (Kessel), a private-sector company in Frankfurt, Germany.
Total no. of products: 23 (This table was last updated in January 2014)						