Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Elizabeth Ziemba, JD, MPH

Background Paper 8.1
Public Private Partnerships

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1. Introduction

Public-private partnerships were mentioned in the 2004 Report as a promising solution for addressing challenges in pharmaceutical innovation. Since 2004 considerable progress has occurred in the development of the public-private partnerships (PPP, for definition: see below) in particular in the product development partnerships (PDP). The current challenges in drug development require the mobilization of significant resources from a wide variety of stakeholders, PPPs can help facilitate this process and capitalize on the benefits of new approaches such as ‘open innovation’. The number of PPPs is increasing rapidly. For example, in Europe the number of disclosed public-private partnerships increased from 151 in 2011 to 243 in 2012. In addition, in the Horizon 2020 draft regulation the importance for the future of public-private partnerships is also emphasised: “A greater impact should also be achieved by combining Horizon 2020 and private sector funds within public-private partnerships in key areas where research and innovation could contribute to Europe’s wider competitiveness goals and help tackle societal challenges.”

A public-private partnership, in its broadest definition, is any form of intended collaboration between public and private parties. The WHO defines a public-private partnership for health as a: “wide variety of ventures involving a diversity of arrangements, varying with regard to participants, legal status, governance, management, policy-setting prerogatives, contributions and operational roles. They range from small, single-product collaborations with industry to large entities hosted in United Nations agencies or private not-for-profit organizations.” In the European Union a public-private partnership is defined as: “a partnership where private sector partners, the Union and, where appropriate, other partners, commit to jointly support the development and implementation of a research and innovation programme or activities”. A definition for a public-private partnership for health that the authors of this background paper prefer, and which combines elements of both the WHO and EU definitions, is: any informal or formal arrangement between one or more public sector entities and one or more private sector entities created in order to achieve a public health objective or to produce a health-related product or service for the public good. In a PPP, the partners share certain risks and may exchange intellectual property, financial, in-kind, and/or human resources in any mutually agreed proportion.

Traditionally, most research and product development was carried out in the private sector, including pharmaceutical and biotechnology companies. Recently, a broadly felt understanding has developed that the traditional way in which pharmaceutical R&D is organized does not adequately address current medical needs and public health challenges, output of medicines has remained constant despite increasing investments. At the same time, demographic and societal trends will lead to increasing health care needs and a growing disease burden for conditions for which limited or no treatment options are available which creates a demand for new medicines developed in a different way.

Additionally, some research and development priorities are not met by pharmaceutical and biotechnology companies because the potential number of patients using a new drug would be limited or there is no economically viable market, or accessing the market is too complex to warrant investment. This is especially the case for neglected tropical diseases, but is
becoming the case for traditional European therapeutic areas such as Gram-negative bacterial infection and psychiatric disease.

Governments and other public actors have an important stake in resolving this double ‘innovation crisis’. In addition to the imperative to address public health needs, a thriving pharmaceutical sector is an important economic asset: it creates a significant number of (knowledge intensive) jobs and is a source of high economical, added value. For these reasons, governments can use public funds as a leverage to align research activities to healthcare needs and to attract private investments. Financial support from government increases the likelihood that private firms will cooperate with public research organizations. The increased ‘knowledge flow’ between the various partners that is potentially one of the results of collaboration that is essential for economic growth.

Public-private partnerships have been mentioned as a ‘disruptive strategy’ to remove bottlenecks in pharmaceutical R&D and as an important element in the road forward to maximize the impact of biomedical research. External partnering and internal capabilities are traditionally considered as complementary rather than substitutes for one another. In a more collaborative innovation model, companies look outside their boundaries for ideas, IP and partnering opportunities. In this way, the cost of developing innovations internally is reduced, and the balance between cost and revenues is improved.

PPP can be seen as part of the movement towards open innovation models: “a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology.” The rise of the open innovation model has been heralded as one of the most important developments in the research-based pharmaceutical and biomedical industry of the past decade. Additionally, PPPs can also play an important role in undertaking drug development for neglected tropical diseases.

This background paper will discuss the more important developments since the 2004 Priority Medicines Report and highlight priorities for future research. The paper consists of six sections. The first section is this introduction. Section 2 focuses on the main arguments for setting up PPPs. Section 3 describes the different types of PPPs. Section 4 highlights some of the main current challenges for PPPs. Section 5 discusses main challenges we see for the future: proper measurement of the performance of PPPs. Section 6 closes this paper and provides some general conclusions and research recommendations.

Below we will use as examples European PPPs that focus on pre-competitive research (such as the Innovative Medicines Initiative [IMI] at the EU level and Top Institute Pharma in The Netherlands), and PPPs that focus on the development of products for neglected tropical diseases (such as the Medicines for Malaria Venture [MMV] and the Drugs for Neglected Diseases Initiative [DNDi]). These two groups of PPPs are described in more detail in Section 3 of this paper. In practice both type of organizations undertake (pre-)clinical and late-stage development.
2. **Rationale for setting up PPPs**

There are several important other reasons for setting up PPPs (both with a pre-competitive and a product development focus). These include: increasing scale, sharing risk, focusing research and development priorities, optimizing use of available knowledge resources, fostering a more competitive private sector to promote economic growth and addressing topics that require a neutral/multi-stakeholder environment.

2.1 **Increasing scale at critical stages of drug development**

Pooling of resources can help to address issues that cannot be addressed by a single entity. For example, because the knowledge or expertise that is needed to answer a question is not available in a single company or institute, or the scale of the activities required is too large. Additionally, PPPs can also help to reduce the amount of duplication and facilitate knowledge transfer.

Attrition rates in drug development are high, especially for drugs in early clinical development (phase I/II). For example, only 11% of drugs that enter Phase II and 66% of drugs that enter phase III will reach the market.\(^1\)\(^7\) This is the case both for diseases prevalent in high-income countries, and for diseases in low- and middle-income countries. Therefore, apart from initiatives that aim to resolve the attrition rates in clinical development, there is a need to have a sufficient number of high quality candidates entering the pipeline. Public-private partnerships can play an important role in this respect by leveraging resources and creating synergies.

A recent example is the European Lead Factory PPP project that was launched in 2013 through the Innovative Medicines Initiative (IMI).\(^1\)\(^8\) A key tool in the earlier stages of drug development is a technique called High Throughput Screening (HTS), in which compounds are screened against potential targets for pharmacological activity. For modern high throughput screening advanced machines are needed that are generally only available within pharmaceutical companies. The same holds for large compound libraries. As a result of this, drug targets developed within academia are rarely screened against large compound libraries. This lack of scale may have hampered drug development. This PPP consortium has set up a large screening centre in which a selection of 500,000 compounds, including high-quality industrial compounds, can be screened annually against promising targets through 48 HTS screens. This project is an important project to watch as such large scale public-private collaboration on HTS has not been seen before in Europe at such a scale. One of the key challenges of the consortium will likely be to assure that such a large consortium can operate as a whole and challenges surrounding IP and its utilization can be tackled.

Moreover, the experience gained with screening consortia such as these can also help to further strengthen R&D in neglected diseases, where current screening, lead identification, and optimization programmes are significantly below what is required to yield a registered drug.\(^1\)\(^9\) The lack of availability of high-quality compound libraries and the resources and expertise to support the prioritization and analysis of any hits is a well-known problem in this field and is being addressed.\(^2\)\(^0\) For example, in the area of neglected diseases DNDi has set up a screening consortium in collaboration with Institut Pasteur Korea with the aim to
identify novel compounds, using libraries from various companies with over 350,000 compounds, for Chagas, visceral leishmaniasis and human African trypanomiasis.21

Also, in 2009 to 2010, MMV and its academic and industry partners screened six million compounds from some of the world’s major compound libraries (GSK, Novartis Institute of Tropical Diseases, St Jude Children’s Research hospital, Rutgers University), yielding more than 25,000 new chemical starting points. Data from this screening exercise has been placed in the public domain to expedite the discovery and development of future antimalarials. In addition, 400 of the most promising compounds with the broadest cross section of structural diversity comprise MMV’s Malaria Box, that has been sent free of charge to over 150 researchers across the world in a bid to catalyse malaria and neglected disease drug discovery and research.22

2.2 Sharing risk through public funding

By sharing risks, for example by government involvement, projects can be made interesting for parties for which, without a subsidy or support, would be unwilling to get involved (for example, repurposing of existing drugs).23

An important aspect of the sharing of risk is the pooling of resources. For example, in the Dutch Technological Top Institute (TTI) model resource sharing is done through a 50% government, 25% public partner (e.g., academia) and 25% private sector (large companies and SMEs) contribution.24 When projects move further along the development pipeline, and trust in the ability of the consortium and the partners to deliver, project risk can be deemed to be lower, and the government contribution can be reduced. This may be less relevant for PDPs for neglected diseases.

In the IMI model the European Commission contributes 50% of the funding to a project (cash) and 50% is provided by EFPIA members (mostly in kind).25 Public partners that participate in a project can receive EC funding at a 75% funding rate of direct eligible costs (comparable to the EU Seventh Framework Programme). In addition, there is a possibility to claim for actual indirect costs.

For the development for neglected diseases, next to government and companies are private sector donations, from organizations such as the Bill & Melinda Gates Foundation and the Wellcome Trust. The international funding landscape is well-captured by the Global Funding of Innovation for Neglected Diseases survey (G-FINDER) which has been created by Policy Cures.26 G-FINDER is currently the primary source for historical multi-year, specified data on funding for research on neglected diseases. One of the important developments since the previous Priority Medicines Report is the sustainability of PDP funding for neglected diseases. The most recent neglected diseases research and development five year review27 shows that of the total funding in the form of grants of about 2 billion US dollars (2011) 20.8% goes to PDPs. Product development partnerships received 451.5 million US dollars in 2011. Four PDPs received somewhat over half of all PDP funding: Program for Appropriate Technology in Health (PATH), Medicines for Malaria Venture (MMV), International AIDS Vaccine Initiative (IAVI) and Aeras. On the donor side, funding sources also quite concentrated, four organisations (the Gates Foundation, UK DFID, USAID
and Dutch DGIS) have provided over three quarters of the funding during the period 2007-2011.
PDP funding peaked in 2008 with 580 million US dollars. The decrease since then has been caused by ‘rational’ cuts (e.g. on completion of clinical trials), artefacts (disbursement of funds for multi-year periods) but also a freeze or decrease on the side of some funders. Some of these cuts came from the Gates Foundation, but the most striking shift has been the reduction in funding from aid agencies and the increase in funding from science & technology agencies such as NIH and the European Commission. Overall, the G-FINDER report characterises the funding situation for PPPs as “steady overall but with significant changes in funding sources.”

2.3 Agenda setting

By defining a strategic research agenda, in consultation with stakeholders, resources can be focused on questions of particular public health interest. These research agendas form the basis for the implementation in calls for proposals.

For defining this research agenda, several approaches can be taken. They can be focused on an explicit priority health care need approach. This approach was taken with the TI Pharma program in the Netherlands, which based its research program on the 2004 Priority Medicines Report from authored by the World Health Organization. Based on this report, a portfolio was built bottom-up which also included a number of projects with a focus on neglected tropical diseases.

The IMI has formulated a Strategic Research Agenda adopted by the IMI Governing Board (representing the European Commission and EFPIA) and which is based on extensive consultations with stakeholders and forms the basis of calls for proposal that are used to build the portfolio. In the IMI set-up EFPIA members have a strong role in the identification of research topics. The rationale behind this is that in this way IMI can assure that the research agenda efficiently addresses gaps in drug development.

In general, project selection in PPPs takes a number of steps that are comparable for most PPPs. Five steps can be discerned:28

1. definition of the research topics (e.g. through a Strategic Research Agenda);
2. launch of a call for proposals;
3. submission of expression of interest/short proposal by applicants.
4. invitations to write full proposal based on peer review
5. final grant agreement and start of consortium.

Within this general set-up there are numerous differences. For example, while in some PPPs a full ‘consortium’ applies, in other set-ups this is not the case. For example, in IMI the expression of interest is submitted by the public partners and full consortium formation, and writing of a full proposal, takes place later with a broader involvement of partners in this process.

2.4 Focusing R&D activities

One of the important advantages of working through PPPs is the possibility to focus resources on potential ‘winners’ and act as a focal point for efforts. MMV has played an important role in this respect when it comes to the selection and progression of candidate
products for malaria. MMV handles a full portfolio of malaria drugs at different stages of development and has played a key role in funding promising projects and bringing them forward to overcome critical hurdles in development.\[29\]

Another striking example from outside of the therapeutic medicine field, is the RTS,S/AS01 vaccine for malaria, which has been developed through a long-standing public-private partnership launched in 2001 between GlaxoSmithKline (GSK), Program for Appropriate Technology in Health (PATH), Malaria Vaccine Initiative (MVI), and the Bill and Melinda Gates Foundation (the Gates Foundation). PATH MVI then co-finances the development with grants from the Gates Foundation, contributes to technical and management decision-making, and supports infrastructure development at the clinical trial sites.\[30\] The aim of the collaboration is to achieve the licensing of RTS,S/AS01 and to enable its use, particularly in infants and young children. Published figures suggest that MVI has contributed more than US$ 200 million in funding from the Gates Foundation to the development of RTS,S. GSK has made an investment, according to self-reported data, of more than US$ 300 million to date and expects to contribute at least another US$ 200 million to complete the project. This would include costs for FDA approval, but excludes potential post-marketing studies.

2.5 Optimizing use of available knowledge and resources

To make progress in many areas, data or expertise that resides with different parties has to be brought together. Also, PPPs can be used to create a research infrastructure for future work (networks, biobanks, research databases, etc.).

This can be done through the creation of certain standards for research. An example from the Alzheimer field is the Critical Path Coalition Against Major Diseases (CAMD) that, together with the Clinical Data Interchange Standard Consortium (CDISC), created a standard for collecting, storing and interchanging Alzheimer clinical trial data. Up until now, seven companies have remapped and shared existing clinical trial datasets to facilitate Alzheimer Disease research. The database currently includes de-identified control arm data of about 6 500 patients from 24 clinical studies in Alzheimer disease and Mild Cognitive Impairment.\[31\]

Research on the performance of PDPs for neglected diseases showed that industry working alone and public groups working alone performed more poorly, in general, than public-private collaborations.\[32\] Metrics that were used in this analysis include health outcomes for target country patients, level of innovation, speed of development and cost-efficiency. On all these measures PPPs performed very well. Although the data used is already several years old (2005), we believe that the findings are still valid. As one reviewer of this background paper commented: “there is a first analysis in the same report showing that Europe’s Poverty-related and Neglected Diseases (PRND) R&D investment has contributed to the creation of technologies that not only save lives and money in the developing world, but have also generated significant value within Europe. Between 2007 and 2010, for every euro that Member States and the EC gave to PRND R&D, approximately 66 euro cents were reinvested back into Europe, going to researchers and product developers working in European laboratories, universities and companies to unravel the science of PRNDs and develop new products to combat them.”
2.6 Foster a more competitive private sector to promote economic growth

Governments that support PPP research can also aim to support new R&D activities within their region or country. In this way, PPPs both aim to address medical need, and generate new economic activity. From a different perspective, this is also an important goal of many of the PPPs in the neglected diseases field.

While this dual goal of addressing medical needs and generating economic activity is often a stated aim of public support for PPPs, this is an area in which additional research is still needed to quantify these benefits. One of the reasons for the lack of information is that PPPs are relatively new in the biomedical sector. However, there are best practice examples from other industry sectors that illustrate these considerations. Imec in Belgium is such an example. It was set up as a partnership to address the increased R&D costs in the microelectronics and semiconductor industry. With imec running for more than 25 years its success can be directly measured by the multiplier on the public investment made: started in 1984 with more than 90% subsidy, it reached a multiplier of more than five in income generated from contract research on its subsidy of €53 million in 2009. The stamina of the Belgium government continuing its investment in imec is now paying off, but it took 12 years before the subsidy part was lower than 50%. In addition, the long time horizon has allowed imec to identify the ‘true winners’ and to set up fruitful cross-disciplinary projects.33,34

Additionally PPPs can help to improve R&D capacities in low- and middle income countries. This was one of the rationales behind the African Network for Drugs and Diagnostics Innovation (ANDI). The mission of ANDI is to “To promote and sustain African-led health product innovation to address African public health needs through efficient use of local knowledge, assembly of research networks, and building of capacity to support economic development.”35 One of the activities that are undertaken to support this mission is the formation, coordination and funding of partnerships with public and private players. The rationale behind ANDI is that significant R&D capacity exists in Africa, but that consolidation and coordination is needed and that research agendas should closely align with African health problems. Moreover, collaboration within Africa is lacking as most partnerships that do exist are with organizations in Europe and the United States.36,37 Assessing the impact of initiatives such as this seem valuable.

2.7 Address topics that require a neutral/multi-stakeholder environment

To make progress on some issues, a ‘neutral’ environment has to be created. A partly publically-funded consortium can be a tool for such a structure. An example could be topics in the regulatory arena and in which regulatory authorities (should) play a role, but input from industry is also needed.

Recently, the IMI has launched a call that focuses on the use of real-life data in drug development.38 The main output of this proposed project is a set of decision frameworks and tools to assist regulators, HTA bodies and decision makers in industry to make a better assessments about the relative effectiveness of new medicines. This could also contribute to a more efficient design of clinical trials thus reducing patient burden, costs and development times. This is a topic that addresses the need for innovation in the regulatory and HTA/reimbursement field (See Chapter 8.2 and 8.3). Future projects may also focus on this
area, for example, when it comes to piloting new developments in the field of the regulation of medicines, such as adaptive licensing.

Such ‘systems innovation’ projects, seem promising and should be further monitored and expanded. One of the main challenges in these projects is to strike a balance between public bodies as ‘participants’ in partnerships, without the risk of ‘binding’ themselves too much for future policy decisions and allowing sufficient room to manoeuvre. One could also envision that these types of projects will have a broader scope and also could involve global players (e.g. from the United States, European Union, Japan and emerging countries). One of the challenges for the future of PPPs is to identify which type of project is best suited for inclusion in a programme.

3. The place for different types of PPPs in the R&D process

In general two different types of PPPs in the life sciences can be identified based on their focus on different parts of the medicines development pipeline, though in practice the two types often stray across what are artificial boundaries. Additionally, both of these PPPs often take on projects that focus on concept development and overall systems strategy.

3.1 Research partnerships focusing primarily on early stage R&D

These initiatives support early stage innovation or create technology platforms in high priority disease areas. Examples of this type are the Top Institute Pharma in the Netherlands which was launched in 2006 with a total funding of €260 million and which has used the 2004 Priority Medicines Report as the foundation for its research programme; and the Innovative Medicines Initiative, which was launched in 2008 with a total funding of €2 billion, at the EU level. Both these examples are discussed in more below.

Often these initiatives focus on so-called ‘pre-competitive’ collaboration. Pre-competitive research can be defined as “science participated in collaboratively by those who ordinarily are commercial competitors.”

Pre-competitive research can take different shapes. For example it can mean preclinical development, phase I or Ila trials or working on new concepts such as developing new enabling technologies such as RNA interference (RNAi) and identifying biomarkers to aid in predicting patient benefit and risks.

A trend can be observed in which PPPs such as IMI are moving beyond this traditional ‘narrow’ definition of pre-competitive research. First, PPPs have also moved into projects aimed at proof-of-concept for the action of lead compounds and even late phase pre-registration trials in areas of high societal need. An example is the New Drugs for Bad Bugs (ND4BB) initiative by IMI. Part of this initiative is COMBACTE (Combatting Antimicrobial Resistance in Europe) a project with a total budget of €194 million which includes designing and implementing efficient clinical trials for novel antibiotics. The COMBACTE project focuses on addressing the barriers to clinical development. Two key outcomes of the project will be a European clinical trial network and a pan-European laboratory network, which will deliver epidemiological information and data from microbial surveillance work to guide the
selection of clinical trial sites. COMBACTE aims to generate innovative trial designs to facilitate the registration of novel antibacterial agents. It will also design and validate tests to support the diagnosis of patients, identify the most appropriate treatments, and monitor the patient’s response. As such, if COMBACTE is successful, it could play a pivotal role in addressing both the issue of growing antimicrobial resistance as well as the dearth of new antibiotics.

Public-private partnerships such as IMI are a relatively new model for collaboration in the development of medicines. Many of such partnerships face a challenge in that funding timelines are often short and it can take a long time (5-10 years or more) to see the impact that such research partnerships can have on the development of drugs or diagnostics that reach patients. Reconciling this tension between short term funding and long term scientific commitments will be necessary for these partnerships to fulfil their great potential.

### 3.2 Product development

Product development partnerships focus activities on concrete medicinal products, in many cases to treat diseases of low- and middle-income countries. These partnerships operate in a different environment. The term pre-competitive does not seem to fit these types of partnerships as there is limited competition without outside support.

Examples in this area are the Medicines for Malaria Venture (MMV), the Foundation for Innovative New Diagnostics (FIND) and the Drugs for Neglected Diseases initiative (DNDi).\(^{42, 43, 44}\) Partnerships focusing on malaria, tuberculosis other neglected tropical diseases as well as diagnostics for neglected diseases have had considerable success since the 2004 Priority Medicines Report. While the previous report indicated challenges for these partnerships with respect to the sustainability of funding, the present outlook for many of these PDPs is that, if they deliver on their targets, access to funding should be expected, notwithstanding the impact of the financial crisis.

### 3.3 Concept development and overall systems strategy

Both types of PPPs can also play an important role in overall discussions and contribute to systems reform. Many broader issues in pricing, market authorization or sustainable models for innovation can only be addressed in projects that involve all stakeholders. These kind of projects could potentially have a broader scope and also involve global players (e.g. the EU, Japan, the United States and emerging market economies). Examples are the Escher Project from TI Pharma and the seventh call for proposals from IMI which called for a project on incorporating real-life clinical data into drug development.\(^{38, 45}\) Such ‘systems innovation’ projects, appear promising and should be further monitored and expanded.

There are several additional forms of public private collaboration, such as public supply partnerships. For example, the Supply Chain Management System managed by the Partnership for Supply Chain Management which focuses on providing a reliable, cost-effective and secure supply of products for HIV/AIDS programmes from PEPFAR.\(^{46}\) These partnerships are not discussed here as they fall outside of the scope of this Report.
Update on 2004 Background Paper, BP 8.1 Public Private Partnership
4. Challenges for PPPs

Within PPPs, irrespective of their overall goal, several challenges can be identified. These are more prominent for PPPs in early stage R&D as we have more limited experience in this area.

4.1 Timelines and sustainability

PPPs generally receive tranches of funding for a three to five year period. Given the long timelines in drug development, this amount of time may be insufficient to achieve the development of new compounds and targets: true value may only be demonstrated after more than 10 years. For PDPs the situation is different in that most funding comes from foundations and development agencies which all have shorter funding cycles than ministries of science & technology and the EC, which usually funds for longer periods.

At the moment, for government funded PPPs, funding cycles are often linked to regular funding cycles for policy programs, in general for a four or five year time period. In the life sciences, this is generally too short a timeframe to make a valid assessment about the success or not of a PPP programme. TI Pharma can serve as an example, although the Dutch government heavily invested in this PPP programme with initial funding of €130 million (2006), follow-up funding in 2010 was of a far smaller scale (€6 million). This means that a program of the scale that was set-up in 2006 cannot be continued, and creates the risk that the potential value that was created through this collaboration (also for projects in the area of neglected diseases) will be lost.

4.2 The role of Small and Medium Enterprises (SME)s and large companies

Properly engaging SMEs is especially important to achieve economic targets (e.g., nurturing new companies, job creation). This aspect of economic development is important to the EU and many other countries.

For IMI, in the project resulting from the first five IMI calls, SMEs accounted for 14.8% of all participants, and received 22.1% of the financial contribution. However, one of the recommendations from a recent report from an independent expert panel on IMI was that ways to strengthen SME involvement should be explored. This also means that the opportunities for non-EFPIA companies to participate in ‘IMI2’ should be opened up.

4.3 Consortium leadership and project management

Managing partnerships requires a different set of competences and skills than managing regular research projects. Capacity building for this skillset is of critical importance for any PPP to be successful.

Additionally, successful public-private partnerships also create a situation where persons working on the project should be aware of differences in culture and expectations with the different partners involved. For example, academic researchers may be used to more freedom in defining goals and adjusting projects, while in companies this is more strictly
controlled and regulated. Working in these two different cultures also requires specific skills from project and programme managers involved in PPPs. Therefore, creating ‘awareness’ of these cultural differences and giving participants the opportunity to learn the skills required to be successful in such a setting, e.g. through a dedicated education and training program, should be part of a PPP support programme.

4.4 The role of the central entity

A central entity or ‘office’ plays a key role in any PPP. Most PPPs work as ‘virtual organizations’ with activities being outsourced to academic or private sector partners. The role of the PPP organization is to play a role as a neutral entity, trusted third party or honest broker. The main responsibility of the central entity is the proper functioning of the individual public-private projects managed by the programme. As such, the central entity needs to balance the interests of academia, companies (both large companies and SMEs) and public funders in order to achieve a successful outcome of the project. Through its activities, the central entity bears a large responsibility for the success of the programme. The central entity needs to be able to assure that the project selection process is of sufficient quality and that the right projects are selected. Additionally, the central entity should be sufficiently empowered to monitor progress and to intervene where necessary.

Moreover, the central office requires strong leadership that has an excellent network in the field and is able to allow the PPP programme to be attuned to developments in the field. This allows the PPP to build a portfolio of products and requires designing tailored portfolio management strategies. Good examples of these strategies can be found in many of the PDPs for neglected tropical diseases.

As an example, the Drugs for Neglected Diseases initiative aims to establish a R&D portfolio that covers the discovery process, from early-stage discovery to clinical development and distribution for kinetoplastid diseases such as human African trypanosomiasis, leishmaniasis, Chagas and diseases such as malaria, paediatric HIV and helminth infections. DNDi divides its portfolio into five categories and hereby creates a portfolio with a long, medium and short-term approach: (i) new drug candidates identified through screening and lead optimization efforts, (ii) new molecules with an existing data package (“low-hanging fruits”), (iii) new indications for existing medicines, (iv) new formulations and combinations of existing drugs, and (v) existing drugs for target diseases (e.g., extensions of registration, completion of dossier). In addition to a number of screening projects for all kinetoplastids disease, DNDi has nine projects in a pre-clinical stage, 11 projects in clinical development and six projects at an implementation stage.

MMV has built a comparable portfolio in the field of malaria. In Q1 2013 the MMV portfolio contained about 37 projects at the research stage (lead generation & optimization) stage, 9 projects at the translational stage (preclinical, Phase I, Phase Ila) and 12 projects at the development stage (Phase IIb/III, Registration, Phase IV) stages. For the purpose of building and managing this pipeline, which consists of projects with multiple public and private stakeholders, both DNDi and MMV have built up significant capacity and experience ‘in house’. For an in depth discussion of malaria and development of new therapeutic products in that field, please consult Background Paper 6.10.
4.5 Intellectual Property (IP) structure and management

The goal of many PPPs is to generate innovative insights into diseases and their diagnosis or treatment. How intellectual property is handled in the consortium is of key importance and provides an important reason for partners to participate or not. In the classical drug development model, the monetization of IP is one of the core incentives for medicines development. Within a PPP, some form of mutually beneficial arrangement has to be made that creates the right incentives, and lack of disincentives, for partnerships.

Although it is outside the scope of this paper, and the expertise of the author, to give an in-depth analysis of the various aspects of intellectual property rights in the context of research partnerships, some general observations can be made.

Before the start of any consortium, clear agreement about how IP (both background and foreground) is treated in the consortium must be established. Some PPPs favour a more clearly defined approach in which strict ground rules exist that apply to all consortia, others take a more case-by-case approach. For example, IMI favours the latter approach. A second issue is: who in the consortium will be the ‘owners’ of any foreground IP that is generated. These could, for example, be the participants who generated the foreground IP (with access rights to other consortium members for work within the context of the consortium), or IP could be jointly owned by the consortium. In the latter case, the central entity in a PPP sometimes is also co-owner of the foreground IP. For example, in the TI Pharma model, TI Pharma itself would have a 10% stake in any IP generated, the rationale behind this is that in such a way, TI Pharma is a full partner in the negotiations about the IP and has a role in seeing to it that IP was used in a manner supportive of the original goals of the consortium.

For partnerships that focus on products for neglected diseases, the main aim is that any products are available and affordable to patients in all endemic countries. This is clearly outlined in the IP policies of, for example, DNDi and MMV. Both MMV and DNDi take a pragmatic approach to IP policies, and assess on an individual basis what best suits the needs to achieve the goal of the partnership. In the words of MMV: “MMV has found that flexible, results-oriented approaches to dealing with IPR best serve their use as a tool to form and manage collaborations that can further MMV’s public health mission.”

DNDi, from 10 years of experience have identified a ‘gold standard’ of licensing terms to ensure equitable and affordable access to patients, which can be summarized as follows:

- perpetual royalty-free non-exclusive sub-licensable licenses in the specific disease areas determined in the contract;
- worldwide research and manufacturing rights;
- commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of income level;
- non-exclusive licensing agreements.

The way in which IP is treated in different PPPs is still a field that would benefit from research investments to identify the range of practices and what types of IP arrangements work best for which objectives. For example, IP rules may play an important role for SMEs, as they are often active in a limited number of therapeutic areas and/or technologies. Safeguarding their IP position is, therefore, of key importance to the sustainability of the
company and the IP set-up will play an important role in their decision-making about participating in a PPP.

5. Performance measurement

To assess whether public-private partnerships succeed in their approach of collaboration and achieving their targets from the perspective of the funders, measurement of the activities of PPPs is essential. Especially from the perspective of public stakeholders, it is critical to justify the use of public funds. This need for agreed key performance indicators is also reflected in article 19(e) of the draft Regulation for the establishment of Horizon 2020. For PDPs, products produced and patients treated are ‘hard’ outcome measures but these would not apply to PPPs focusing on early stage R&D.

However, methods by which the added value of a PPP in pharmaceutical sciences can be measured, is still a relatively unexplored terrain. At this moment, value measurement protocols of PPPs, in particular for early R&D, often use measures that are used for traditional evaluations of research, such as citation scores. Although such measures are important, for a full evaluation of the performance of PPPs a more holistic approach is needed.

A key challenge for partnerships is to measure what the real added value of the partnership. This is important from the perspective of the efficient and responsible allocation of their different resources. Pardoe et al. provide three ‘core principles’ that should ensure that a scoring method is valuable and relevant for a R&D partnership. These principles are also applicable to PPPs:

1. Enable meaningful comparison of partnerships: partnerships can focus on all stages of R&D, therefore, comparing cost-per-deliverable should be done with caution;
2. Apply weighting profiles to highlight important factors: some elements are more important than others. Each element must be weighted according to its individual importance to the partnership;
3. Recognise that the value a partnership delivers often changes over time: recently started partnerships may not yet be able to deliver full results, while more can be expected from partnerships that start later;

Denee et al. introduced a framework for measuring the value of PPPs in the pharmaceutical sector, taking into consideration the complexities of the operating environment. This has been published elsewhere in abbreviated form. The key table from this paper is depicted below in Table 8.1.1 and explanatory remarks will follow in the text.
### Table 8.1.1: Measurement of key indicators for PPPs

<table>
<thead>
<tr>
<th>Networks</th>
<th>Input</th>
<th>Process</th>
<th>Output</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Network coverage in number and diversity of partners</td>
<td>Exchange of information between partners (meetings, intranet use, etc)</td>
<td>Percentage of projects continued after PPP funding</td>
<td>Number and size of new partnerships inspired by PPP</td>
</tr>
<tr>
<td>Knowledge</td>
<td>Formal knowledge sharing, e.g. background IP in consortia</td>
<td>Knowledge sharing through personnel exchange and number of consortia meetings</td>
<td>Number and citation score for joint publications</td>
<td>Number of products in clinical development based on (partial) knowledge generated in PPP</td>
</tr>
<tr>
<td>Human capital</td>
<td>Number of experts involved, based on citation impact</td>
<td>Percentage of researchers trained via PPP specific courses</td>
<td>Percentage of completed PhD’s and post-doctoral positions</td>
<td>Percentage of trained researchers working in (R&amp;D) positions in the sector</td>
</tr>
<tr>
<td>Financials &amp; operations</td>
<td>Total research funding available in partnership</td>
<td>Percentage use of intranet on regular basis by researchers &amp; staff</td>
<td>Percentage of milestones achieved in consortia</td>
<td>Return on investment after five years at industrial partners and in startups</td>
</tr>
</tbody>
</table>


### 5.1 Stages

Performance of PPPs can be measured at different stages. In general, we identify four stages for indicators: input, process, output and outcome.

An input indicator can be defined as “the human, financial, and physical resources received to support programs, activities, and services.” The input indicators should measure the ability of the PPPs to bring together the people, funds and knowledge to create the network for public-private collaboration. Measurement of input is most useful at partnership level, covering all projects. This can include quantitative (e.g. funding) and qualitative measures (e.g. types of stakeholders involved).

A process indicator can be defined as “the means or method used to deliver programs, activities, and services.” Process indicators should measure how the different parties in the partnership work together. These indicators should be used to monitor the R&D progress at the individual project level. In addition to measuring operational aspects, one also wants to measure in more detail how knowledge and resources are shared in the partnership.

An output Indicator is defined as an indicator that reflects “the quantity of products or services actually produced”. Output indicators express the results of projects in the short term. Measurement of output should be closely related to the input, and should also be undertaken at partnership level. Furthermore, the focus should be on the actual use of knowledge created in a PPP and not just the ‘production’ of knowledge. Thus, merely
counting the number of scientific publications or patents is insufficient, it is what is being done with the publications that matters (e.g., by looking at citations).

An outcome indicator is defined as an indicator that reflects “the quality of the benefit for or impact on stakeholders of programs, activities, and services.” Outcome indicators show the eventual social and economic impact of the PPP, and thus provide useful information when measured at program level. Preferably, all outcome indicators are translated into clear measures of value, e.g. costs saved and QALY gained. However, it is very difficult to link an ultimate outcome directly to the work of a PPP, especially when you have to take into account the pre-competitive nature of the research. Consequently, most outcome indicators can therefore only be shown and measured by case examples and expert analysis.

5.2 Domain for measurement of valued

The four domains for creating value encompass the incentives for collaborating in a PPP. Although the exact definitions may vary, and therefore also the indicators, we believe that the domains identified below have a certain level of generalizability.

Networks – A main driver for stakeholders to participate in a PPP is the network created by the bundling of parties in the partnerships. The public private platform serves as a bridge between the various stakeholders.

Knowledge & expertise - Access to new techniques and proprietary knowledge to tackle biomedical problems is another important driver for collaboration. Output measurements for PPPs often focus on this domain.

Human capital - Next to formalized knowledge in the form of, e.g., Intellectual Property (IP), tacit knowledge or “know-how” is very important. Therefore attracting the right people to make a success of the project is crucial. In addition, the training of a new generation of biomedical researchers is critical to transfer and disseminate knowledge, and often an important driver for participation, for example by industry.

Finance & operations - The eventual economic benefits which should arise from partnerships are an important driver to participate. This could be realised by joint risk sharing and, of course, the ultimate outcome of the research: a new product or a process innovation. The financial contribution of governments can also form an important driver to participate in public private partnerships as it creates a multiplier. However, one of the main research challenges is that these multipliers are often hard to quantify in a robust manner.
6. Conclusions and recommendations for future research

As has been said earlier, PPPs in early stage R&D are a relatively new development. Although there is some experience with this model for collaboration, we are in the early stages and still have a lot to learn.

For PDPs that focus on neglected diseases, the situation developed positively since the last Priority Medicines Report. Concerns about their sustainability have been overcome. Although the funding situation is stable, with some reductions in funding in recent years, the overall picture is positive.

We believe that in terms of research recommendations, some general recommendations can be made that are relevant for both types of PPPs discussed in this background paper.

For future research, our key recommendation is that we need to learn more about what constitutes successful models for PPP collaboration. At this moment little is known about what constitutes proper measures for assessing successful public private collaboration. This is an area in which industry, governments and academia have to invest, in particular by the sharing of information and experience. Knowledge about what are the most useful structural, process, output or outcome indicators of successful partnerships would be beneficial for all partners involved.

When we know more about what constitutes a successful partnership, apart from better prioritisation, this will also allow us to make realistic assessments of what can be achieved with the resources invested (goals/objectives). At this moment, it is unclear what can actually be achieved within the funding timeframe of a typical PPP programme. Also, it can help us to identify which projects are most suited for PPPs.

As is also discussed in Chapter 8.5, the involvement of patients and citizens is a topic of specific interest. How stakeholders such as patients can be involved in PPPs is another topic for future research. Furthermore, the optimal ways for involvement of SMEs in agenda setting, and in the actual research work also warrants further investigation.

Public-private partnerships are playing an increasingly important role in pharmaceutical R&D. When the previous Priority Medicines Report was published they were still in their early stages. At this moment, we have about one decade of additional experience. However, we are still in the early stages of this innovation model and we have much to learn about how we can unlock the full potential of PPPs and how they can optimally serve public health needs.

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