

## Ensuring sustained incentives for pharmaceutical companies to develop medicine for the poor



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*Pharmaceutical companies are key in developing and deploying much needed medicine. However, when it comes to the diseases of poverty, there are few market incentives to engage and invest. Over the past decade, the Access to Medicine Foundation has tracked progress in the engagement of major pharmaceutical companies in research and development (R&D) for these diseases. We have seen that models such as product development partnerships, are extremely successful in incentivising access-friendly R&D, for example by mitigating risk, pooling resources in priority disease areas and ensuring future access is taken into account early in product development. By learning from the experiences and successes of product development partnerships, we can set up a system that systematically engages the industry and others to drive R&D for contemporary global health needs of the poor.*

### **Acknowledging market failure**

Over the years, the focus on the financial bottom line has led many pharmaceutical companies to cut research into diseases that predominantly affect the poor. Drug development has become heavily oriented towards commercially-viable targets: meeting the health needs of people in developed countries, while largely neglecting R&D for diseases of poverty.

Market shaping and pooled procurement mechanisms, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, have helped create market incentives to increase access to medicines. However, these incentives only function if there are new medicines emerging from the R&D pipeline. There remains a high need for R&D of innovative products targeting poverty-related diseases, and for products to be adapted to meet specific needs- such as new fixed-dose combinations, heat-stable formulations, and adaptations targeting new demographic segments. Unless these disease areas overlap with those affecting populations

in developed countries, limited market incentives exist for companies to engage in relevant R&D.

A model for product development has been set up that helps to re-engage pharma companies with R&D for poverty-related diseases. This model features centralised organisations, and many are called Product Development Partnerships, or PDPs. By reflecting on the value and impact that these mechanisms bring, we can set up a system that drives the industry into greater action when it comes to addressing the health concerns of the poor.

The Access to Medicine Foundation stimulates companies to compete with each other as global corporate citizens- bringing forward their best ideas and innovations to solve the greatest access-to-medicine challenges. Over the past ten years, we have observed a successful stimulation of R&D for poverty-related diseases, especially where new mechanisms and incentives such as PDPs were introduced. This R&D has included engagement of critical support from companies and governments to address barriers in product attributes, quality, supply and affordability.

### **Sparking engagement from public and private players**

PDPs came of age at the turn of the century. Notably, the Medicines for Malaria Venture (MMV) was established in 1999, supported by multiple governments as well as the World Bank and the Rockefeller Foundation, to facilitate cross-sectoral R&D for anti-malarials. Médecins Sans Frontières used its money from the 1999 Nobel Peace Prize to stimulate R&D for neglected tropical diseases (NTDs). This led to the establishment of the Drugs for Neglected Diseases Initiative (DNDi) in 2003.

Over the past two decades, PDPs have revealed their strength as a unique tool. They incentivise innovation for poverty-related diseases in three ways:

- (1) They facilitate financial risk-sharing across the public and private sectors**, for R&D in disease areas where market failures exist;
- (2) They catalyse pharmaceutical industry engagement in open research collaborations** with academia, accelerating product development; and
- (3) They ensure access to successful innovations is systematically considered** early in product development.

### **‘Virtual’ organisations**

PDPs are centralised non-profit organisations that can coordinate expertise and enable product development according to global health priorities. Key disease areas targeted by these partnerships include neglected tropical diseases, HIV/AIDS, malaria and tuberculosis. PDPs in themselves are often ‘virtual’ organisations, having no infrastructure for research or manufacturing themselves, but supplying funding, project management, business development and outsourcing expertise to the projects they are engaged with. The open, cross-sectoral collaborations emerging from PDPs bring together the strengths of different stakeholders: the academic sector often contributes key knowledge and skills in discovery and early-stage research, while the pharmaceutical industry contributes important expertise and resources in its ability to bring new products to market. Key activities stimulated by PDPs include compound screening, medicinal chemistry and compound optimisation, benchmarking compounds in both preclinical and clinical models, enhancing clinical trial capacity and standardising trial design.

Uniquely, PDPs often facilitate access to comparator products, allowing the value of different product development projects to be compared. Any project must therefore undergo a strict selection process. Further, PDPs can actively manage portfolios of R&D projects and rapidly redeploy resources from projects that are not working to projects that have a higher potential impact.

PDPs and their research programmes are supported financially by donors. This support helps to distribute the financial risks associated with investing in product development for disease areas with low likely profitability. This is a key step in incentivising the private sector to conduct R&D in these areas. Many governments, including those of Canada, the Netherlands and the UK, now sponsor PDPs directly, as do major global health donor organisations like the Bill and Melinda Gates Foundation and the Wellcome Trust. Their involvement also helps ensure that the resulting drugs can be prioritised for the poorest patients.

Several public funders channel substantial proportions of their research funding into PDPs: for example, in 2007, the Canadian government exclusively disbursed its R&D funding through PDPs; Ireland spent 97% of funds this way; the Netherlands 95%; and the UK 70%.<sup>1</sup>

<b>9 benefits of product development partnerships</b>
1. Enabling product development in disease areas with few market incentives
2. Pooling multi-stakeholder expertise
3. Facilitating access to comparator products and strict selection of products
4. Ensuring rapid deployment of resources towards those with higher impact

5. Mitigating financial risk through donor support
6. Channelling public health knowledge from the public sector, including endemic country stakeholders
7. Incentivising substantial contributions from the private sector
8. Promoting open, collaborative intellectual property sharing
9. Ensuring systematic management of access, maximising impact upon market entry

### Public sector support: beyond funding

The role for donors and governments goes beyond providing financial support. The public sector contributes important public health knowledge to the strategic direction of PDPs. As such, their projects systematically target defined disease priorities and address specific access needs. Many PDPs, such as DNDi, coordinate expertise from endemic country stakeholders through board representation.

More broadly, many governments are actively collaborating in initiatives that demonstrate their commitment to ensure products are developed to address poverty-related diseases. One such initiative is The London Declaration on Neglected Tropical Diseases, which pledges to eradicate 10 high-burden diseases by 2020. Substantial progress has been seen in this area, with a 35% increase in the number of drugs donated to disease-endemic countries between 2011 and 2013 and diverse stakeholders contributing to over 150 unique R&D projects targeting NTDs.<sup>2</sup>

Further, in 2013 the Japanese government partnered with private and civil sector organisations to form the Global Health Innovative Technology Fund (GHIT). This is the first-ever product development fund specifically dedicated to global health. It has

led to investment in over 40 new products and 6 clinical trials in low- and middle-income countries. For example, through GHIT, Takeda shares its compound library with MMV to develop a product against liver stage malaria infection.

In another key example, the Accelerating Children's HIV/AIDS Treatment Initiative, launched in 2014, brings together pharmaceutical companies and governments to actively improve the development and uptake of new, high-priority paediatric anti-retroviral co-formulations for first- and second-line treatment. Founding members include UNITAID, the Clinton Health Access Initiative, DNDi, the Medicines Patent Pool and the World Health Organization.

### **Incentives for pharma**

Public sector and donor engagement in PDPs- via financial risk sharing, contribution of public health knowledge, and multi-lateral commitments and other non-financial incentives- plays an important role in stimulating private sector engagement in these collaborations. In addition, working on diseases of poverty offers certain benefits to pharmaceutical companies, including staff motivation and a better understanding of how low- and middle-income markets operate. Further, the low likelihood of profitability from new products for poverty-related diseases provides a unique opportunity for testing new collaborative research models.

In tracking major pharmaceutical companies' R&D activities over time, the Access to Medicine Foundation has observed substantial industry engagement with PDPs, like the DNDi, MMV, International Partnership for Microbicides, PATH and the Infectious Disease Research Institute. Since 2012, there has been a 35% increase in company engagement with

PDPs and intellectual property (IP) sharing partnerships primarily for NTDs, malaria and tuberculosis. For example, 13 major pharmaceutical companies are involved in compound screening via DNDi, seven of which have engaged in projects from hit-to-lead to phase III clinical trials.

It is important to recognise that the specific drivers for pharmaceutical companies to engage in R&D for poverty-related diseases differ. The flexible nature of the PDP model responds to this diversity, stimulating various forms of industry engagement that aligns with companies' unique requirements. One fascinating development in this context comes from AbbVie, which does not directly lead projects, but rather supplies expertise and internal resources for neglected disease projects that are being managed by the company's commercial competitors. There are also some examples of PDPs collaborating with smaller biotechnology firms, like Anacor, which has spoken up about the diverse value that engagement with PDPs brings. These are somewhat rarer, given the shorter term commercial imperatives operating in the biotechnology sector. Interestingly, some mid-tier companies with strong family ties have played a major role in R&D collaborations because of the personal commitment of their founding families. This includes Germany's Merck KGaA, the US's Celgene, South Korea's Shin Poong Pharmaceuticals, India's CIPLA, Italy's SigmaTau and Egypt's Pharco.

### **The power of sharing intellectual property**

Increased focus on the role of sharing IP for early-stage research has also been critical, for example through the establishment of WIPO Re:Search by the World Intellectual Property Organization in collaboration with BIO Ventures for Global Health. Through Bio

Ventures Global Health, 100 projects have started that use many of the principles of socially responsible R&D, similar to those used by PDPs: connecting expertise, IP and technologies for the development of new products. Through this initiative, almost half of the 20 leading pharmaceutical companies share IP to facilitate R&D for neglected tropical diseases, malaria and tuberculosis. In the last two years, three of these companies- Eisai, GSK and Merck & Co.- have engaged in a total of 10 new IP-sharing agreements with private- and public-sector research organisations.

### **Engagement with PDPs lead to new products**

As a result of the industry's greater engagement, new innovations that are highly important to global health have been launched. Some important examples include fixed-dose artemisinin-based combination therapies that associate artemisinin derivatives with amodiaquine, lumefantrine, piperaquine, pyronaridine or mefloquine. These are now delivered by over a dozen companies with over 200 million treatments shipped each year. Further, archaic, unsafe treatments for sleeping sickness are now replaced with the safer nifurtimox-eflornithine combination, developed in a consortium led by DNDi and now manufactured by Sanofi and Bayer. The development of the meningococcal vaccine, MenAfriVac, was led by Serum Institute of India in a consortium including PATH.

### **Ensuring that products reach people**

Importantly, the PDP model ensures that access to successful innovations is considered early in the product development process. This means that, right from the beginning, target product profiles include aspects like cost of manufacturing, price commitments and the

ability of the product to withstand conditions in the field. Often, PDPs address such factors in the terms and conditions of their partnership agreements, meaning companies working with PDPs are more likely to take access into consideration during R&D. In 2014, 40% of all product development by major pharmaceutical companies occurred in collaboration. Over one third of these included clear provisions to promote access in their research contracts.

Two important access considerations that PDPs often take into account during product development are sufficient supply and the affordability of successful innovations. Ensuring supply through multiple manufacturing sources is particularly important for products lacking a competitive market. PDPs facilitate this by ensuring that products in development are eventually licensed to external manufacturers. In this regard, PDPs play a key role in ensuring, once approved by a major regulatory authority, that products are quickly registered and deployed in those countries where they are needed most.

PDPs also facilitate affordability of medicines once they arrive in these markets, for example by planning, in advance of product approval, to utilise price caps and prices with marginal or no profit margins. In one example, GlaxoSmithKline has committed to sell Mosquirix (RTS,S), a malaria vaccine developed with PATH Malaria Vaccine Initiative, at only 5% above cost price, and to reinvest profits into research for tropical diseases. Establishing effective pricing structures is a complex task- if prices are too low, no one will manufacture, while if prices are too high the medicine will be unaffordable. PDPs play a critical role in facilitating the dialogue between manufacturers and public health stakeholders, necessary to ensure this delicate balance.

## **New global health threats require renewed commitments**

As we enter an era where the global need for product development is heightened, it is essential to continue incentivising the pharma industry to collaborate to develop products that will be made accessible to those in need. Target 3b of the Sustainable Development Goals expresses the need for R&D of vaccines and medicines for diseases primarily affecting the poor. Compounding this is the need for coordinated global R&D to respond to the threat of emerging infectious diseases, recognised in important policy discussions such as the G7 Health Minister’s Meeting in 2015. Increased awareness of these threats is reflected in media attention towards the recent disease outbreaks of the Ebola virus in West Africa and the Zika virus in Latin America. In parallel with this, the private sector is demonstrating increased commitment to respond to global health threats, for example by signing the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance in January this year. Interestingly, to manage the portfolio of R&D, the Global Antibiotic R&D (GARD) Partnership has been established by WHO and DNDi.

## **Setting up a system to drive action**

To set up a system that will drive R&D aligned with contemporary global health needs, it is important to learn from the experiences and successes of the PDP model. Critically, PDPs represent the only mechanisms that work with the current patent and pricing systems for drugs. We need these mechanisms to flourish – and that calls for deeper engagement from governments and donor organisations. It is

clear, from our research at the Access to Medicine Foundation, that such a system will require four core elements:

### **(1) Application of legitimate processes to define global R&D priorities**

Evidence-informed consensus-building processes must be applied to identify product gaps and define global R&D priorities. This is not a simple process; normally the prioritisation could be set based on public health benefits produced by a new therapy, vaccine or diagnostic. However, to build upon this, political will and commitment to support evidence-based priority-setting processes must be renewed on the international stage, which will often need to overcome strong voices of local priorities or politics.

### **(2) Continuous support from governments, private foundations and the pharmaceutical industry itself**

To translate commitment into action, the activities of all players that drive research, development and access to medicines must be brought together. It may be argued that one of the great successes of the PDP model is bringing the pharmaceutical companies, and their decades of expertise, back into the sphere of drug discovery and development. As such, an effective system should facilitate cross-sectoral collaboration that is able to draw on the expertise of diverse stakeholders, including the private sector. Political drive must be sustained to keep pharmaceutical companies as integrated players, since success requires cross-sectoral collaboration. The complexity of contemporary global health challenges calls for substantial cooperation in this space.

### **(3) Mainstreaming the integration of access provisions into early-stage R&D**

In addition to stimulating R&D, this system must be able to take access barriers into

account early in development to ensure populations in need will benefit from successful innovations. The considerations that have long been implemented by PDPs to ensure access to products must be applied accordingly to any new mechanisms of product development. These include the need to design, compare and prioritise products according to needs in resource-limited settings, compare product attributes, and- as early in development as possible- consider how IP, registration targets, affordability and supply can be managed to promote access. These considerations are critical to ensure that, upon market entry, there is widespread uptake and access of new products.

**(4) Monitoring mechanisms to hold key players, including the pharmaceutical industry, to account and incentivise their continued engagement**

Finally, there must be an adequate combination of regulatory, financial and non-financial incentives to engage the private sector in priority R&D. A system that will effectively drive innovation according to global health priorities, and ensure successful products are actually accessible, must have built-in mechanisms such as the Access to Medicine Index and other accountability tools to ensure progress is tracked and monitored.

**References**

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