

Assembling the pharmaceutical R&D puzzle for needs in the developing world

An assessment of new and proposed delinking initiatives aimed at encouraging R&D into neglected and tropical diseases and specific Type II diseases

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Pugatch Consilium

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Executive summary

Outline

- 1) This report was commissioned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).
- 2) The report examines and evaluates the opportunities and challenges associated with existing and proposed initiatives aimed at stimulating research and development (R&D) of drugs and other treatments targeting neglected and tropical diseases (NTDs) and specific Type II diseases.¹
- 3) The concept of delinking, which is described in detail in this report, refers to all efforts which seek to mitigate the risk and cost associated with developing new drugs and treatments aimed at these diseases, while at the same time ensuring that populations which need these treatments the most are able to access them.
- 4) This report notes that the existing biopharmaceutical R&D model is undergoing a process of evolution to fit new conditions, demands and capabilities – economic, social, scientific and structural. Still, even in light of these changes, the underlying principles behind the biopharmaceutical R&D model remain sound. These elements include: robust scientific and technological life science capabilities and infrastructure, facilitative regulatory and clinical environments, effective exclusivity periods derived from intellectual property rights (IPRs) and market incentives for the launch of both innovative and generic products.
- 5) Nevertheless, there are several systemic gaps in the R&D model for NTDs and specific Type II diseases that should be further addressed in order to create an effective forward pathway. They include: insufficient dedication to basic research efforts aimed at these diseases; inadequate financial and commercial incentives for further investment in these diseases during the applied research and development stages; and the possibility that even if developed, these drugs may still be too costly for populations in developing countries.

Analysis

- 6) In order to promote R&D into NTDs and specific Type II diseases, various push and pull mechanisms which delink the cost of R&D from the price of medicines have been developed and proposed. These models operate at different points in the pharmaceutical innovation process, including at the stages of research & discovery, preclinical & clinical research and

¹ See the Introduction, p.11 for a full definition of the diseases which are collectively referred to “Type II and III diseases” throughout the report.

development, and postmarketing & delivery. The report provides an overview of the following key delinking models:

- **Open databases or compound libraries** – Provision of access to proprietary databases of technologies and know-how to other R&D actors in order to facilitate drug discovery
- **R&D grants** – Additional funding in advance of R&D aimed at specific research outcomes
- **R&D prizes** – Payments to R&D entities in lieu of sales; conditional on achieving a particular outcome
- **Targeted R&D tax credits** – A direct contribution to research entities in order to promote R&D in specific research areas by increasing returns to R&D in these areas
- **Orphan drug-like schemes** – A combination of additional market exclusivity, tax credits, accelerated market authorisation and other funding support to incentivise product development and marketing
- **Patent pools** – Platforms for the cross-licensing of intellectual property for use in R&D
- **Product development partnerships** – Public private partnerships involving a combination of grant funding and R&D partnerships focused on product development
- **Advanced market commitments** – Agreements to develop and supply a product in exchange for a temporary purchase guarantee
- **R&D treaty** – International agreement to increase funding commitments targeted towards open innovation and delinking mechanisms for R&D into NTDs and specific Type II diseases

7) The report identifies several key enablers or criteria for success of mechanisms aimed at incentivising R&D into NTDs and Type II diseases. These criteria capture the topline elements that should be present in such mechanisms, including a concrete objective, targeted problem or problems within the R&D process (including access to new medicines), effectiveness and sustainability. The following table provides a proposed blueprint of these success factors and their key components.

Blueprint for Success – A model for evaluating mechanisms incentivising R&D into NTDs and specific Type II diseases

Success factors	Key components
Accurate identification and definition of systemic gaps in the R&D process	<p>Relevant gaps include:</p> <ul style="list-style-type: none"> • Scientific gaps (a given stage or stages of R&D, including basic research, compound discovery, preclinical research and translational and clinical development) • Financial gaps (ability and willingness of actors at different stages in the R&D process to invest in R&D activities) • Logistical gaps (manufacturing, availability and distribution of new products)
Mitigation of cost and risk of relevant R&D	<ul style="list-style-type: none"> • Accurately identifies incentives of various R&D actors (based on the type of R&D inputs provided and the environment in which each operates) • Creates and targets rewards accordingly
Leveraging of capabilities of partners to translate research into clinical outcomes	Successfully leads to creation of an end-product, milestone in the R&D process, or supporting technology
Sustainability of R&D funding for specific disease areas	Enjoys sustained funding over the long-term for achieving R&D commitments
Effective access to end product	<p>Including through:</p> <ul style="list-style-type: none"> • Affordable prices • Necessary administrative and logistical arrangements for delivery • Coordination with local health care authorities to develop regime for patient compliance and disease prevention
Compatibility with other mechanisms	<ul style="list-style-type: none"> • Able to function in tandem with other push and pull mechanisms targeting different aspects of the R&D process • Does not erode the effectiveness of these other mechanisms

Source: Pugatch Consilium (2012)

8) Using this set of criteria, the report provides a preliminary assessment of the delinking mechanisms analysed in this report. Obviously, there are several cases in which a mechanism partially meets or fails to meet a given success factor. An excerpt of the extent to which these mechanisms meet or are relevant to identified success factors is provided below (a full analysis and discussion is provided in the report itself).

An assessment of push and pull mechanisms using the Blueprint for Success

R&D stage	Research		Development		Access	
Success factor	Accurate identification and definition of systemic gaps in the R&D process	Mitigation of cost and risk of relevant R&D	Leveraging of capabilities of partners to translate research into clinical outcomes	Sustainability of R&D funding for specific disease areas	Effective access to end product	Compatibility with other mechanisms
Open databases	✓	✓	✓	NA	✓	✓
R&D grants	✓	✓	✓	✗	✗	✓
R&D prizes	✓	✗	✗	✗	✗	✗
R&D tax credits	✓	✗	✗	✗	NA	✓
Orphan drug-like schemes, including additional exclusivity & priority review vouchers	✓	✗	NA	✓	✗	✓
Patent pools	✗	✗	✗	NA	NA	✗
Product development partnerships (PDPs)	✓	✓	✓	✗	✓	✓
Advanced market commitments (AMCs)	✓	✓	✓	✓	✓	✓
R&D treaty	NA	NA	NA	✗	✓	✗

Source: Pugatch Consilium (2012)

✓ = success factor exists; ✗ = success factor does not exist; NA = success factor is not relevant or is unknown at this point

Findings and recommendations

9) The above matrix and the existing evidence on delinking mechanisms suggest that certain mechanisms, most notably prizes and patent pools, may not be as effective as suggested, particularly compared to other mechanisms analysed in the report. Specifically, open compound databases, R&D grants, product development partnerships and advanced market commitments have demonstrated a success in stimulating significant R&D activities in various stages.

- 10) Furthermore, delinking models today are constantly evolving, as new approaches and mechanisms for stimulating R&D into these diseases are discussed and introduced.
- 11) In light of this, the way forward is to apply highly targeted, yet complementary, push and pull delinking mechanisms in the key stages of the biopharmaceutical R&D process.
- 12) The key objective should be to identify effective push and pull delinking mechanisms which may be integrated and together drive a complete cycle of research, development and access to new medicines. Below is an illustration of how a full R&D cycle could be incentivised using a mix of delinking mechanisms.

Integration of delinking mechanisms in a full cycle of biopharmaceutical innovation



Source: Pugatch Consilium (2012)

- 13) The report concludes that implementing a high-level, yet pragmatic method for identifying the most appropriate mechanisms, such as the matrix proposed in this report, should help provide a more coherent and practical framework for evaluating and scaling up efforts in the future.

List of abbreviations

AMC	Advanced market commitment
ART	Antiretroviral therapy
CEWG	WHO Consultative Expert Working Group on Research and Development: Financing and Coordination
DNDi	Drugs for Neglected Diseases Initiative
EMA	European Medicines Agency
FDA	US Food and Drug Administration
G-FINDER	Global Funding of Innovation for Neglected Diseases
HIV/AIDS	Human immunodeficiency virus/Acquired immunodeficiency syndrome
NGO	Non-governmental organisation
NIH	US National Institutes of Health
NTD	Neglected and tropical disease
PDP	Product development partnership
R&D	Research and development
SME	Small and medium enterprises
TB	Tuberculosis
TRIPS	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organisation
WIPO	World Intellectual Property Organisation

1 Introduction

Which factors incentivise the creation of new and affordable treatments aimed at neglected and tropical diseases (NTDs) and specific Type II diseases such as malaria and tuberculosis (TB)?² To what extent does the evolving model of biomedical and biopharmaceutical R&D provide these factors, and where are additional mechanisms needed to enhance it? Which mechanisms exist or are being proposed to enhance and support R&D into these diseases? Based on what we know about these mechanisms, and of the R&D process, is there a set of criteria for success that may be used by policymakers and stakeholders to assess these and other initiatives? These questions form the basis of this report.

Since the late 1990s there has been a growing focus in the international community and academic and policy circles on the fact that relatively small amounts of biopharmaceutical R&D have gone into the development of new drugs and treatments for diseases that disproportionately affect middle and low income countries. These diseases are usually denoted as Type II and III diseases and include malaria, TB and NTDs such as dengue, Chagas disease and leprosy. One of the most frequently cited studies found that between 1975 and 1999 out of a total of 1,393 new chemical entities marketed in the period, only 16 were for NTDs.³

More recent research by the Tufts Center for the Study of Drug Development shows a rise in R&D outputs over the past decade. Between 2000 and May 2009, 26 products for these types of diseases were marketed (with over half of approvals occurring in malaria).⁴ International funding for R&D into these diseases has also increased. The Global Funding of Innovation for Neglected Diseases (G-FINDER) survey finds that in 2010 \$3.2 billion was allocated for research relating to neglected diseases – a stark increase from a decade or two before.⁵ Among the top public, private and philanthropic funders are the US National Institutes of Health, the Bill and Melinda Gates Foundation and the research-based biopharmaceutical industry.⁶

Nevertheless, in its 2010 report *Working to Overcome the Global Impact of Neglected Tropical Diseases* the World Health Organisation (WHO) estimated that today 1 billion people are still impaired by these diseases,⁷ and emphasised that further R&D is central to sustaining progress in fighting these diseases.⁸ New partnerships and initiatives involving industry, governments and

² See p.12 for a full definition of Type II diseases.

³ Trouillier P, Olliaro P, Torreale E, Orbinski J, Laing R & Ford N (2002), “Drug development for neglected diseases: a deficient market and a public-health policy failure”, *Lancet*, 359, 2188–94

⁴ Cohen J, Staroselsky D & Wilson A (2010), “Development of and Access to Products for Neglected Diseases”, *PLoS ONE*, May 2010, 5:5, e10610

⁵ Moran M, Guzman J, Henderson K, Abela-Oversteegen L, Wu L, Omune B, Gouglas D, Chapman N & Zmudzki F (2010), *Neglected disease research and development: Is the global financial crisis changing R&D?*, Policy Cures

⁶ Ibid.

⁷ World Health Organisation (WHO) (2010), *Working to Overcome the global impact of neglected tropical diseases*, Geneva, p.iii

⁸ Ibid.

philanthropic groups have increased the funding for neglected diseases substantially. For example, the European Union's new programme for funding and promoting R&D, Horizon 2020, reiterates its focus on encouraging access to health care globally within its partnerships with low and middle income countries and meeting of the UN Millennium Development Goals.⁹

Most recently, in January 2012 a number of prominent foundations, governmental aid agencies and biopharmaceutical companies launched the "London Declaration", a commitment to eradicating and controlling 10 neglected and tropical diseases by 2020.¹⁰ The stated purpose of the declaration is to mobilize and coordinate the development and dissemination of drugs and treatments for a number of NTDs. Specifically, the declaration seeks to eliminate 5 NTDs (Guinea worm, Leprosy, Lymphatic filariasis, Blinding trachoma and Sleeping sickness) and control 5 others (Schistosomiasis, River blindness, Soil-Transmitted Helminthes, Chagas and Visceral Leishmaniasis) by 2020.

The London Declaration is a good starting point for this report. It highlights the international interest and support for intensified efforts into fighting these diseases, and the manner in which new forms of collaborative R&D efforts are playing a key role in the continued development of drugs and vaccines for these diseases.

This report analyses these and other R&D efforts in detail, including the way in which they incentivise R&D into these diseases, the challenges that exist with regards to each mechanism and the degree to which they are sustainable over the long term. Drawing on this analysis, the report also identifies a checklist of the key criteria for mechanisms which aim to stimulate R&D into these diseases, against which these and other proposed initiatives may be measured and evaluated.

The paper has been divided into four sections.

Section 2 briefly outlines the evolving biopharmaceutical R&D model. While it will identify a number of changes that the R&D model is currently undergoing, it will also consider some of the enabling fundamentals that continue to be in place as these changes occur.

Section 3 discusses current systemic failures or problems in the R&D model for drugs which adequately treat neglected and tropical diseases as well as specific Type II diseases such as malaria and TB. It will seek to identify where there seem to be challenges in different

⁹ Europa Press Release, "Europe 2020: Commission proposes new economic strategy in Europe", 3 March 2010 <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/10/225&format=HTML&aged=1&language=EN&guiLangua>

¹⁰ The public and private partners included the Gates Foundation, USAID, DfID, the WHO, DNDi, the Governments of Mozambique, Tanzania, Brazil GlaxoSmithKline, Merck, Eisai, Johnson & Johnson, Sanofi, Novartis, Bayer and Abbott. See: Uniting to Combat Neglected Tropical Diseases, "Table of Commitments", <http://www.unitingtocombatntds.org/> (Accessed February 2012)

dimensions of the R&D process and distribution of medicines, and why the traditional model may not suffice in these areas.

Section 4 analyses existing push and pull initiatives that involve the delinking of the cost of R&D from the price of medicines, and which are specific to R&D into NTDs and certain Type II diseases. It presents new evidence on their relative effectiveness in producing R&D and filling the systemic gaps outlined in Section 3. Based on this empirical research, the paper will seek to identify the factors in these initiatives which have led to greater R&D output as well as the challenges and limitations surrounding each one.

Section 5 introduces a new framework for measuring the potential for success of initiatives aimed at stimulating R&D into NTDs and specific Type II diseases, the Blueprint for Success, based on five factors which are crucial for addressing the gaps in R&D outlined in Section 3. It then uses this tool to evaluate the mechanisms discussed in Section 4, identifying what level of success can reasonably be expected from each mechanism.

Section 6, Conclusions and recommendations, summarises the paper's findings about new mechanisms for stimulating R&D into NTDs and specific Type II diseases.

The methodological complexity of defining neglected diseases

There are no set or agreed definitions for what constitute neglected diseases or those which disproportionately affect developing countries. The WHO Expert Working Group (EWG) on Public Health, Innovation and Intellectual Property distinguishes between Type I, II and III diseases:

*Type I diseases are incident in both rich and poor countries, with large numbers of vulnerable populations in each. Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries. Type III diseases are those that are overwhelmingly or exclusively incident in developing countries.*¹¹

Examples of Type I diseases include communicable diseases such as measles and hepatitis B and non-communicable diseases such as diabetes and cardiovascular disease.¹² Type II diseases include HIV/AIDS, TB and malaria; more than 90% of cases occur in poor countries.¹³ Finally, Type III diseases typically comprise a range of tropical diseases (which the WHO refers to as “neglected and tropical diseases”, or NTDs), including Buruli ulcer, Chagas disease and dengue.¹⁴

¹¹ Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) (2006), *Public health, innovation and intellectual property rights*, WHO, Geneva, p.13

¹² Ibid.

¹³ Ibid.

¹⁴ WHO, “Diseases covered by NTD Department”, http://www.who.int/neglected_diseases/diseases/en/ (Accessed February 2012)

Among these diseases, the WHO identifies the following as diseases which have not been adequately addressed:

*...[D]iseases or conditions of significant public health importance in developing countries for which an adequate treatment does not exist for use in resource poor settings – either because no treatment exists whatsoever, or because, where treatments exist, they are inappropriate for use in countries with poor delivery systems, or unaffordable.*¹⁵

Furthermore, Policy Cures and the Bill and Melinda Gates Foundation in the G-FINDER survey use the term ‘neglected diseases’ to refer to developing country diseases that have a low incidence in developed countries or have different disease profiles when occurring in developing countries; and as such have seen a lack of R&D investment in developing country-specific product development.¹⁶ These diseases include:¹⁷

- HIV/AIDS (mainly limited to vaccines, diagnostics and microbicides)
- Malaria (including *P. falciparum* and *P. vivax* strains)
- Tuberculosis
- Kinetoplastids, including Chagas disease, Leishmaniasis and Sleeping Sickness
- Diarrhoeal diseases, including Rotavirus, Enterotoxigenic *E. coli*, Cholera, Shigella, Cryptosporidium, Enteroggregative *E. coli* and Giardia
- Salmonella infections, including non-typhoidal *Salmonella enterica*, Typhoid and Paratyphoid fever
- Dengue
- Helminths, including Roundworm (Ascariasis), Hookworm (Ancylostomiasis & Necatoriasis), Whipworm (Trichuriasis), Strongyloidiasis and other intestinal roundworms, Lymphatic Filariasis (Elephantiasis), Onchocerciasis (River Blindness), Schistosomiasis (Bilharziasis) and Tapeworm (Cysticercosis/Taeniasis)
- Bacterial Pneumonia and Meningitis (*S. pneumoniae*, *N. meningitidis*)
- Leprosy
- Buruli Ulcer
- Trachoma
- Rheumatic Fever

This report will amalgamate these terms and refer to the above diseases collectively as ‘Type II and III diseases’.

¹⁵ CIPIH (2006), pp.13-14

¹⁶ Global Funding for Innovation for Neglected Diseases (G-FINDER), “Definitions for terms used in G-FINDER”, http://g-finder.policycures.org/gfinder_report/registered/docs/glossary.jsp (Accessed February 2012)

¹⁷ G-FINDER, “G-FINDER Diseases, Products and Technologies”, <https://g-finder.policycures.org/g-finder/registered/docs/G-FINDER-disease-product-matrix.pdf> (Accessed February 2012)

As a methodological note, the priority disease areas for global funding, i.e. those which are lacking the greatest funding and require the most immediate attention from delinking mechanisms, are NTDs, and to a lesser extent, malaria and TB.

In contrast, over the last decade the HIV/AIDS epidemic in developing countries has attracted a relatively large amount of investment in research, development and access to new treatments. Figures from the WHO are one indicator of this level of investment – the number of people in low and middle income countries receiving antiretroviral therapy (ART) increased from 400,000 in 2003 to 6.65 million in 2010 (which represents 47% coverage of people eligible for treatment).¹⁸

In this sense, HIV/AIDS is not a ‘neglected disease’ in the same way as the above diseases. Having said this, there is still a need for greater R&D into HIV/AIDS products with specific application to developing countries, such as vaccines, microbicides, combination therapies and paediatric label extensions.¹⁹

As a result, certain initiatives do not consider HIV/AIDS as a neglected disease, such as the WIPO Re:Search consortium (discussed in greater detail in Section 4).²⁰ Other entities, such as GFINDER, restrict eligible R&D into HIV/AIDS drugs to very specific applications, such as fixed dose combinations and paediatric formulations (R&D related to diagnostics, microbicides and vaccines is also eligible).²¹ Therefore, in this report ‘neglected diseases’ only includes HIV/AIDS in reference to these specific types of HIV/AIDS-related R&D.

¹⁸ WHO (2011), *Global HIV/AIDS Response: Epidemic update and health sector progress towards Universal Access*, Progress Report 2011, p.2

¹⁹ Food and Drug Administration (FDA) (2010), *Advancing the Development of Medical Products Used in the Prevention, Diagnosis, and Treatment of Neglected Tropical Diseases*, Public Hearing, 23/09/2010, pp.114-115. See also: Cohen et al (2010).

²⁰ WIPO Re:Search, “Neglected Tropical Diseases”, http://www.wipo.int/research/en/about/neglected_tropical_diseases.html (Accessed March 2012)

²¹ Moran et al (2011), p.13

2 The biopharmaceutical R&D model

In order to understand the systemic challenges faced today in relation to R&D into Type II and III diseases, and the way in which new initiatives seek to overcome these challenges, it is first important to understand the biopharmaceutical R&D model. In fact, the R&D model that has been implemented for over 50 years in the developed world is in an exciting period of change on many different levels with new initiatives and ideas based on collaboration and partnerships being introduced. Nonetheless, underlying principles of the model remain sound and relevant in the current R&D context.

2.1 The evolving pharmaceutical R&D model

Biopharmaceutical research and development differs in many important aspects from other areas of R&D. In particular, biopharmaceutical research is a costly, time-consuming and risky task. Today the total cost of developing and getting new drugs approved for the market is an estimated \$1.3 billion.²² Furthermore, the total development of a new drug can take between 10 to 14 years.²³ Finally, industry estimates for pharmaceutical drugs suggest that only 1 out of 5,000 molecules screened actually make it onto the market;²⁴ and academic studies suggest that only 3 of 10 prescription drugs that make it onto the market generate enough revenue to cover or exceed the average R&D costs.²⁵ Figure 1 gives a general overview of the biopharmaceutical R&D process and the estimated time and chance of success of development at each stage.

Biopharmaceutical innovation today is advancing at a high rate and undergoing unprecedented changes, with the models and approaches to R&D evolving and adapting. The ever-growing complexity of biopharmaceutical technologies, including the integration of biologics and gene-based technologies; globalisation of the R&D process; shifting economic and social conditions; and increasing diversification within the industry have all driven many changes to the way in which new drugs are developed. In particular, companies are taking increasingly creative and non-linear approaches to R&D, with many different parties involved at different stages.²⁶ Today there is more collaboration, knowledge and data sharing, partnerships and strategic alliances at various stages in the R&D process than ever before.

²² DiMasi JA, Hansen RW & Grabowski HJ (2003) "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economics*, Vol. 22, pp. 151-185; and Tufts Center for the Study of Drug Development (2011), "Drug Developers Are Aggressively Changing the Way They Do R&D", http://csdd.tufts.edu/news/complete_story/pr_outlook_2011 (Accessed January 2012)

²³ Pugatch MP (2004), *The International Political Economy of Intellectual Property Rights*, Edward Elgar

²⁴ Association of the British Pharmaceutical Industry (ABPI) (2005) *Briefing paper: The Development of Medicines*.

²⁵ Pugatch MP (2007), *If it ain't broke, don't fix it*, Stockholm Network, p.30

²⁶ Lean M, Mann J, Hoek J, Elliot R, et al (2008), "Translational research: from evidence-based medicine to sustainable solutions for public health problems", *British Medical Journal*, Vol.337, No.7672, p.705-706

Figure 1: The pharmaceutical R&D process

	Research & discovery	Preclinical development	Phase I	Phase II	Phase III	Registration	Phase IV
R&D stage							
Main activities	Drawing on basic exploratory research to identify targets, initial research on new compounds is carried out in the laboratory (high throughput screening, lead identification & optimisation) to select the most promising compounds	Selected compounds are studied in animals under Good Laboratory Practice for toxicity and safety; in parallel, specific analytical methods are developed for further development	Successful compounds are then tested in humans in 3 phases of clinical trials: <ul style="list-style-type: none"> • Phase I – safety 120 and tolerability in healthy volunteers • Phase II – safety, efficacy and bioequivalence studies in small groups of patients • Phase III – large trials with different populations to demonstrate proof of efficacy, safety and value 			If the results of clinical trials are satisfactory in terms of quality, efficacy and safety, a regulatory dossier is presented to the regulatory authorities for approval	Postmarketing studies involving thousands of patients are initiated after the launch of the medicine, to identify any previously unforeseen side effects
Duration	4-6 years	1 year	1-1.5 years	1-2 years	2-3 years	1-2 years	Several years
Cumulative duration	4-6 years	5-7 years	6-8.5 years	7-10.5 years	9-13.5 years	10-15.5 years	Several years

Source: IFPMA (2007)²⁷

Examples of greater collaboration within the biopharmaceutical R&D sector include public-private research consortiums and the development and sharing of large databases, such as the Human Genome Project and the Biomarker Consortium.²⁸ Biopharmaceutical companies are also partnering with universities; recent partnerships include Sanofi Aventis with the French Life Sciences and Healthcare Alliance; Genentech with University of California, San Francisco; Pfizer with King’s College, London; Eisai with Brain Science Institute at Johns Hopkins University.²⁹ Moreover, new collaborations within industry involving leading pharmaceutical companies such as Roche, Merck, GSK, Novartis, Eli Lilly and Pfizer, biotechnology firms and clinical research organisations around the world are on the rise.³⁰ To illustrate, the development and use of pharmacogenetics and biomarkers to, among other elements, streamline drug

²⁷ International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (2007), *The Pharmaceutical Innovation Platform: Meeting Essential Global Health Needs*, Geneva, p.18. This table is copied verbatim.

²⁸ OECD (2009), *The Bioeconomy to 2030: designing a policy agenda*, OECD, p.171

²⁹ *Nature Reviews Drug Discovery*, “More pharma-academia R&D collaborations”, Vol. 9, p.259

³⁰ Fierce Biotech, “CROs scramble as Big Pharma lines up strategic partnerships”, 20/04/2011, <http://www.fiercebiotech.com/story/cros-scramble-big-pharma-lines-strategic-partnerships/2011-04-20> (Accessed March 2012); In Vivo Blog, “What Biotech Wants from Big Pharma Partners: Survey Says!?”, 22/03/2011, <http://invivoblog.blogspot.com/2011/03/what-biotech-wants-from-big-pharma.html> (Accessed March 2012); Daily Finance, “The Next Trend in Biotech Partnerships”, 23/12/2011, <http://www.dailyfinance.com/2011/12/23/the-next-trend-in-biotech-partnerships/> (Accessed March 2012)

development is altering the timeframe and scope of clinical evaluation and increasing biopharmaceutical drug sponsors' collaboration with biotechnology companies or research laboratories.³¹

2.2 Underlying principles of the biopharmaceutical R&D

While deep changes are taking place in this model, it is still possible to identify a set of underlying principles of biopharmaceutical R&D which has contributed to the model's success in producing new drugs and treatments over the past half century.³² These principles include: human capital, infrastructure and R&D capacity; regulatory and clinical environment; exclusivity periods as provided by various forms of intellectual property protection; market incentives that support the effort to launch developed drugs; and frameworks which allow for the entry of cheaper generic drugs in due course.

Human capital, infrastructure and R&D capacity

Human capital, infrastructure and R&D capacity refer to the physical and human resources available and utilised for biopharmaceutical innovation. They include a sufficient quantity of highly-skilled biomedical professionals and researchers; the presence of research clusters; science and clinical infrastructure; and financial support for R&D, including both public and private investment.³³ For instance, federal funding aimed at fundamental biomedical research by universities and public research institutions has been identified as a key element of biomedical discovery in the US, and the basis for successful drug development by the pharmaceutical industry.³⁴

Regulatory and clinical environment

Clinical procedures, standards and conditions are to a large extent dependent on the regulatory framework and regulations in place in a given country. The most advanced and innovative pharmaceutical markets in the world are also those which have implemented high standards of Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) as well as post-marketing surveillance through pharmacovigilance programmes.

Exclusivity periods as provided by intellectual property protection

The market exclusivity period provided by IPRs (including patents and regulatory data protection) and additional incentives for the production of orphan drugs gives drug manufacturers the protection needed to recoup R&D investments. As such, market exclusivity

³¹ IMS Health (2011), *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape*; OECD (2011), *Policy Issues for the Development and Use of Biomarkers in Health*, p.34

³² DeVol R, Bedroussian A & Yeo B (2011), *The Global Biomedical Industry: Preserving US Leadership*, Milken Institute, pp.5-6 and 17-18

³³ Chu R & Pugatch MP (2010), *From Test Tube to Patient: National Innovation Strategies for the Biomedical Field*, Stockholm Network, p. 17

³⁴ Loscalzo J (2006), "The NIH Budget and the Future of Biomedical Research", *New England Journal of Medicine*; 354, pp.1665-1667

periods provide the incentive to invest vast sums in the discovery and development of new drugs and health technologies. Indeed, some studies estimate that between 60 and 65% of pharmaceutical products would not have been introduced or developed in the absence of patent protection.³⁵

Market incentives supporting the launch of products

Part of the traditional model is the recouping of investment made in R&D once a drug is launched in the market. Generally, prices and pricing are thought of acting as a reward to the innovator, reflecting levels of innovation and risk, but in many cases pricing is not at the complete discretion of the innovator. Countries adopt various pricing models in order to reward products based on different factors. Some models involve mainly free pricing (such as in the US), while others are more controlled (such as the different models employed across the EU). Altogether, due to price negotiations and controls, health technology assessment models and other instruments determining the launch of new medicines, it is clear that today a direct link between the actual cost of development of a given drug and its final price in many cases does not exist.

Framework for generic entry

Generic competition is also highly important for the biopharmaceutical market. It not only releases additional resources for addressing public health needs by reducing the prices of medicines, but also allows innovators to focus on the next generation of medicines, including new health technologies and improvements to existing ones.

Altogether, these principles have been successfully implemented over the last several decades to produce a steady stream of new drugs and health technologies, and generally speaking remain a sound foundation for the various current approaches to R&D.

³⁵ Mansfield E (1986), "Patents and Innovation: An Empirical Study", *Management Science*, February, 1986, pp. 173-181

3 Key systemic gaps in the R&D process

The fact that the majority of new drugs target developed countries, and that developing countries lack treatments for diseases which disproportionately affect them,³⁶ seems to indicate that there are systemic gaps in the development of new and affordable therapies targeting these diseases. This section will discuss where these gaps in the major R&D stages occur, the innovators they affect and their impact on different phases of R&D.

3.1 Research and discovery

Basic or upstream research in the biopharmaceutical sector is typically conducted by various research entities including universities, hospitals, public and non-profit institutions, consortiums and biotechnology firms.³⁷ These entities have limited incentives and financial resources to invest in research into Type II and III diseases. In particular, public research funding in the developed world (which represents the bulk of early research funding) is mainly directed at domestic health priorities and disease burdens, namely Type I diseases.³⁸

Private funding for drug discovery is also limited. The size of the paying market for drugs in developing countries is generally small; consequently, the financial and commercial incentives for downstream R&D on Type II and III diseases are lacking,³⁹ and this has a knock-on effect on privately funded upstream research.⁴⁰

As a result, key elements of drug discovery, including mapping diseases, isolating target points on these diseases, identifying ‘hit’ molecules which are selective for a given target and have potential for use in treatments, and transforming them into ‘lead series’, are missing for Type II and III diseases. This is the case both in terms of individual research entities possessing their own resources to conduct drug discovery as well as collaborating with other entities which own key compounds and knowledge.⁴¹

In the words of the International AIDS Vaccine Initiative (IAVI), “What is lacking are effective mechanisms to harness the necessary global talent and infrastructure for an applied research

³⁶ Trouillier et al (2002), WHO (2010)

³⁷ Cockburn I (2004), “The Changing Structure of the Pharmaceutical Industry”, *Health Affairs*, Vol.23, No.1, pp.10-22

³⁸ CIPIH (2006), p.43

³⁹ Maurer S (2005), *The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research*, Goldman School of Public Policy, University of California at Berkeley, p.10; Kremer M (2002), “Pharmaceuticals and the Developing World”, *Journal of Economic Perspectives* Vol.16, pp.67-72

⁴⁰ CIPIH (2006), pp.35-40

⁴¹ Cross G (2005), “Trypanosomes at the Gates”, *Science*, Vol.309, Iss.5733, p.355

problem solving agenda”.⁴² Translating new knowledge about target, hit and lead compounds into product development is also an important bottleneck in upstream research.

3.2 Preclinical and clinical development

Where biopharmaceutical companies and other translational R&D entities would typically conduct downstream R&D (including licensing promising lead compounds and platform technologies, optimising them to develop actual drugs or vaccines, and testing them in the laboratory and in patients in order to ensure their quality, safety and efficacy),⁴³ once again these activities take place on a relatively limited basis for R&D into Type II and III diseases.⁴⁴ The smallness of developing country markets (in terms of ability to pay for new drugs) and financial uncertainty surrounding these markets result in inadequate incentives for investing in the high cost of acquiring lead compounds and technologies, conducting clinical development, preparing the product portfolio for market authorisation and manufacturing the final product.⁴⁵ In addition, developing countries – where the treatments need to be tested – often lack the clinical, technical and administrative capacity to manage clinical trials; this makes the cost for developers even higher.⁴⁶ Public or non-profit funding for translational R&D has so far proved insufficient to take many promising candidates through full development.⁴⁷

3.3 Postmarketing and delivery

In order to recoup the huge expenses made in developing and/or manufacturing neglected disease treatments, biopharmaceutical companies may nominate a price that purchasers in developing country markets (including governments, local health care authorities and patients) may sometimes not be able afford.⁴⁸ In this context, various legal and regulatory mechanisms for negotiating price reductions on the one hand, and initiatives taken by manufacturers themselves to reduce prices voluntarily and provide product donations on the other hand (discussed further in the following section), work to fill this gap to some extent, but are insufficient methods on their own.

Beyond the issue of price, developing countries often lack effective delivery systems including logistical and administrative capacity.⁴⁹ As such, patients in developing countries frequently do

⁴² CIPIH (2006), p.72

⁴³ Cockburn (2004)

⁴⁴ Ibid., p.73

⁴⁵ Maurer (2005); Kremer (2002)

⁴⁶ Bramley-Harker E, Lewis D, Farahnik J & Rozek R (2007), *Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry*, NERA Economic Consulting, prepared for UK Trade and Investment and the Association of the British Pharmaceutical Industry

⁴⁷ Ibid., p.77

⁴⁸ Ganslandt M, Maskus K & Wong E (2005), “Developing and Distributing Essential Medicines to Poor Countries: The Defend Proposal”, in Fink C & Maskus K (eds), *Intellectual Property and Development: Lessons from Recent Economic Research*, (New York, NY: World Bank and Oxford University Press, 2005), pp.211-14; Lanjouw J (2002), “A New Global Patent Regime for Diseases: U.S. and International Legal Issues”, *Harvard Journal of Law and Technology*, Vol.16, p.88

⁴⁹ Mattke S, Haims M, Ayivi-Guedehoussou N, Gillen E, Hunter L, Klautzer L & Mengistu T (2011), *Improving Access to Medicines for Non-Communicable Diseases in the Developing World*, RAND Corporation; Brorchert M, Haines A & Kuruvilla S (2004), “Bridging the implementation gap between knowledge and action for health”, *Bulletin of the World Health Organization*,

not have access to the new therapies that are actually developed for Type II and III diseases, or to existing treatments for Type I diseases. Also, because the financial incentives do not exist, investment is lacking in the development of domestic capacity for scaling up supply of medicines over the long-term, including adequate local manufacturing capabilities⁵⁰ and health care systems focused on implementation, compliance and prevention.⁵¹

Figure 2 below outlines the key systemic gaps discussed here, who they affect and their impact on different phases of R&D.

Figure 2: Key gaps in R&D into Type II and III diseases

R&D Stage	Research & discovery	Preclinical development	Clinical development	Registration	Postmarketing & delivery
Key innovators & actors	Universities Public research institutions Biotechnology firms		Research-based biopharmaceutical companies Local health care authorities		Local health care authorities
Key systemic gaps	Inadequate financial and commercial incentives for further investment in these diseases during the applied research and development stages				
	Insufficient dedication to basic research efforts aimed at R&D into Type II and III diseases				Financial, logistical & regulatory gaps impeding access to newly developed technologies
Key R&D areas lacking	Target discovery Hit discovery	Preclinical tests Development of platform technologies	Conducting of phase I, II, and III clinical trials Capacity for developing country trials (infrastructure, volunteers, administration)	Preparation of portfolio Sponsorship	Purchase by and delivery to developing countries Effective delivery systems Local manufacturing capacity Conducting of postmarketing studies

Source: Pugatch Consilium (2012)

3.4 Efforts to improve access to medicines in low and middle income countries

There have been some successful measures taken to address access to existing medicines. These include single-drug donations by multinational companies as well as inter-country/regional tiered pricing programs for medicines marketed in developing countries, which take into consideration

Vol.82, pp.724–731; Kegels G & Marchal B (2003), “Health workforce imbalances in times of globalization”, *International Journal of Health Planning and Management*, Vol.18, Iss.1, pp.89–101

⁵⁰ Bramely-Harker, et al (2007)

⁵¹ CIPIH (2006), p.155

the relative cost, ability to pay and burden of disease.⁵² In addition, other emerging markets such as China and India are increasingly supplying low-cost generic medicines, not least ARTs in the treatment of HIV/AIDS.⁵³

International agreements also allow for certain flexibilities with regards to the ability to manufacture generic substitutes to innovative medicines that are still protected by patents and other forms of intellectual property. For example, there are a number of provisions in the TRIPS Agreement which allow WTO members to issue compulsory licenses to produce medicines in special circumstances such as public health emergencies (see TRIPS Article 31bis, and the so called Paragraph 6 mechanisms which became an amendment to TRIPS in 2005).

Furthermore, the TRIPS Agreement also established clear and defined mechanisms which seek to address the humanitarian needs of least developed countries that do not have the manufacturing capacity to produce their own domestic substitutes to existing medicines. In such cases WTO members may use the system of compulsory licensing to produce the required products under their own compulsory licenses and export them to the affected country, subject to strict guidelines and procedures which ensure that the humanitarian instrument is not subject to commercial abuse. For example, in 2007 Canada issued a compulsory license in order to allow its generic industry to produce medicines that would meet Rwanda's need for antiretroviral drugs.

However, it is important to note these and similar measures only impact access by developing countries to existing medicines; they do not address incentives for conducting the R&D needed to develop new treatments for diseases that disproportionately affect their populations, especially diseases which have not received sufficient attention thus far.

In conclusion, it is clear that the 'pull' function of the market (i.e. rewarding the creation of R&D outputs) does not operate adequately in relation to R&D into Type II and III diseases, and as a result market push factors (i.e. which stimulate research inputs) are also insufficient to spur more than a small amount of R&D aimed at developing countries. Therefore, mechanisms which act as supplements to both the push and pull functions of the market, and do so mainly by delinking the two, are needed. The following section will analyse various existing and proposed push and pull mechanisms.

⁵² Drugs for Neglected Disease Initiative (DNDi) (2012), "Uniting to Combat Neglected Diseases", Press Release, 30 Jan 2012, http://www.dndi.org/images/stories/press_kit/PressRoom/NTDs/NTD_Event_Press_Release.pdf; See also: Trouillier et al (2010)

⁵³ RiskMetrics Group (2010), *Access to Medicine Index 2010*, Access to Medicines Foundation http://www.accesstomedicineindex.org/sites/www.accesstomedicineindex.org/files/general/Access_to_Medicine_Index_2010.pdf (Accessed February 2012)

4 Push and pull mechanisms for delinking the cost of R&D from the price of medicines

As discussed in the introduction, there is a significant commitment by the international community and various other entities to speed up the development of medicines targeting neglected diseases. Several different push and pull mechanisms, which seek to delink in varying degrees the cost of developing drugs from the financial arrangements used to supply them, are either being executed or proposed.⁵⁴ This section will first discuss the concept of delinking in its use in the current international discussion on R&D into Type II and III diseases. It will then review the empirical evidence on several of these mechanisms, identifying areas in which each can be expected to achieve success, as well as areas that present challenges and how they might be addressed.

4.1 The concept of delinking

Generally speaking, the term ‘delinking’ refers to all efforts which seek to mitigate the risk and cost associated with developing new drugs and treatments, while at the same time ensuring that access to affordable treatments once they are developed is in place for customers who are not otherwise able to afford them.

The concept of delinking the cost of R&D from the price of medicines has been raised in various discussions in the international community.

The World Health Organisation (WHO) Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of May 2008 called for further exploration of R&D models that delink the cost of R&D from the price of medicines:

*...[E]xplore and, where appropriate, promote a range of incentive schemes for research and development including addressing, where appropriate, the delinkage of the costs of research and development and the price of health products, for example through the award of prizes, with the objective of addressing diseases which disproportionately affect developing countries...*⁵⁵

Similarly, the EU Council Conclusions on Global Health in May 2010 charged the EU and its member states with:

⁵⁴ Muller-Langer F (2011), *Neglected Infectious Diseases: Are Push and Pull Mechanisms Suitable for Promoting Research?*, Max Planck Institute for Intellectual Property and Competition Law Working Paper

⁵⁵ WHO 61st World Health Assembly (WHA) (2008), “Annex: Global Strategy on Public Health, Innovation and Intellectual Property”, 5.3(a), *Resolutions and Decisions*

*...[E]xploring models that dissociate the cost of Research and Development and the prices of medicines...including the opportunities for EU technology transfer to developing countries.*⁵⁶

Most recently, the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) was commissioned with considering, among other elements, the appropriateness of delinking and of related proposals for innovative funding allocation such as ‘milestone’ and ‘end’ prizes.⁵⁷ The CEWG report, released in April 2012, identified delinking as a key criterion of the mechanisms assessed in the report. Furthermore, it recommends including the element of delinking (among others) in negotiations on a new global framework aimed at Type II and III diseases:

*Promoting R&D...by means which secure access and affordability through delinking R&D costs and the prices of the products.*⁵⁸

Recent work by Love (2011)⁵⁹ considers delinking in further detail. In Love’s view, the delinking approach involves decentralising the various aspects of the R&D value chain, separating the reward for investing in each step along the way.⁶⁰ The idea is that investment in R&D will be spread across various entities and is not influenced by an expected market return, such that the total cost of development is not borne by a single entity and that the price of the end product need not encompass the total cost.⁶¹ Moreover, investment decisions will not be disproportionately influenced by an expected market return.⁶² Altogether, in this way the end product may be made available at affordable prices.

In Love’s delinking paradigm:

*The de-linkage approach can accommodate a variety of funding and spending mechanisms, so long as they do not require high prices to drive R&D investments. A balanced R&D program will include both “push” and “pull” funding mechanisms.*⁶³

Furthermore, pull mechanisms may or may not involve intellectual property protection; the use of alternative reward programs, such as prizes, is emphasised.⁶⁴ Love also suggests that ‘push’

⁵⁶ Council of the European Union, *Council conclusions on the EU role in Global Health*, 3011th Foreign Affairs Council Meeting, 10 May 2010, 18(c)

⁵⁷ WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), *Background and Terms of Reference*; see also Sixty-Third World Health Assembly, *Resolutions and Decisions*, 63.28

⁵⁸ WHO CEWG (2012), *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*, p.9

⁵⁹ Love J (2011), *De-linking R&D costs from product prices*, Knowledge Economy International, http://www.who.int/phi/news/phi_cewg_1stmeet_10_KEI_submission_en.pdf

⁶⁰ Ibid., p.2

⁶¹ Ibid.

⁶² Ibid., pp.2-3

⁶³ Ibid., p.5

⁶⁴ Ibid., p.3

funding could include existing mechanisms such as research grants from public and private donors targeting basic science and pre-commercial development.⁶⁵

The following section will provide an in-depth examination of these and other push and pull delinking mechanisms for incentivising R&D into Type II and III diseases.

It is worth noting that the mechanisms discussed here may be applied at different stages in the process of creating and delivering new medicines to patients in low and middle income countries. Drawing on the biopharmaceutical R&D model discussed in Section 2, it is possible to make a distinction between the stages of research (including basic scientific research and drug discovery); development (including pre-clinical research and Phase I, II and III clinical trials); and access (including product registration, purchase and delivery, and postmarketing studies).

4.2 Research

The following sections analyse mechanisms which may primarily be applied in the stage of basic research and drug discovery.

4.2.1 Open compound databases

In the last several years, providing access to proprietary databases or compound libraries has been identified as a potential mechanism for enabling early and in some cases, late-stage research targeting neglected diseases. With discovery of target, hit and lead compounds being some of the missing links in R&D into Type II and III diseases, the ability to trawl through existing databases and access promising compounds as well as key information on their use is of strategic importance.

In this vein, in 2008 the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, among other measures, called for:

*...the creation of voluntary open databases and compound libraries including voluntary provision of access to drug leads identified through the screening of such compound libraries.*⁶⁶

It is also worth mentioning that the London Declaration involved the announcement of additional collaborations (including new levels of access to compound libraries) between the product development partnership Drugs for Neglected Diseases Initiative (DNDi) and several biopharmaceutical companies.⁶⁷

⁶⁵ Love J (2011), p.5

⁶⁶ WHO 61st World Health Assembly, “Annex: Global Strategy on Public Health, Innovation and Intellectual Property”, 2.4(c), *Resolutions and Decisions*

⁶⁷ Uniting to Combat Neglected Tropical Diseases, “Table of Commitments”

In addition to private, bilateral and multilateral agreements, the first public database and major platform for knowledge and technology-sharing is the WIPO Re:Search consortium, which was initiated in 2011. WIPO Re:Search is sponsored by the World Intellectual Property Organisation (WIPO) and a number of other multilateral and national bodies, and provides access to a growing library of compounds in different stages of discovery and development, as well as platform and supporting technologies. The intention is that access to this information will lead to further collaboration and development activities, both in early and later stage R&D.

The purpose of the database is to share knowledge in a targeted and voluntary way, in which users and contributors come to bilateral agreements on access to contributed assets. The database helps with identification of useful material and networking of relevant parties. Under the Guiding Principles of the consortium, contributors can choose whether to license their proprietary assets on a case by case basis, although any license agreements aimed at R&D, manufacturing or delivery of products for least developed countries⁶⁸ must be royalty-free.⁶⁹

WIPO Re:Search currently has 17 members who have indicated they are willing to contribute assets and services for license or use by other members; at least 8 members have shown interest in licensing these technologies and services.⁷⁰ Potential users of WIPO Re:Search include the Emory Institute for Drug Discovery (EIDD), iThemba, a South African drug discovery company, GALVmed, the Sabin Vaccine Institute, DNDi, the Brazilian public health institution Fiocruz, Medicines for Malaria Venture (MMV) and Medical Research Council (the latter four are also listed as providers). Table 1 shows the type and number of assets contributed up to now. Table 2 outlines which diseases are so far being addressed in the database and to what extent.

This data indicates that contributions to date are mostly product-driven; only a small amount are applicable to basic research, although some companies have made a substantial submission of preclinical candidates with potential applicability to all neglected diseases. In terms of quantity, the majority of the more ‘visible’ assets are patents. Yet, given the complexity of biopharmaceutical R&D, the fact that additional, and not less valuable, assets involving know-how and services have been contributed is particularly significant. It can also be noted that the database already covers a wide range of diseases; besides those with established R&D efforts, such as malaria and TB, other neglected diseases also receive significant attention, particularly kinetoplastids, dengue, helminths and leprosy.

⁶⁸ Least developed countries are those defined by the United Nations Office of the High Representative for the Least Developed Countries, Landlocked Developing Countries and the Small Island Developing States, as of November 2010.

⁶⁹ World Intellectual Property Organization (WIPO), “Guiding Principles of WIPO Re:Search”, http://www.wipo.int/research/en/about/guiding_principles.html (Accessed February 2012)

⁷⁰ WIPO, “WIPO Re:Search Members”, <http://www.wipo.int/research/en/about/members.html> (Accessed February 2012)

Table 1: Type and number of WIPO Re:Search contributions

Type of contributions									
Screening, Hits Data	Hits-to-Lead	Lead Series	Pre-Clinical Candidate	Marketed Product	Enabling Technology (Platform)	IP (Patents)	Vaccine Technology	Other Data, Know-How, Services, Resources	Total
7	4	9	36	6	4	91	1	9	167

Pugatch Consilium calculations based on the WIPO Re:Search database⁷¹

4.2.2 Research grants

Grant-giving to research entities, in which funding is afforded for future research with the goal of achieving a pre-determined research outcome, is one of the most established elements for incentivising basic scientific research.⁷² As an illustration, the US National Institutes of Health (NIH), which is the largest global funder of basic research⁷³ (including on neglected diseases⁷⁴), awards more than 80% of its funding through competitive grants to universities and research institutions around the world.⁷⁵

Yet, in the context of funding R&D into Type II and III diseases, especially by many philanthropic organisations, grants are also increasingly targeted at later stage R&D such as product development partnerships. Most notably, one of the key pillars of the Gates Foundation, the third largest funder of neglected disease research,⁷⁶ is grant-making to global health initiatives.⁷⁷

By eliminating or reducing the upfront investment in R&D by research entities, the grant model of allocating funding in advance of research is intended to incentivise R&D which is otherwise unfeasible or where a return on spending is uncertain. However, if not designed properly the grant model can be problematic for both grantees and grantors. Among other factors, the temporary or piecemeal nature of grants (generally allocated for 1-5 years, renewal is possible but not certain) may incentivise short-term projects which, once completed, do not have the funds to be advanced to full product development. On the grantors' side, they lack control over the way grantees apply funds once they are released, both in terms of achieving the agreed output and in making it affordable to users.

⁷¹ Data drawn from the WIPO Re:Search website, <http://www.wipo.int/research/en/search/> (Accessed February 2012)

⁷² Hanson R (1998), *Patterns of Patronage: Why Grants Won Over Prizes in Science*, University of California, Berkeley

⁷³ DeVol et al (2011), p.8

⁷⁴ Moran M, Guzman J, Abela-Oversteegen L, Liyanage R, Omune B, Wu L, Chapman N & Gouglas D (2011), *Neglected disease research and development: Is innovation under threat?*, Policy Cures, p.86

⁷⁵ National Institutes of Health (NIH), "NIH Budget", <http://www.nih.gov/about/budget.htm> (Accessed February 2012)

⁷⁶ Moran et al (2011), p.85

⁷⁷ Gates Foundation (2010), Foundation Brochure, <http://www.gatesfoundation.org/about/Documents/brochure-bill-and-melinda-gates-foundation.pdf> (Accessed February 2012)

Table 2: WIPO Re:Search contributions by disease and contributing entity

Disease	Contributing company											Total contributions by disease*	
	Alnylam	Astra Zeneca	CWHM (USA)	DNDi	GSK	Eisai	Merck (USA)	NIH	Novartis	PATH	Pfizer		Sanofi
Buruli Ulcer		6	3		2			1					12
Chagas Disease				1	3	1	1	1		1	1		9
Cysticercosis (tapeworm)					2		1						3
Dengue fever					2			11		1			14
Dracunculiasis					2		1						3
Echinococcosis					2		1						3
Endemic treponematoses					2		1						3
Foodborne trematode infections					2		2						4
Human African trypanosomiasis				1	3		2	1			1	3	11
Leishmaniasis	4	3	3	3	3	1	2	3			1	2	22
Leprosy	6	3			2			1					12
Lymphatic filariasis	4	3			2		1	1			6		17
Malaria	6	3			4		1	39	1	1		1	56
Onchocerciasis (river blindness)	4	3			2		1				6		16
Podoconiosis	4	3			2								9
Rabies			3		2			2		1			8
Schistosomiasis			3		2		1	1			4		11
Snakebite					2								2
Soil transmitted helminthiasis					2		1				4		7
Trachoma					2			5					7
Tuberculosis		10			3			9	1	1		1	25
Unknown or others	1	28				6					7	9	51

Pugatch Consilium calculations based on the WIPO Re:Search database⁷⁸

*Some contributions relate to multiple diseases.

⁷⁸ Data drawn from the WIPO Re:Search website, <http://www.wipo.int/research/en/search/> (Accessed February 2012)

Therefore, not least in the scope of R&D into Type II and III diseases, it is desirable that grants be complemented by additional funding mechanisms which are also sustainable in the product development phase.

4.2.3 R&D prizes

A targeted prize is a payment made to a research entity that is conditional on achieving a particular outcome (a kind of pay-for-performance mechanism).⁷⁹ The idea behind a prize targeting R&D into Type II and III diseases is to reward the accomplishing of certain research milestones, such as discovery and isolation of a lead compound or development of a technology which facilitates the R&D process. Prizes are also proposed for the development of entire treatments, as a way of ensuring that funding directed at neglected diseases leads to the development of an effective treatment that provides a needed health impact in developing countries. Some prizes do not involve innovators retaining ownership of the developed technology, while others allow the winner to maintain the patent or patents on the technology.

The prize model is a relatively new idea when it comes to the topic of R&D into Type II and III diseases. Among existing prize programmes, InnoCentive is one which awards prizes to innovators who create a solution to a research problem or need, including in the life sciences field.⁸⁰ The idea is to ‘crowd source’ R&D by leveraging the knowledge and skills of innovators from the public using the incentive of prizes.⁸¹ InnoCentive’s notable solutions in the global health area (which are focused on ‘milestone’ technologies) include a biomarker that speeds up and reduces the cost of clinical trials for ALS disease and a process for simplifying the manufacturing process for a TB drug.⁸² InnoCentive has also acquired UK-based OmniCompete, which is engaged in similar innovation competitions including in the area of health.⁸³

In addition, the X Prize Foundation (partnered with the Gates Foundation) has been successful in generating research solutions in other fields, including space travel, and has just recently begun to focus on biomedical R&D. X Prize is in the process of developing its first prize related to R&D into Type II and III diseases, specifically a more effective point-of-care diagnostic test for TB than the existing smear microscopy tool.⁸⁴

A number of prize programmes aimed at the development of medicines and other therapies have also been proposed in different contexts. For example, in May 2011, a bill was introduced in the

⁷⁹ Muller-Langer (2011), p.12

⁸⁰ InnoCentive, “Solutions of Note”, <https://www.innocentive.com/about-innocentive/innovation-solutions-of-note> (Accessed March 2012)

⁸¹ InnoCentive, “Solutions of Note”

⁸² Ibid.

⁸³ InnoCentive, “InnoCentive Acquires OmniCompete Limited”, <http://www.innocentive.com/omnicompete> (Accessed March 2012)

⁸⁴ X Prize Foundation, “Prize Development”, <http://www.xprize.org/prize-development/life-sciences> (Accessed February 2012)

US Senate which would establish a Medical Innovation Prize Fund.⁸⁵ The proposed prize fund, originally developed by Love and Hubbard (2007),⁸⁶ would give a financial reward to innovators that produce specified therapies which result in sufficient benefit to patients, a percentage of which would be dedicated to neglected diseases.⁸⁷ The bill is still under consideration by the Senate Health Committee.⁸⁸

A second, slightly different example is the Health Impact Fund (HIF) proposed by Hollis and Pogge (2008),⁸⁹ which would be financed mainly by government donors and offer drug sponsors the option of being rewarded according to a new product's health impact, in return for selling it 'at cost'.⁹⁰ It is envisioned that for every year that the sponsor sells the product at cost, they would receive a pay-out from the reward fund, in proportion to the assessed health impact of the product in the preceding year.⁹¹ For the HIF, financing would have to be substantial and maintained over the long-term. The HIF is still in the development stage; work is currently focused on developing pilots in various countries to determine robust performance measurements.⁹²

The existing evidence, which is limited given that the prize model is still in the initial stages, appears to suggest that in some circumstances prizes may represent a useful tool for incentivising milestones in the R&D process or supporting technologies, i.e. pieces of the R&D puzzle. Evidence on the use of prizes for the development of medicines and other therapies does not yet exist; however, it is important to note that the prize model is unlikely to meet the financial needs of innovators for later stage R&D (particularly in covering the huge costs of clinical development). This is because inherently, only the first successful innovator is rewarded and even for the 'winner' there is still no guarantee that the prize amount will cover costs of development sufficiently. Hence, prizes alone may not provide the necessary incentives or financial capabilities to fully develop and produce medicines for use in low and middle income countries.

⁸⁵ See S.1137: Medical Innovation Prize Fund Act, <http://www.govtrack.us/congress/bill.xpd?bill=s112-1137> (Accessed March 2012)

⁸⁶ Love J & Hubbard T (2007), "The Big Idea: Prizes to Stimulate R&D for New Medicines", *Chicago Kent Law Review*, Vol.82, p.1519

⁸⁷ Kaiser Family Foundation, "Policy Tracker: S.1147 – Medical Innovation Prize Act", 26.05/2011, <http://globalhealth.kff.org/Policy-Tracker/Content/2011/May/26/S1137-Medical-Innovation-Prize-Fund-Act.aspx> (Accessed March 2012)

⁸⁸ See S.1137 (2011-2012) at <http://www.govtrack.us/congress/bill.xpd?bill=s112-1137&tab=committees> (Accessed March 2012)

⁸⁹ Hollis A & Pogge T (2008), *The Health Impact Fund: Making New Medicines Accessible for All*, New Haven, CT: Incentives for Global Health

⁹⁰ Health Impact Fund, "Proposal and Pilot", <http://www.yale.edu/macmillan/igh/pilot.html> (Accessed March 2012)

⁹¹ Ibid.

⁹² Health Impact Fund, "Proposal and Pilot"

4.3 Development

The following sections analyse mechanisms which may primarily be applied in later stage and preclinical research and clinical development.

4.3.1 Targeted tax credits

Targeted R&D tax credits are a direct contribution to research entities in order to promote R&D in specific research areas by increasing returns to R&D in these areas.⁹³

General tax credits have been shown to boost R&D,⁹⁴ but tax credits directed at research on diseases with small or uncertain markets have shown mixed results. One of the most well established is the 50% tax credit for orphan drugs in the US, which is part of a scheme that has shown success in bringing new products to the market and will be discussed in further detail in a later section.

In contrast, the UK's tax credit specifically for vaccine research aimed at the developing world, introduced in 2003, has had a relatively low uptake. The Vaccine Research Relief Programme, which gives a 40% credit for investment in vaccines and treatments for HIV/AIDS, TB, malaria and NTDs, only saw an average of 10 claims per year between 2003 and 2010.⁹⁵ Average annual claims for all R&D credits in the UK (including SME-targeted schemes) over the same period were 7,370.⁹⁶ As a result, during 2011-2012, the programme will be gradually abolished for SMEs, but will be retained for large companies.

The US has also introduced a tax credit of up to 50% for research in the drug discovery phase which is aimed at small biotech firms. The Qualifying Therapeutic Discovery Research Project Program (which also offers a direct grant for companies which are not yet profitable) is still in the early stages – it was introduced for tax years 2009 and 2010 – and does not strictly target diseases affecting the developing world. The main criterion for the programme is that the research must result in therapies which either treat areas of unmet medical need or are preventative, but special attention is also paid to projects which help boost employment in the US.⁹⁷ In 2010, around 3,000 awards totalling \$1 billion were given,⁹⁸ and a survey conducted by the Biotechnology Industry Organization (BIO) of eligible companies found that the program

⁹³ World Trade Organisation (WTO) (2006), *World Trade Report 2006: Exploring the Links between Subsidies, Trade and the WTO*, Geneva

⁹⁴ Bloom N, Griffith R & Van Reenen J (2000), "Do R&D tax credits work? Evidence from an international panel of countries 1979–1994", Institute for Fiscal Studies Working Papers, W99/08

⁹⁵ HM Revenue and Customs (HMRC), "Cost of support claimed for the R&D tax credit by scheme and financial year on an accounting period basis, 2000-01 to 2009-1", http://www.hmrc.gov.uk/stats/corporate_tax/rd-accrualsbasis.pdf (Accessed February 2012)

⁹⁶ HMRC, "Cost of support..."

⁹⁷ Internal Revenue Service (IRS), "Qualifying Therapeutic Discovery Projects Basic Information: Questions and Answers", <http://www.irs.gov/newsroom/article/0..id=224011.00.html> (Accessed February 2012)

⁹⁸ BIOTechNOW, "Reason to Give Thanks: 2,923 Companies Qualify for QTDP Grants, Tax Credits", 29 Nov 2010, <http://8.21.237.15/section/business-biotech/2010/11/29/reason-give-thanks-2923-companies-qualify-qt-dp-grants-tax-credits> (Accessed February 2012)

was crucial to the ability to survive for four out of five companies.⁹⁹ Although the R&D targeted here is not necessarily aimed at the developing world, nonetheless by accelerating early stage R&D it could facilitate later stage R&D which does target the developing world.

Altogether, R&D tax credits targeting Type II and III diseases are relatively untested and, moreover, are only applicable to entities which generate profits, or have tax liabilities.

4.3.2 Orphan drug-like schemes

Schemes which mimic or draw on orphan drug legislation existing in key markets, particularly the US and EU, are also proposed for enhancing market-based incentives for R&D into Type II and III diseases.

The basic idea of orphan drug schemes is to provide several benefits for companies developing a drug which is aimed at diseases affecting a relatively small numbers of people (in the US, orphan drug legislation applies to drugs developed to treat diseases which affect less than 200,000 people, and in the EU those which affect 5 people out of every 10,000 or fewer). These may include additional marketing exclusivity, accelerated market authorisation and other funding support, in addition to tax credits (which were discussed earlier).

Looking at the key markets with orphan drug legislation – the US and the EU – it can be said that both schemes have been successful in increasing the number of new orphan drugs or new indications of existing orphan drugs available in the market. The US Orphan Drug Act (1983)¹⁰⁰ provides three major incentives to develop drugs treating rare diseases – a 7 year market exclusivity to sponsors of approved orphan drugs; a tax credit of 50% of the cost of clinical trials; and federal research grants for conducting clinical testing. Since 1997, orphan drug sponsors are also exempt from FDA application or ‘user’ fees. In addition, orphan drugs may qualify for various benefits associated with clinical testing and market authorisation, including advice from the FDA on clinical trial design, priority review (within six months of submission)¹⁰¹ and approval based on smaller and shorter clinical trials (i.e. based on surrogates, or substitute endpoints likely to predict clinical benefit, in lieu of longer-term endpoints such as mortality rates).¹⁰²

⁹⁹ Biotechnology Industry Organization (BIO), “Therapeutic Discovery Project: 7 Companies, 1 Year Later”, 11 Nov 2011, <http://www.bio.org/articles/therapeutic-discovery-project-7-companies-1-year-later> (Accessed February 2012)

¹⁰⁰ US Public Law 97-414

¹⁰¹ In order to qualify for Priority Review a drug must “offer major advances in treatment, or provide a treatment where no adequate therapy exists”. See FDA, “Fast Track, Accelerated Approval and Priority Review”, <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccessstoimportantnewtherapies/ucm128291.htm> (Accessed February 2012)

¹⁰² These benefits fall under the FDA’s Fast Track and Accelerated Approval schemes, which apply to drugs that “treat serious diseases and fill an unmet medical need”. See: Ibid.; Department of Health and Human Services (2001), *The Orphan Drug Act: Implementation and Impact*, <http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf> (Accessed February 2012). The Fast Track Program has been shown to reduce overall development time by about three years on average (2-2.5 year cut in clinical development time and 1 year cut in approval time). See: Moran M (2005), “Fast Track Options as a fundraising mechanism to

It is generally agreed that the Orphan Drug Act has resulted in an increase in clinical trials and the introduction of orphan drugs.¹⁰³ According to FDA data¹⁰⁴ 392 orphan drugs were approved between November 1983 and December 2011.¹⁰⁵ In contrast, in the decade before the enactment of the Orphan Drug Act, only 10 drugs were marketed for rare disease indications.¹⁰⁶

In the EU, orphan drug legislation was introduced in 1999 (EC 141/2000) along the same lines as the Orphan Drug Act, including a framework for designating orphan drug status. Included in this, the EU scheme provides marketing exclusivity (10 years); total or partial fee reduction for marketing authorisation, inspections, etc.; access to the EU’s centralised authorisation procedure (a single authorisation procedure valid in all of the EU); and protocol assistance (scientific advice) on the clinical tests needed for authorisation.¹⁰⁷ In addition, orphan drug sponsors may be eligible for specific grants and tax credits from EU and member state programmes.¹⁰⁸ According to one study, only 8 drugs treating rare disease were developed prior to 2001;¹⁰⁹ in the decade after the introduction of orphan drug legislation, at least 62 drugs designated with orphan status were approved by EMA (see Table 10). In addition, an industry survey by the UK consultancy Office of Health Economics strongly suggests that, among the other components afforded in the EU orphan drug directive, the period of exclusivity seems to have the most significant impact on the pharmaceutical industry’s R&D decisions and activities related to orphan drugs.¹¹⁰

Table 3: Number of Products with Orphan Drug Designation Authorised in Key Markets

Location	Total prior to introduction of orphan drug scheme	Total following introduction of orphan drug scheme
US	10*	392
EU	8	62

Pugatch Consilium calculations based on FDA and EMA data¹¹¹; *1972-1982
 Additional sources: Lichtenberg & Waldfogel (2009)¹¹²; OHE (2010)¹¹³

support R&D into Neglected Disease”, Pharmaceutical R&D Policy Project, London School of Economics, <http://www.who.int/intellectualproperty/submissions/Mary.Moran2.pdf> (Accessed February 2012)

¹⁰³ Lichtenberg F & Waldfogel J (2009), “Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act”, *Michigan Telecommunications and Technology Law Review*, Vol. 15, pp.335-357; Yin W (2007), “Market Incentives and Pharmaceutical Innovation”, University of Chicago, Harris School

¹⁰⁴ FDA, “Orphan Drug Designations and Approvals”, <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm> (Accessed February 2012)

¹⁰⁵ In the decade from 2000, orphan drug products represented 22% of all new molecular entities. See: Tufts Center for the Study of Drug Development (2010), Impact Report, January/February 2010.

¹⁰⁶ House of Representatives Subcommittee Report (1982), *Preliminary Report of the Survey on the Drugs for Rare Diseases. Subcommittee on the Health and the Environment*, Government Printing Office

¹⁰⁷ Rare Diseases Europe (EURORDIS), “Promoting orphan drug development”, <http://www.eurordis.org/content/promoting-orphan-drug-development> (Accessed February 2012)

¹⁰⁸ Ibid., see also: Belgian Health Care Knowledge Centre (2009), *Policies for Rare Diseases and Orphan Drugs*, KCE Reports 112C

¹⁰⁹ OHE Consulting (2010)

¹¹⁰ Ibid.

¹¹¹ Data drawn from FDA and EMA websites. See: FDA, “Orphan Drug Designations and Approvals”; and EMA, “Register of designated Orphan Medicinal Products”, <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm> (Accessed February 2012).

Based on the success of orphan drug legislation in the US and Europe in enhancing the number of orphan drugs produced in these markets, it has been suggested that a similar scheme could be applied specifically to therapies treating NTDs.

One application of a policy similar to that for orphan drugs is the US FDA's issuing of "priority review vouchers", which entitle entities which submit new drug applications for treatments aimed at Type II and III diseases (as defined by the FDA) to the expedited review of *another* new drug application.¹¹⁴ Given that the idea of a priority review voucher is quite new, at this point there is not enough evidence to assess its effectiveness.

It should be emphasised again that any orphan drug like-scheme involving the provision of exclusivity would be likely to only attract commercial, profit-seeking entities, mainly biopharmaceutical companies. Furthermore, because the paying market for drugs treating Type II and III diseases is arguably even smaller than the market for orphan drugs in developed countries, it would likely be necessary to complement such a scheme with other measures that would ensure a sufficient paying market (while also making the drugs affordable in that market).

4.3.3 Patent pools

Patent pools are a specific arrangement involving the cross-licensing of patents and other forms of intellectual property (IP) by participants with the goal of accessing essential technologies for particular products.

In its 2008 Global Strategy for Public Health Innovation and Intellectual Property, the WHO made it a priority to

*...[E]xamine the feasibility of voluntary patent pools of upstream and downstream technologies to promote innovation of and access to health products and medical devices...*¹¹⁵

The idea is that patent pools are able to provide a 'one-stop shop' for licensing several patents from multiple owners at once,¹¹⁶ and in this way make the process of acquiring essential technologies (for drug discovery, development or other) more cost-effective, especially for non-profit or developing country research entities and small firms.

Patent pools have been successfully applied to information and communication technologies (ICT), consumer electronics and other industries with a high volume of patents. In the ICT field,

¹¹² Lichtenberg & Waldfoegel (2009)

¹¹³ OHE Consulting, *Assessment of the impact of Orphan Medicinal Products (OMPs) on the European Economy and Society*, Commissioned by the Joint EBE-EuropaBio Task Force on Rare Diseases and Orphan Medicinal Products, p.2

¹¹⁴ FDA (2008), *Guidance for Industry: Tropical Disease Priority Review Vouchers*, October 2008

¹¹⁵ WHO (2008), *Global strategy and plan of action on public health innovation and intellectual property*, p.14

¹¹⁶ CIPIH (2006), p.52

patent pools have generally been used for the application of multiple technologies in a single (and final) product.

In the past few years, two major patent pools arose with the specific purpose of sharing patents related to therapies targeting neglected diseases.

Medicines Patent Pool

The Medicines Patent Pool is a voluntary pool which was initiated in 2008, originally within the scope of UNITAID, as part of efforts to support the production of treatments for HIV/AIDS, malaria and TB treatments aimed at developing countries.¹¹⁷

The patent pool is mainly focused on increasing access in developing countries to newer antiretroviral medicines by increasing the number of generic producers of these medicines, as well as encouraging the development of adapted formulations.¹¹⁸

The Medicines Patent Pool currently has two contributors.¹¹⁹ The NIH has donated patents for one molecule, darunavir, and Gilead has donated patents on five molecules. It should be noted that other patent holders would also need to share their patents in order to fully enable licensees to engage in R&D, and certainly to produce a medicine. The pool is in negotiations with Boehringer-Ingelheim, Bristol-Meyers Squibb, Sequoia and Viiv Healthcare to expand its pool.

So far, all licensing has been to generic companies to produce generic forms of existing therapies. These include four molecules licensed to Aurobindo, five to MedChem.

Pool for Open Innovation against Neglected Tropical Diseases (POINT)

As discussed earlier, the other major patent pool, the Pool for Open Innovation against Neglected Tropical Diseases (POINT), has been absorbed into WIPO Re:Search. POINT was initiated by GlaxoSmithKline (GSK) in 2009, with the aim that contributors would donate the IP (patents and, at the contributors' discretion, know-how) required to facilitate R&D into 16 neglected tropical diseases (excluding HIV). The pool's donors included GSK, Alnylam Pharmaceuticals, Massachusetts Institute of Technology, University of California Berkeley, California Institute of Technology (CalTech) and the Medicines for Malaria Venture (MMV). In its early stages, the pool's customers included Emory Institute for Drug Development (EIDD), South Africa's Technology Innovation Agency (TIA) and iThemba Pharmaceuticals (which is a partner of

¹¹⁷ International Centre for Trade and Sustainable Development (ICTSD), "UNITAID Launches Patent Pool for HIV/AIDS Drugs", 9 June 2010, <http://ictsd.org/i/news/bridgesweekly/77693/> (Accessed February 2012)

¹¹⁸ UNITAID (2010), "The Medicines Patent Pool Initiative", UNITAID Factsheet, http://www.unitaid.eu/images/NewWeb/documents/Publications_July2010/pp_facts_en_jul10.pdf (Accessed February 2012)

¹¹⁹ Medicines Patent Pool website, <http://www.medicinespatentpool.org/> (Accessed February 2012)

EIDD).¹²⁰ Both the donors and customers, and the agreements reached within the POINT framework, now exist as part of the larger WIPO Re:Search framework. Prior to the initiation of WIPO Re:Search, there were over 2,300 patents available in the Pool for Open Innovation.¹²¹

The purpose of POINT was broader than the Medicines Patent Pool, with an emphasis on access to contributors' know-how and compound databases as well as to GSK's Tres Cantos laboratory.¹²² The main outputs from the pool while it was in existence were two Memorandums of Understanding to collaborate.

In sum, the application of patent pools to the biopharmaceutical field and to R&D into Type II and III diseases is relatively new and limited at this time. Patent pools have mainly been used to license patents for the production of generic drugs. However, the lack of R&D output from either patent pool, and the fact that POINT is now integrated into a much broader and flexible platform, suggest that patent pools in and of themselves will not have a widespread application in R&D into Types II and III diseases.

It is possible that they may act as a platform for adapting existing technologies for use in the developing world, such as adapted formulations and delivery systems, as well as in very specific fields such as vaccines. This is because a large number of technologies related to vaccines are owned by different entities and consequently, it is quite complex to identify, track and obtain licenses for patented technologies.¹²³

It can be noted that although there is certainly some overlap, the concept of a database or compound library (as discussed above) is somewhat different from a patent pool; compound databases are intended to provide access to a wider range of assets than patent pools, as well as both proprietary and non-proprietary assets.

4.3.4 Product development partnerships

PDPs are a relatively new type of public-private partnership which has emerged in the last decade and a half with a specific focus on addressing public health problems in low and middle-income countries by stimulating the development of pharmaceutical products targeted at neglected diseases.¹²⁴

¹²⁰ Bio Ventures for Global Health, "Medicines for Malaria Venture Becomes First Product Development Partnership to Contribute Patents to the Pool for Open Innovation Against Neglected Tropical Diseases", 16 Aug 2010, <http://www.bvgh.org/News/BVGH-News/Press-Releases/Article-16-August-2010.aspx> (Accessed February 2012)

¹²¹ GSK, "Creating a pool of intellectual property to fight neglected tropical diseases", <http://www.gsk.com/collaborations/patentpool.htm> (Accessed February 2012)

¹²² iThemba, "iThemba Pharmaceuticals (Pty) Ltd Will Partner with GlaxoSmithKline on Drug Research for Neglected Tropical Diseases", Press Release, 20 January 2010, http://www.ithembapharma.com/ithemba_gsk_partnership_release.doc (Accessed February 2012)

¹²³ CIPIH (2006), p.53

¹²⁴ G-FINDER, "Definition for terms..."

The PDP model

One of the first PDPs aimed at global health, the International AIDS Vaccine Initiative (IAVI), arose in 1996 to address the gap in financial incentives to develop AIDS vaccines protecting against variants common in developing countries. The PDP model was quickly replicated, spurred on by funding from major foundations, particularly the Gates Foundation. Sixteen PDPs were founded between 1999 and 2003,¹²⁵ and today, the Global Funding of Innovation for Neglected Diseases (G-FINDER) survey counts at least 18 PDPs. Existing PDPs focus on several major Type II and III diseases in addition to the ‘big three’, HIV/AIDS, malaria and tuberculosis.

PDPs work by bridging public and private research entities with donors in order to facilitate development of health technologies that individual research actors would otherwise not have the incentive or means to develop, mainly because of small paying markets in developing countries. Among other factors, PDPs are ground breaking in the sense that they provide a platform for integrating the owners of a wide range of inputs to the product development process, such that a single company or entity does not bear the full cost and risk of R&D.¹²⁶ These inputs range from product components – such as active ingredients, platform and supporting technologies – to operations and infrastructure related to conducting preclinical and clinical development, preparing the portfolio for market authorisation, and delivering and implementing the product. Crucially, PDPs also bring actors and inputs from developed and developing countries together, with the intention of incorporating local decision-makers, public researchers, SMEs, clinicians and facilities into the development process. From such a vantage point, PDPs are able to identify optimal pathways to product development and spearhead coherent and product-driven programmes to carry them out, in some cases from discovery to full development.¹²⁷

Funding from governments, government agencies, international organisations, foundations, NGOs and corporations enables collaboration by providing financial support for licensing of essential technologies, access to research facilities, actual laboratory and clinical testing, and purchasing and supplying to end users. Biopharmaceutical companies also invest substantially in the development process. Beyond direct R&D spending, industry’s in-kind contribution may include technology transfer, technical expertise (on clinical development, manufacture, registration, distribution and utilisation of products), access to intellectual property (licenses, databases and compound libraries) and regulatory assistance (i.e. covering the cost of regulatory filing and portfolio preparation).¹²⁸

Given that they coordinate such a wide range of actors, different PDPs have different operational strategies, particularly in the way in which they stimulate participation by various actors

¹²⁵ Grace C (2010), “Product Development Partnerships (PDPs): Lessons from PDPs established to develop new health technologies for neglected diseases”, DFID Human Development Resource Centre, p.4

¹²⁶ CIPIH (2006), p.72

¹²⁷ CIPIH (2006), p.70

¹²⁸ Moran et al (2011), p. 84

throughout the product development process. Specifically, it is worth noting that engaging owners of key inputs is a challenge that some PDPs seem to be able to overcome on an increasingly larger scale. The announcement of several collaborations aimed at product development as part of the London Declaration is an illustration of this.¹²⁹

Certainly, involvement of research institutions and biotechnology and biopharmaceutical companies may be driven by an array of factors simultaneously, including both goodwill and commercial objectives. As discussed in Section 1, R&D entities recoup costs in part by leveraging products (both in the market they were developed for as well as in other markets or in another aspect of the company's R&D pipeline). In the context of PDPs, R&D partners may be interested in the broader use of a technology developed within a PDP (e.g. new technologies or methodologies for testing combination products which have been utilised for tuberculosis combination therapies). They may also be interested in its application to more commercial research programs (i.e. as a new target for drug discovery or for application to new indications, such as has been done with 'broad spectrum' anti-infective medicines).¹³⁰ As such, the way in which research partners are compensated and have control over technologies or products developed in a PDP, including through patenting or another form of intellectual property protection, may be one factor of incentivising participation in PDPs, especially if the PDP model continues to be scaled up.

One illustration of this is PATH's Malaria Vaccine Initiative (MVI), which allows partners that contribute proprietary technologies to maintain ownership and income from the end product. To illustrate, in return for PATH supporting an effective Stage III clinical trial of a malaria vaccine candidate, RTS,S, of which GSK owns many of the essential technologies, GSK will be able to price the final product but has agreed to supply it at a preferred price of the cost of manufacturing, plus 5%.¹³¹

Current use of the PDP model

How is the PDP model being utilised today and what level of support exists for it?

Analysis of the G-FINDER survey results¹³² indicates that funding to PDPs represents a substantial portion of global funding directed at R&D into Type II and III diseases. In 2010

¹²⁹ Uniting to Combat Neglected Tropical Diseases, "Table of Commitments"

¹³⁰ CIPIH (2006), pp.69, 73

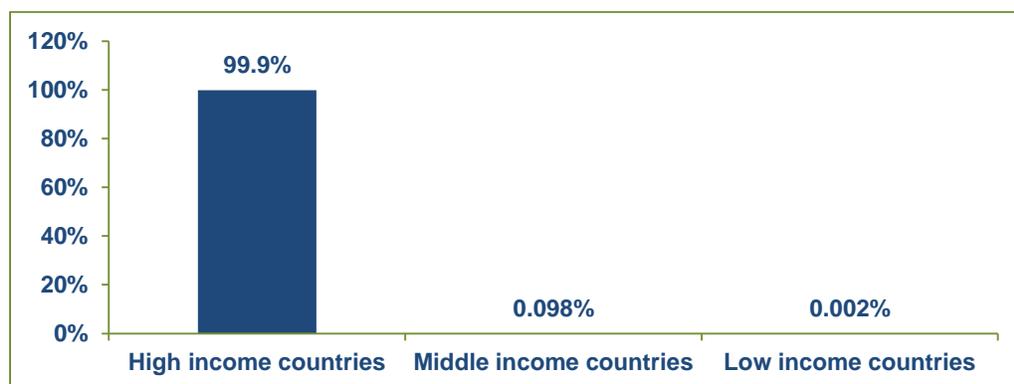
¹³¹ GlaxoSmithKline, "First results from ongoing Phase III trial show malaria vaccine candidate, RTS,S* reduces the risk of malaria by half in African children aged 5 to 17 months", Press release, 18 Oct 2011, <http://www.gsk.com/media/pressreleases/2011/2011-pressrelease-676305.htm> (Accessed February 2012)

¹³² The G-FINDER survey is conducted by Policy Cures and funded by the Gates Foundation, with the goal of helping funders to better target their investments into neglected diseases product R&D. It annually surveys funding activity of all key public, private and philanthropic organisations involved in funding for pharmaceutical tools used to prevent, control and treat 31 neglected diseases, from basic research through full clinical development. The analysis in this report is drawn from full datasets from 2007 through 2009, and a partial dataset from 2010 (the full dataset was not available at the time of writing). See the G-FINDER website, http://g-finder.policycures.org/gfinder_report/ for further information.

global funding to PDPs was \$483.2 million, representing over 42% of global grants to downstream, R&D into Type II and III diseases (excluding NIH grants).¹³³

Looking at the period 2007-2009, contributions to R&D into Type II and III diseases still came almost entirely from developed countries (99.9% of total funding to PDPs).

Figure 3: Funding by country groups as a % of total PDP funding (2007-2009)¹³⁴



Pugatch Consilium calculations based on GFINDER data¹³⁵

Table 4 shows that philanthropic organisations are the most important funders of PDPs; this reflects the major role of foundations, particularly the Gates Foundation, in the initiation and growth of the PDP model.

However, it is also clear that public funding bodies are increasingly key players in PDP funding. Taking a closer look at individual PDPs, it is evident that among several, public sector funding represents a greater portion of support than philanthropic funding (which also echoes the trend in overall spending on R&D into Type II and III diseases, where public funding represented 65% of global funding in 2010¹³⁶). Furthermore, government development agencies represent eight of the top ten funders of PDPs (see Table 5).

It can be noted that among the top philanthropic and public funders of PDPs, the large majority deliver funding in the form of research grants.¹³⁷

¹³³ G-FINDER isolates NIH grants from total global grant funding because although the NIH is a very large funder of neglected disease research, it only provides a small amount to PDPs, and thus skews the percentage of grant funding going to PDPs. This is arguably because the NIH provides the majority of its funding to basic research. See Moran (2011), pp.86.

¹³⁴ High income countries refer to those with a 2008 GNI per capita of \$11,906 or more; middle-income to those with a 2008 GNI per capita of \$976 – \$11,905; and low income to those with a 2008 GNI per capita of \$975 or less. For further information, see World Bank, “Country and Lending Groups”, http://data.worldbank.org/about/country-classifications/country-and-lending-groups#High_income (Accessed February 2012)

¹³⁵ Data drawn from G-FINDER Survey Data, 2007-2009, http://g-finder.policycures.org/gfinder_report/search.jsp (Accessed February 2012)

¹³⁶ Moran et al (2011), p.10

¹³⁷ See, for instance, the UK DFID, USAID, Norwegian NORAD, Irish Aid, Spanish MAEC and AECID, and Swedish SIDA.

Table 4: Type of funder as a % of total PDP funding by recipient (2007-2009)

Recipient PDP Name	Philanthropic	Public Sector
Program for Appropriate Technology in Health (PATH)	94%	6%
International AIDS Vaccine Initiative (IAVI)	9%	89%
Medicines for Malaria Venture (MMV)	75%	25%
Aeras	84%	16%
International Partnership for Microbicides (IPM)	28%	70%
Global Alliance for TB Drug Development (TB Alliance)	66%	34%
World Health Organization (WHO/TDR)	8%	88%
Drugs for Neglected Diseases initiative (DNDi)	49%	49%
Foundation for Innovative New Diagnostics (FIND)	82%	18%
OneWorld Health (OWH)	95%	5%
International Vaccine Institute (IVI)	93%	7%
Infectious Disease Research Institute (IDRI)	72%	19%
Sabin Vaccine Institute	100%	0%
Innovative Vector Control Consortium (IVCC)	100%	0%
European Vaccine Initiative (EVI)	0%	100%
Tuberculosis Vaccine Initiative (TBVI)	100%	0%
All PDPs	60%	39%

Pugatch Consilium calculations based on GFINDER data

In addition, industry contributions play an important role in PDPs. Among all sectors, in 2010 industry was the only one to increase its funding to R&D into Type II and III diseases. While both philanthropic and public funding dropping (by 12.4% and 6.5%, respectively), investment by multinational companies was up by over 35% in 2010, reaching \$503 million.¹³⁸

Other calculations indicate that PDPs are an increasing focus of industry investment in R&D. Table 6 shows the number of drug and vaccine projects undertaken by biopharmaceutical companies in key disease areas mainly affecting developing countries. Of these programs, 76 of them are carried by companies working with PDPs, while 17 (or 22%) are by companies on their own.¹³⁹

¹³⁸ Moran et al (2011), p.92

¹³⁹ IFPMA (2011), *Status Report – Pharmaceutical Industry R&D for Diseases of the Developing World*, November 2011

Table 5: Top funders of PDPs (2007-2009)

No.	Top funders	Amount (US\$)	% of total PDP funding
1	Bill & Melinda Gates Foundation	871,352,698	55%
2	UK Department for International Development (DFID)	139,016,385	9%
3	United States Agency for International Development (USAID)	118,559,718	8%
4	Dutch Ministry of Foreign Affairs - Directorate General of Development Cooperation (DGIS)	71,431,531	5%
5	Royal Norwegian Ministry of Foreign Affairs/Norwegian Agency for Development Cooperation (NORAD)	37,329,040	2%
6	Irish Aid	35,634,268	2%
7	Canadian International Development Agency (CIDA)	32,385,221	2%
8	Spanish Ministry of Foreign Affairs and Cooperation for Development (MAEC)/Agency of International Cooperation for Development (AECID)	30,865,719	2%
9	Swedish International Development Agency (SIDA)	29,647,028	2%
10	Global Alliance for Vaccines and Immunizations (GAVI)	24,896,295	2%
Total (top 10 funders)		1,391,117,903	88%
Total (all funders)		1,579,526,151	100%

Pugatch Consilium calculations based on GFINDER data

Table 6: Industry R&D into Type II and III diseases (as of November 2011)

Diseases	Ongoing medicines R&D projects	Ongoing vaccines R&D projects
Tuberculosis	28	3
Malaria	29	5
Other tropical diseases	25	3
Total	82	11

Source: IFPMA (2011)¹⁴⁰

Moreover, the collaborative initiatives with other companies, research organisations and donors, such as those announced in the London Declaration,¹⁴¹ also reflect industry's active and increasing participation in R&D into Type II and III diseases, including in the context of PDPs.

After more than 15 years in existence, PDPs are today addressing many of the major neglected diseases. Figure 4 shows funding to PDPs by disease as a percentage of their total funding between 2007 and 2009. While the 'big three' diseases continued to draw almost three quarters

¹⁴⁰ Adapted from IFPMA (2011), *Status Report*

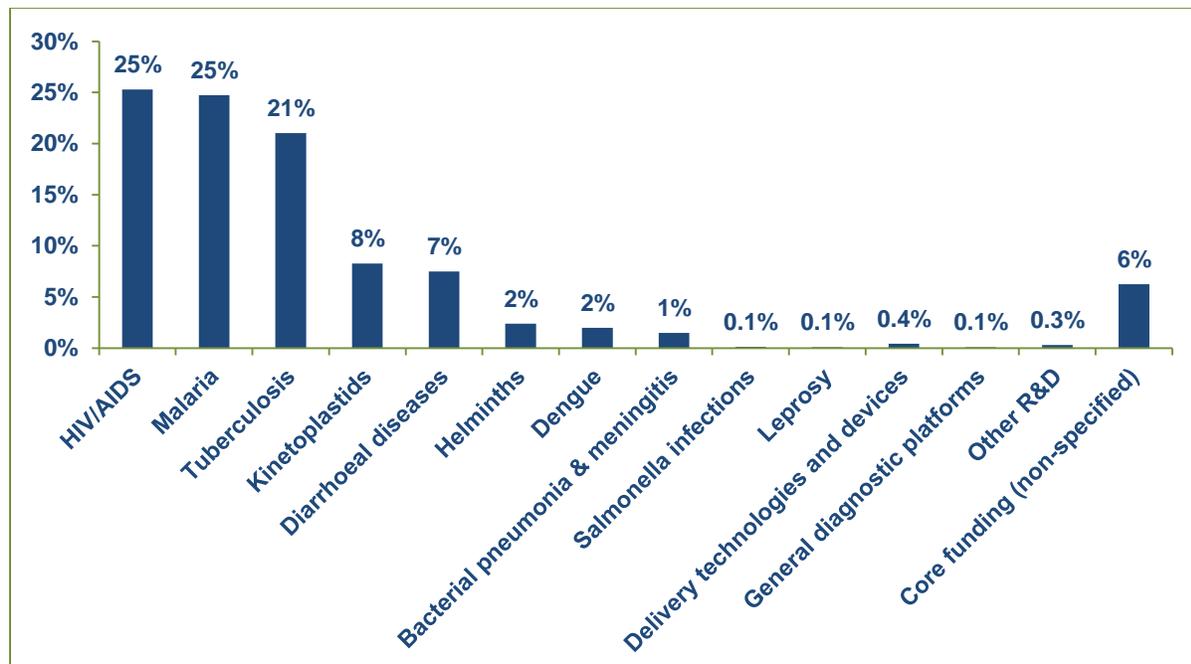
¹⁴¹ Uniting to Combat Neglected Tropical Diseases, "Table of Commitments"

of global funding, a significant portion of funding is also focused on Type II diseases such as kinetoplastids and diarrhoeal diseases. Other Type II and III diseases seem to be drawing greater attention in the last couple of years; again, it is worth noting that the London Declaration focused on several of the diseases which received a minimal amount of funding in the period 2007-2009.¹⁴²

Looking at the research output of the major PDPs, it appears that overall, the disease areas with the greatest funding are also the areas in which PDPs are carrying out the greatest clinical activity (see Figure 5). The main exception is the area of kinetoplastids, in which, relative to the ‘big three’ diseases which are also the best funded, a high number of clinical trials are taking place.

Overall, it appears that there are many clinical trials in the early stages, suggesting that the research pipeline is substantial, if somewhat young. Of course, this data is missing preclinical candidates and products which are already being implemented.

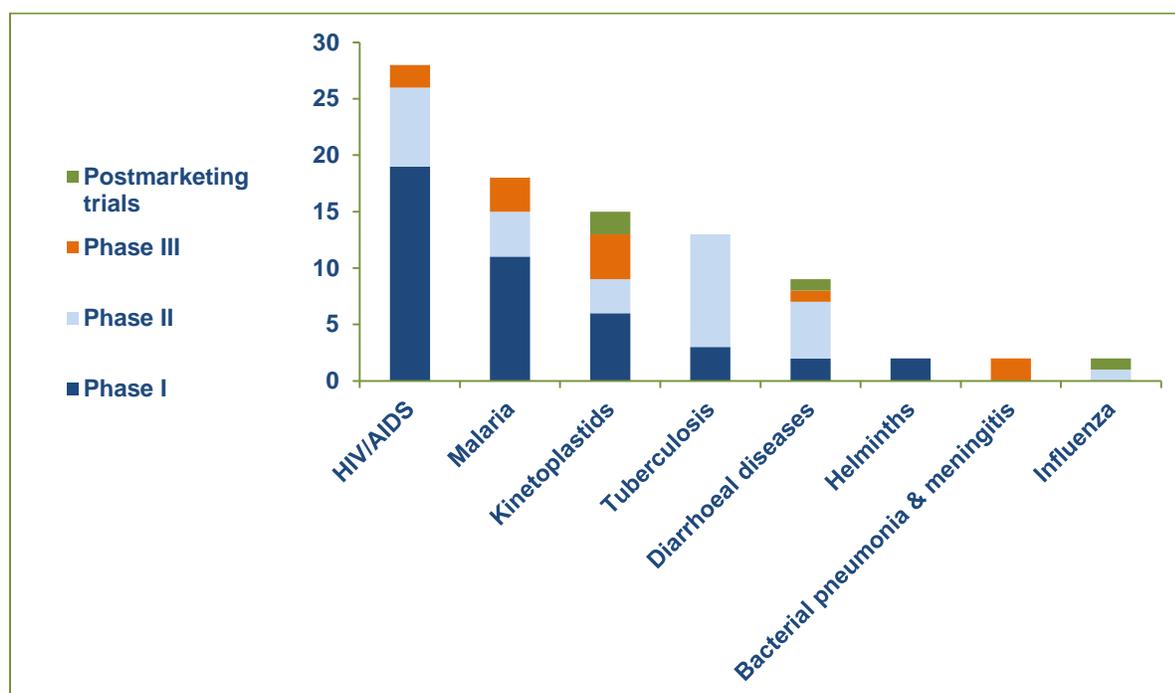
Figure 4: Funding to PDPs by disease (as a % of total funding to PDPs, 2007-2009)



Pugatch Consilium calculations based on GFINDER data

¹⁴² Uniting to Combat Neglected Tropical Diseases, “Table of Commitments”

Figure 5: Clinical activity by disease (with PDPs as lead sponsors, 2007-2012)



Pugatch Consilium calculations based on Clinicaltrials.gov data¹⁴³

Table 7 shows that among the major PDPs, the stages of clinical activity vary considerably, with at least 13 large scale Phase III trials taking place between 2007 and February 2012.

It is also worth noting that many PDPs emphasise delivery of the products they develop, although the delivery model varies considerably across and within PDPs. For example, for two Moxifloxacin combination therapies being advanced through Phase III trials in partnership with the TB Alliance, Bayer has committed to sponsoring regulatory filings and to making the products affordable in developing countries.¹⁴⁴ The malaria combination drugs ASAQ and ASMQ developed by DNDi (the latter in a partnership with Sanofi-Aventis) are being sold using locally adjusted prices and at cost to public sector entities.¹⁴⁵

¹⁴³ Data drawn from ClinicalTrials.gov; includes all clinical trials with the PDP as lead sponsor initiated or in progress during the period 01/2007-02/2012.

¹⁴⁴ TB Alliance, "Gates Foundation Awards \$104M, Five-Year Grant to Global TB Drug Alliance", 25 May 2006, <http://new.tballiance.org/newscenter/view-innews.php?id=163> (Accessed February 2012)

¹⁴⁵ Sanofi, "Sanofi-aventis and DNDi welcome the Clinton Foundation announcement on ACTs and commit to providing fixed dose combination ASAQ at equally low price", 21 July 2008, http://en.sanofi.com/our_company/highlights/malaria/treatments/treatments.aspx (Accessed February 2012); and DFID (2008), *A New Product Delivered by an Innovative Partnership ASMQ to Treat Malaria*, Press Pack, p.7, http://www.dfid.gov.uk/R4D/PDF/Outputs/DNDI/ASMQ_Press_Pack.pdf (Accessed February 2012)

Table 7: Clinical activity by PDP (with PDPs as lead sponsors, 2007-2012)

PDP	Phase I	Phase II	Phase III	Post-marketing trials	Non-specified	Total
International Partnership for Microbicides (IPM)	9	4	2	0	0	15
International AIDS Vaccine Initiative (IAVI)	10	3	0	0	0	13
Medicines for Malaria Venture (MMV)	7	3	3	0	0	13
Program for Appropriate Technology in Health (PATH)	2	1	3	1	4	11
Drugs for Neglected Diseases Initiative (DNDi)	3	2	4	1	0	10
International Vaccine Institute (IVI)	1	3	1	0	5	10
Aeras	3	5	0	0	0	8
European Vaccine Initiative (EVI)	4	1	0	0	0	5
Global Alliance for TB Drug Development (TB Alliance)	0	5	0	0	0	5
Infectious Disease Research Institute (IDRI)	3	1	0	0	0	4
Sabin Vaccine Institute	2	0	0	0	2	4
OneWorld Health (OWH)	0	0	0	1	1	2
Total	44	28	13	3	12	100

Pugatch Consilium calculations based on Clinicaltrials.gov data

4.4 Access

The following sections analyse mechanisms which are primarily applied to encourage the supply and delivery of new medicines to patients in low and middle income countries.

4.4.1 Supply and purchase guarantees

The use of supply and purchase guarantees (which are also called ‘advance market or purchase commitments’ in the discussion on R&D into Type II and III diseases) to incentivise development and access to new treatments is still in the early phases.

The WHO defines an advance market commitment (AMC) as “an agreement, in advance of the development of a product, to purchase guaranteed amounts of the product, meeting pre-established criteria, at a specified price”.¹⁴⁶ AMCs involve *ex ante* financial commitments by national governments, international organisations and private foundations to ‘top up’ the price paid by the purchaser (which is quite low) in order to reach a price agreed with the manufacturer, which covers the cost of production and perhaps also provides a certain profit for the manufacturer. AMCs replicate or mimic demand, thereby creating a sufficiently large expected

¹⁴⁶ CIPIH (2006), p.191

market for a given product where none exists; this makes the market somewhat more similar to a developed country market, which is aimed at strengthening incentives to invest in the R&D and manufacturing of that product.

AMCs are generally intended to exist temporarily, until a ceiling in the number of purchased treatments has been reached, after which the supplier is committed to either selling further treatments at an affordable price over the long-term, or to licensing the technology to other manufacturers.

Simulations by Berndt et al (2007) of the malaria vaccine market suggest that AMCs may be effective in stimulating substantial research towards a desired vaccine (while also being cost-effective).¹⁴⁷ Their estimates suggest that a commitment to a manufacturer of \$3.1 billion in net present value of sales would be comparable to the value of sales earned by an average of a sample of recently launched commercial products (the top-selling products among 118 new chemical entities introduced between 1990 and 1994), and as such provide a comparable incentive for R&D. In addition, they calculate that a malaria vaccine commitment that sets the price for the immunization of the first 200 million individuals at \$15 per person would cost less than \$15 per estimated year of life lost or lived with the disability (Disability Adjusted Life Years, DALYs) saved.¹⁴⁸ Obviously, this estimate is based on the assumption that the cost of vaccine development would be comparable to the average cost of development of the sample of products.

In practice, only one AMC initiative has actually been introduced. The PneumoAMC, advanced by a partnership between the Gates Foundation, the Global Alliance for Vaccination and Immunisation (GAVI) and various donor governments, has resulted in price and accelerated supply guarantees for at least two pneumococcal vaccines.¹⁴⁹ As part of the PneumoAMC, GSK and Pfizer committed to scaling up their manufacturing capacity in order to supply 30 million doses each per year for a ten year period. The initial purchase price is \$7 per dose (with half of the price paid by GAVI and developing country governments that introduce the vaccine), and after 6 million doses are sold the purchase price decreases to \$3.50 per dose. The two pneumococcal vaccines were approved by the WHO in 2010, and have experienced huge demand from developing countries (including Benin, Cameroon, the Central African Republic of Congo, Guyana, Honduras, Kenya, Mali, Nicaragua and Yemen). The goal is to reach a total of 40 recipient countries.

Furthermore, because AMCs are intended to considerably reduce the cost to developing countries to purchase new therapies, the idea is that introduction and uptake would occur at much

¹⁴⁷ Berndt E, Glennerster R, Kremer M, Lee J, Levine R, Weizsäcker G & Williams H (2007), "Advance Market Commitments for Vaccines against Neglected Diseases: Estimating Costs and Effectiveness", *Health Economics*, 16: 491

¹⁴⁸ Ibid.

¹⁴⁹ GAVI Alliance, "Pneumococcal AMC", <http://www.gavialliance.org/funding/pneumococcal-amc/> (Accessed February 2012)

faster rate than would otherwise happen (i.e. in the case of raising funds to purchase existing treatments or waiting for new treatments to be developed based on current funding arrangements). For example, Pfizer's pneumococcal vaccine reached Nicaragua in only 10 months as a result of the PneumoAMC; in comparison, one calculation estimates a 10 to 15 year lag between when new vaccines are launched in developed countries and when they are accessed in the developing world.¹⁵⁰

At this stage, the AMC model has been applied to vaccine candidates that were arguably fully developed and simply needed to be made available under the right conditions. Critics of the AMC model have raised the concern that until AMCs sponsor actual development of a vaccine or drug (not only the introduction in the market), they are not any more cost-effective than existing, and arguably simpler, purchasing procedures utilised by UNICEF and other aid agencies.

The prime target of the AMC model has been viewed by the WHO and others as late stage development (particularly Phase III clinical trials).¹⁵¹ Indeed, with later stage candidates it is possible to be concrete about technical parameters reflecting the efficacy and safety of a drug or vaccine, and about the costs and price. Therefore, it would be important for AMCs to target efforts at the R&D stage that is most cost-effective for all parties.

4.4.2 R&D treaty

The R&D treaty is a proposed mechanism which seeks to combine several push and pull elements, not least mechanisms involving preferential pricing and the development of local supply chains.

The WHO referred to the concept of an R&D treaty in the 2008 Global Strategy for Public Health Innovation and Intellectual Property, paragraph 2.3c, calling for member states to:

*...[E]ncourage further exploratory discussions on the utility of possible instruments or mechanisms for essential health and biomedical research and development, including inter alia, an essential health and biomedical research and development treaty...*¹⁵²

Following the submission of a number of different proposals from developing countries and other stakeholders,¹⁵³ the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) recommended in April 2012 report that a

¹⁵⁰ Scudellari M (2011), "Are advance market commitments for drugs a real advance?", *Nature Medicine*, 17:139

¹⁵¹ CIPIH (2006), p.89

¹⁵² WHA (2008), 61.21, 2.3(c)

¹⁵³ See, for instance, *Proposal by Bangladesh, Barbados, Bolivia and Suriname: Proposal for WHO Discussions on a Biomedical R&D Treaty* (2009), WHO, http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_R_DTreaty.pdf (Accessed March 2012); *An Essential Health and Biomedical R&D Treaty* (2011), Submission by Health Action International Global, Initiative for Health & Equity in Society, Knowledge Ecology International, Médecins Sans Frontières, Third World Network (TWN), WHO website, http://www.who.int/phi/news/phi_1_joint_submission_en.pdf (Accessed March 2012)

“global framework that combines the different elements and recommendations [on various mechanisms proposed] into a concerted mechanism” be introduced.¹⁵⁴ Such a “binding global convention” would fall under Article 19 of the WHO Constitution.¹⁵⁵ A wide range of objectives for the convention are suggested, including:¹⁵⁶

- Implementing states’ obligations under international instruments;
- Promoting R&D through delinking;
- Sustainable funding;
- Improving the coordination of R&D; and
- Enhancing innovative capacity in developing countries.

In addition, the CEWG has said that the binding convention would not represent a replacement for the existing intellectual property system, but instead “supplement where the current system does not function”.¹⁵⁷

The CEWG also recommends establishing a financing mechanism for the treaty on the basis of determined contributions by governments. Specifically, it concludes that:

*[A]ll countries should commit to spend at least 0.01% of GDP on government-funded R&D devoted to meeting the health needs of developing countries in relation to product development for those types of diseases... [and] that developing countries with a potential research capacity should aim to commit 0.05–0.1% of GDP to government-funded total health research and that developed countries should aim similarly to commit 0.15–0.2% of GDP to government-funded health research in general*¹⁵⁸.

It suggests that funds be generated from existing taxpayer revenues, new national revenue-raising measures or a new international mechanism.¹⁵⁹

As it stands, key aspects related to funding and R&D will need to be further explored to ensure the mechanism stimulates R&D into Type II and III diseases. For instance, the proposed principles of the treaty could go beyond the initial consideration of delinking R&D costs and the prices of products. A narrow approach would leave little flexibility for implementing broader approaches to delinking, such as the use of various push and pull mechanisms that do not fully separate price from cost. A broader approach would then address both the funding of R&D and the provision of access to new treatments. In other words, the R&D treaty should take into account the complex and flexible nature of R&D, as well as the manner in which it should draw on different push and pull mechanism depending on the unique circumstance of each challenge.

¹⁵⁴ WHO CEWG (2012), *Research and Development to Meet Health Needs in Developing Countries...*, p.113

¹⁵⁵ *Ibid.*, p.121

¹⁵⁶ *Ibid.* p.123

¹⁵⁷ *Ibid.*, p.122

¹⁵⁸ WHO CEWG (2012), *Research and Development to Meet Health Needs in Developing Countries...*, p.110-111

¹⁵⁹ *Ibid.*, p.123

In summary, this section has examined several existing and proposed delinking mechanisms intended to supplement the R&D process in order to improve incentives for investing in R&D into Type II and III diseases. The following section assesses the factors in these mechanisms which seem to lead to greater R&D output as well as the challenges and limitations surrounding each mechanism, using a new blueprint and set of criteria.

5 A proposed blueprint for evaluating push and pull delinking mechanisms

This section sets out a new model for measuring and assessing the mechanisms discussed in Section 4.

It should be noted that since many of these mechanisms are in the early development stages and that the biopharmaceutical R&D process is long-term in nature, it is difficult to fully assess their effectiveness and what we can expect them to achieve. More time and further development of the mechanisms is necessary for a clear picture of the most effective manner for incentivising the needed levels of research and development of affordable treatments.

Still, it is nonetheless important to be able to concretely assess these and other mechanisms as much as possible. This paper provides a set of factors for success, against which the wide range of push and pull mechanisms under discussion in international forums may be benchmarked. The criteria proposed here represent a concise and measureable framework for evaluating whether a delinking model can be expected to be effective or not. They capture the topline elements that should be present in such mechanisms, including a concrete objective, targeted problem or problems within the R&D process (including access to new medicines), effectiveness and sustainability. The first five success factors relate to the three pillar cycle of research, development and access discussed in Section 4. The final criterion, which is independent of the above factors, provides an assessment of the extent to which different mechanisms can function together and be integrated successfully.

5.1 Blueprint for success

These success factors are:

- **Accurate identification and definition of systemic gaps in the R&D process:** A given mechanism should clearly and accurately identify and target areas where the R&D model does not meet the needs of low and middle income countries. The relevant gaps range from scientific (i.e. a given stage or stages of R&D, including basic research, compound discovery, preclinical research and translational and clinical development) to financial (i.e. the ability and willingness of actors at different stages in the R&D process to invest in R&D activities) and logistical (i.e. manufacturing, availability and distribution of new products).
- **Mitigation of cost and risk of relevant R&D:** A given mechanism should accurately identify the incentives of various R&D actors to perform the needed R&D, based on the

type of R&D inputs provided and the environment in which each operates. Moreover, it should create and target rewards accordingly.

- **Leveraging of capabilities of partners to translate research into clinical outcomes:** A given mechanism should successfully lead to the creation of an end-product, milestone in the R&D process, or supporting technology.
- **Sustainability of R&D funding for specific disease areas:** A given mechanism should enjoy sustained funding over the long-term for achieving its R&D commitments.
- **Effective access to end product:** A given mechanism should involve provisions that ensure affordable prices of medicines developed through the mechanism. In addition, to ensure patients actually access the medicine, it should involve logistical and administrative arrangements for its delivery, as well as coordination with local health care authorities to develop a regime for patient compliance and disease prevention.
- **Compatibility with other mechanisms:** A given mechanisms is able to function in tandem with other push and pull mechanisms targeting different aspects of the R&D process, and does not erode the effectiveness of these other mechanisms.

5.2 Assessing push and pull delinking mechanisms

Based on these factors, it is possible to assess the potential for success among the mechanisms discussed in the previous section. A table summarising this section may be found in the Appendix.

Open databases

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; open databases target scientific gaps, including basic research and preclinical and translational R&D, as well as associated financial gaps.
- **Mitigation of cost and risk of relevant R&D:** Yes; open databases reduce the cost of discovering essential compounds and technologies.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Yes, although open databases are still in the early stages; thus far, there has been some success in increasing research collaboration that may lead to translation of research into clinical outcomes.
- **Sustainability of R&D funding for specific disease areas:** Not applicable; funding is not an essential component of the success open databases.
- **Effective access to end product:** Yes; licenses involving R&D or product supply to least developed countries must take place on a royalty-free basis.
- **Compatibility with other mechanisms:** Yes; open databases complement other mechanisms targeting the research stage, as well as the development and access stages.

R&D grants

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; R&D grants fill various scientific gaps, including basic research (for example, NIH grants for university research) and clinical development (for example, from government development agencies and philanthropic foundations) by providing the financial capability to conduct these types of R&D.
- **Mitigation of cost and risk of relevant R&D:** Yes; R&D grants mitigate the cost and risk of conducting R&D at a given stage. However, there are important exceptions; additional funding support may be necessary to fully fund certain R&D activities, particularly clinical development, manufacturing and market authorisation.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Yes; R&D grants have been one of the most successful models for basic R&D activities, and are the predominant funding model used by successful PDPs.
- **Sustainability of R&D funding for specific disease areas:** No; the frequency and amount of R&D grants depend on the financial capability and political will of public and philanthropic donors.
- **Effective access to end product:** No, although there are important exceptions. For grants aimed at product development, many donors require the affordable delivery of such products to low and middle income countries; however, such a requirement is not explicitly part of the grant model.
- **Compatibility with other mechanisms:** Generally, yes; however, there are important exceptions, including grants with conditions on the delivery of end products which may not be compatible with certain mechanisms aimed at access, such as AMCs and manufacturer pricing programmes.

R&D prizes

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; R&D prizes target various scientific gaps, including basic research and the development of preclinical compounds, which exist due to gaps in financial support for these types of R&D.
- **Mitigation of cost and risk of relevant R&D:** Overall, no; this is because for the majority of the prize models aimed at Type II and III diseases, proposed or in existence, financial support is only afforded to ‘winners’; those who are not awarded are not afforded any mitigation of the costs of R&D, and therefore bear all of the risk of engaging in that R&D. In addition, the amount awarded through a prize is not necessarily sufficient to cover all of the R&D costs.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Generally no; at this point, there have been very few tangible outcomes aimed at Type II and III diseases.

- **Sustainability of R&D funding for specific disease areas:** No; as with grants, the frequency and amount of R&D prizes depend on the financial ability and political will of public, philanthropic and private donors.
- **Effective access to end product:** Generally speaking, no; thus far, the prize model has only led to milestones in the R&D process or supporting technologies. Prize models aimed at the development of end-products are expected to involve commitments to delivering an affordable product to low and middle income countries, however no such prize is in use at this time.
- **Compatibility with other mechanisms:** Generally, no. Prizes entail the possibility of operating in tandem with other mechanisms aimed at the research and development stages, but whether they actually do or not depends on implementation (which is so far limited). However, prizes which fully separate the price of products from the cost of R&D may erode mechanisms aimed at access, such as AMCs and manufacturer pricing programmes.

R&D tax credits

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; R&D tax credits target general financial incentives to invest in any stage of the R&D process.
- **Mitigation of cost and risk of relevant R&D:** Generally speaking, no; tax credits are only available to profit-making entities, and are predicated on the existence of a large paying market, which for the most part does not exist for R&D into Type II and III diseases.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Overall, no; tax credits for R&D into Type II and III diseases have only had a limited application so far, and where they have been introduced, such as in the UK, they have not been shown to be successful. A programme in the US is in the initial stages; therefore it is difficult to judge its success at this time.
- **Sustainability of R&D funding for specific disease areas:** No; the availability of public funding for tax credits depends on political will and the government budget.
- **Effective access to end product:** Not applicable; R&D tax credits specific to Type II and III diseases are thus far not linked to the delivery of the medicines to low and middle income countries.
- **Compatibility with other mechanisms:** Yes; R&D tax credits have the ability to complement other mechanisms targeting the research stage, as well as the development and access stages.

Orphan drug-like schemes (including additional exclusivity and priority review vouchers)

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; orphan drug-like schemes target general financial incentives to conduct R&D at any stage of the process. They also reduce the burden of market authorisation and preparing the approval dossier, and as such partially fill gaps in the clinical development stage.
- **Mitigation of cost and risk of relevant R&D:** Generally speaking, no. This is because orphan drug-like schemes only target profit-making entities, and the headline component of such schemes, additional exclusivity, is predicated on the existence of a large paying market, which for the most part does not exist for R&D into Type II and III diseases.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Not applicable; although such schemes have largely been successful in producing medicines and R&D into rare diseases, at this point their usefulness in stimulating R&D into Type II and III diseases is unproven.
- **Sustainability of R&D funding for specific disease areas:** Yes; this is because generally speaking no additional funding is required to operate such schemes.
- **Effective access to end product:** No; thus far, no such schemes are in existence.
- **Compatibility with other mechanisms:** Yes; orphan drug-like schemes would be able to complement other mechanisms targeting the research and development stages, as well as those aimed at access.

Patent pools

- **Accurate identification and definition of systemic gaps in the R&D process:** Generally speaking, no. Patent pools are aimed at the sharing and licensing of essential patents; however, there do not seem to be a great deal of demand for such patents, at least at this point in time. Nevertheless, there may be important exceptions, including for incremental modifications to existing products as well as in the field of vaccines, although there areas are relatively untested.
- **Mitigation of cost and risk of relevant R&D:** Overall, no. So far, patent pools only serve to mitigate the cost of manufacturing generic drugs. However, if there were to be demand for essential patents, patent pools would reduce the cost of drug discovery and translation to an actual product.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Thus far, no. Patent pools are still in the very early stages; however thus far, they have not produced any tangible clinical outcomes with regards to new or improved products treating Type II and III diseases.
- **Sustainability of R&D funding for specific disease areas:** Not applicable; funding is not an essential component for the success of patent pools.
- **Effective access to end product:** Not applicable; at this point, there is no evidence to suggest that collaboration in the scope of patent pools involves special arrangements for pricing and delivery of end products resulting from the pool.

- **Compatibility with other mechanisms:** No, not in their current use to promote the manufacturing of generic drugs, since this overrides the development stage and hence, also overrides other mechanisms aimed at development as well as those supporting access.

Product development partnerships (PDPs)

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; PDPs fill various scientific gaps, particularly translation of research into actual products and their clinical development, by providing the financial capability and collaboration to carry out these types of R&D.
- **Mitigation of cost and risk of relevant R&D:** Yes; PDPs mitigate the cost and risk of product development. However, there are also important exceptions; as with grants, additional funding and other types of support may be necessary to fully fund clinical development, manufacturing and market authorisation.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Yes; PDPs have been very successful in the last ten years in leading clinical development, and in many cases production and delivery, of new products targeting Type II and III diseases.
- **Sustainability of R&D funding for specific disease areas:** No. This is because most PDPs rely heavily on grants from public and philanthropic donors, as well as on contributions by industry, all of which are affected by financial capabilities and political will (to varying degrees). The most recent data shows that funding to PDPs is somewhat volatile, particularly from government development agencies and philanthropic donors such as the Gates Foundation.
- **Effective access to end product:** Yes; PDPs generally involve affordable pricing of end products as well as delivery arrangements.
- **Compatibility with other mechanisms:** Generally, yes; however, there are important exceptions, including PDPs or funding with conditions on the delivery of end products which may not be compatible with certain mechanisms aimed at access, such as AMCs.

Advanced market commitments (AMCs)

- **Accurate identification and definition of systemic gaps in the R&D process:** Yes; AMCs target the financial incentives of R&D entities, mainly biopharmaceutical companies, to fully develop, manufacture, market and deliver a new product to low and middle income countries.
- **Mitigation of cost and risk of relevant R&D:** Yes; although they have had limited application thus far, they have been successful in replicating market incentives (i.e. providing a profit to sponsors of a new product for a certain period of time).
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Yes; although the use of AMCs is still in the early stages, thus far they have successfully enabled end-stage development, production and marketing of two vaccines.

- **Sustainability of R&D funding for specific disease areas:** Yes; although the frequency and amount of funding available to AMCs depend in part on the financial capability and political will of government and philanthropic donors, AMCs are also heavily reliant on other entities dedicated to the express purpose of providing funding to them (e.g. the GAVI Alliance).
- **Effective access to end product:** Yes; AMCs enable the production and generally, the supply and distribution, of affordable end products to low and middle income countries.
- **Compatibility with other mechanisms:** Yes; AMCs complement other mechanisms targeting the development stage, as well as those aimed at research.

R&D treaty

- **Accurate identification and definition of systemic gaps in the R&D process:** Not applicable at this time; the treaty is still in the proposal stage and therefore there is no evidence to suggest that it will accurately target systemic gaps.
- **Mitigation of cost and risk of relevant R&D:** Not applicable at this time, given that the treaty is still in the proposal stage.
- **Leveraging of capabilities of partners to translate research into clinical outcomes:** Not applicable at this time, given that the treaty is still in the proposal stage.
- **Sustainability of R&D funding for specific disease areas:** No. The treaty relies on a commitment by countries to raise funding, including through taxation, in order to meet obligations under the treaty; developments on this point are subject to the political will to agree to this level of commitment as well as be able to meet funding obligations over the long-term.
- **Effective access to end product:** Generally, yes. The affordable access and delivery of end products to low and middle income countries is a key principle of the treaty; however, it remains to be seen how this will occur in practice (it will depend on the type of delinking mechanisms which are implemented as part of the treaty).
- **Compatibility with other mechanisms:** Generally, no. It depends on the push and pull mechanisms that would be promoted as a result of the treaty; however, if it promotes delinking mechanisms which fully separate the price of products from the cost of R&D, it may erode mechanisms aimed at access, such as AMCs and manufacturer pricing programmes.

The matrix in Table 8 provides a concise representation of the above assessment.

Table 8: An assessment of push and pull delinking mechanisms using the Blueprint for success

R&D stage	Research		Development		Access	
Success factor	Accurate identification and definition of systemic gaps in the R&D process	Mitigation of cost and risk of relevant R&D	Leveraging of capabilities of partners to translate research into clinical outcomes	Sustainability of R&D funding for specific disease areas	Effective access to end product	Compatibility with other mechanisms
Open databases	✓	✓	✓	NA	✓	✓
R&D grants	✓	✓	✓	✗	✗	✓
R&D prizes	✓	✗	✗	✗	✗	✗
R&D tax credits	✓	✗	✗	✗	NA	✓
Orphan drug-like schemes, including additional exclusivity & priority review vouchers	✓	✗	NA	✓	✗	✓
Patent pools	✗	✗	✗	NA	NA	✗
Product development partnerships (PDPs)	✓	✓	✓	✗	✓	✓
Advanced market commitments (AMCs)	✓	✓	✓	✓	✓	✓
R&D treaty	NA	NA	NA	✗	✓	✗

Source: Pugatch Consilium (2012)

✓ = success factor exists; ✗ = success factor does not exist; NA = success factor is not relevant or is unknown at this point

This assessment here draws on empirical evidence and a pragmatic analysis of the R&D process. It is important to keep in mind that the objective of the mechanisms discussed here is not only to stimulate R&D but to fully develop and supply new products aimed at Type II and III diseases. In order to create a complete cycle of R&D, i.e. from drug discovery all the way to access, effective mechanisms need to be applied at each stage in the process. Figure 6 provides an

illustration of how a full R&D cycle could be incentivised using a mix of push and pull mechanisms.

Figure 6: Integration of delinking mechanisms in a full cycle of biopharmaceutical innovation



Source: Pugatch Consilium (2012)

6 Conclusions & recommendations

6.1 Four underlying questions and their answers

This report has sought to answer four key questions, which were raised in the introduction.

First, which factors incentivise the creation of new and affordable treatments aimed at neglected and tropical diseases and specific Type I and Type II diseases, including malaria and tuberculosis? The report has highlighted that many scientific, financial, regulatory and logistical factors play important roles at different stages in the R&D process. With regards to financial incentives to engage in R&D into these diseases, this report has emphasised the role of various delinking mechanisms.

Second, to what extent does the evolving model of biomedical and biopharmaceutical R&D provide these factors, and where are additional mechanisms needed to enhance it? The report has argued that while the existing biopharmaceutical R&D model is undergoing a process of evolution to fit new conditions, demands and capabilities, the underlying principles behind the model remain sound. Nevertheless, the report has identified several systemic gaps in the model for Type II and III diseases that should be further addressed in order to create an effective forward pathway. They include: insufficient dedication to basic research efforts aimed at R&D into Type II and III diseases; inadequate financial and commercial incentives for further investment in these diseases during the applied research and development stages; and the possibility that even if developed, these drugs may still be too costly for populations in developing countries.

Third, which mechanisms exist or are being proposed to enhance and support neglected disease R&D, including those which delink the cost of R&D from the price of medicines? The report has provided an overview of several key delinking models which are applied in different stages of biopharmaceutical innovation, including R&D tax credits, open databases or compound libraries, R&D grants, product development partnerships, patent pools, orphan drug-like schemes, advanced market commitments, R&D prizes and an R&D treaty.

Fourth, based on what we know about these mechanisms and of the R&D process, is there a set of criteria for success that may be used by policymakers and stakeholders to assess these and other initiatives? The report has drawn on this analysis to build a blueprint for success, which identifies several topline factors for the success of mechanisms and proposals aimed at incentivising R&D into Type II and III diseases. Moreover, it provides an assessment of the push and pull mechanisms analysed using this framework. Among other findings, the existing evidence on delinking mechanisms suggests that certain mechanisms – most notably R&D prizes

and patent pools – may not be as effective as suggested, particularly compared to other mechanisms analysed in this report. Specifically, open compound databases, R&D grants, product development partnerships and advanced market commitments have all demonstrated success in stimulating significant R&D activities in key stages in the R&D process. Finally, the report suggests that delinking models are constantly evolving, as new approaches and mechanisms for stimulating R&D into these diseases are discussed and introduced.

6.2 The way forward

In conclusion, the way forward is to apply highly targeted, yet complementary, push and pull delinking mechanisms in the key stages of the biopharmaceutical R&D process. The key objective should be to identify effective mechanisms which may be integrated and together drive a complete cycle of research, development and access to new medicines.

Implementing a high-level, yet pragmatic method for identifying the most appropriate mechanisms, such as the matrix proposed in this report, should help provide a more coherent and practical framework for evaluating and scaling up efforts in the future.

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Appendix

Table 9: An assessment of push and pull delinking mechanisms using the Blueprint for success – explanation of scoring

Open databases

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Scientific gaps (basic research and preclinical and translational R&D), associated financial gaps
Mitigation of cost and risk of relevant R&D	✓	Reduce the cost of discovering essential compounds and technologies
Leveraging of capabilities of partners to translate research into clinical outcomes	✓	In early stages; some success in increasing research collaboration that may lead to translational R&D
Sustainability of R&D funding for specific disease areas	NA	Funding is not an essential component for success
Effective access to end product	✓	Royalty-free licences for R&D and products aimed at least developed countries
Compatibility with other mechanisms	✓	Complements other mechanisms targeting the research stage, as well as the development and patient access stages

R&D grants

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Scientific gaps, from basic research to clinical development; associated financial gaps
Mitigation of cost and risk of relevant R&D	✓	Exception: additional funding support may be necessary to fully fund clinical development, manufacturing and market authorisation
Leveraging of capabilities of partners to translate research into clinical outcomes	✓	One of most successful models for basic R&D activities, and the predominant funding model used by successful PDPs
Sustainability of R&D funding for specific disease areas	✗	Frequency and amount of R&D grants depend on financial capability and political will of public and philanthropic donors
Effective access to end product	✗	Not explicitly part of model; however grants aimed at PDPs often require affordable delivery
Compatibility with other mechanisms	✓	Complements other mechanisms targeting the research and development stages; however in some cases grants with conditions on the delivery of the end product may not be compatible with certain mechanisms aimed at access, e.g. AMCs and manufacturer pricing programmes

R&D prizes

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Scientific gaps (basic research, preclinical development); financial gaps
Mitigation of cost and risk of relevant R&D	✗	Funding is given only to winners in majority of models; no mitigation of costs for non-winners, thus they bear all of the risk; also award amount not necessarily sufficient to cover total cost of R&D
Leveraging of capabilities of partners to translate research into clinical outcomes	✗	Few tangible outcomes aimed at Type II and III diseases
Sustainability of R&D funding for specific disease areas	✗	Frequency and amount depend on financial ability and political will of public, philanthropic and private donors
Effective access to end product	✗	No programmes aimed at end products thus far
Compatibility with other mechanisms	✗	Possibility of operating in tandem with other mechanisms aimed at research and development stages, but depends on implementation; may erode mechanisms aimed at access, e.g. AMCs and manufacturer pricing programmes

R&D tax credits

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Financial gaps
Mitigation of cost and risk of relevant R&D	✗	Only available to profit-making entities; predicated on existence of a large paying market
Leveraging of capabilities of partners to translate research into clinical outcomes	✗	Limited application thus far; seem to show early success in US
Sustainability of R&D funding for specific disease areas	✗	Availability of public funding for tax credits depends on political will and government budget
Effective access to end product	NA	No evidence thus far that they involve such commitments
Compatibility with other mechanisms	✓	Complements other mechanisms targeting the research stage, as well as the development and access stages

Orphan drug-like schemes, including additional exclusivity and priority review vouchers

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Financial gaps, regulatory gaps
Mitigation of cost and risk of relevant R&D	✗	Only available to profit-making entities; exclusivity predicated on existence of a large paying market
Leveraging of capabilities of partners to translate research into clinical outcomes	NA	Non-existent, usefulness unproven

Sustainability of R&D funding for specific disease areas	✓	No additional funding required
Effective access to end product	✗	No evidence thus far
Compatibility with other mechanisms	✓	Complements other mechanisms targeting the research and development stages, as well as the access stage

Patent pools

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✗	Not aimed at significant scientific or financial gaps (little demand at this point for essential patents; some potential for incremental modifications or vaccines)
Mitigation of cost and risk of relevant R&D	✗	So far, patent pools only serve to mitigate the cost of manufacturing generic drugs
Leveraging of capabilities of partners to translate research into clinical outcomes	✗	Thus far no tangible clinical outcomes with regards to new or improved products
Sustainability of R&D funding for specific disease areas	NA	Funding is not an essential component for success
Effective access to end product	NA	No evidence thus far that they involve such commitments
Compatibility with other mechanisms	✗	In current use, may override development stage and hence, mechanisms aimed at development and access

Product development partnerships

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Scientific gaps, particularly translational and clinical development; associated financial gaps
Mitigation of cost and risk of relevant R&D	✓	Exception: additional funding support may be necessary to fully fund clinical development, manufacturing and market authorisation
Leveraging of capabilities of partners to translate research into clinical outcomes	✓	Very successful in the last ten years in leading clinical development, and in many cases production and delivery, of new products
Sustainability of R&D funding for specific disease areas	✗	Most rely heavily on grants and contributions by industry, which are affected by financial capabilities and political will (to varying degrees); confirmed by 2010-2011 data
Effective access to end product	✓	Generally involve affordable pricing of end products as well as delivery arrangements
Compatibility with other mechanisms	✓	Complements mechanisms targeting the research stage; however in some cases PDPs or funding with conditions on the delivery of the end product may not be compatible with certain mechanisms aimed at access, e.g. AMCs

Advanced market commitments

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	✓	Scientific gaps (clinical development), Financial gaps
Mitigation of cost and risk of relevant R&D	✓	Limited application thus far; successful in replicating market incentives (i.e. providing a profit)
Leveraging of capabilities of partners to translate research into clinical outcomes	✓	Successfully enabled end-stage development, production and marketing of two vaccines
Sustainability of R&D funding for specific disease areas	✓	Although dependent on financial capability and political will of donors, heavily reliant on other dedicated entities (e.g. GAVI Alliance)
Effective access to end product	✓	Enable production and generally, the supply and distribution, of affordable end products
Compatibility with other mechanisms	✓	Complements other mechanisms targeting the development stage, as well as mechanisms aimed at research

R&D treaty

Success factor	Rating	Explanation
Accurate identification and definition of systemic gaps in the R&D process	NA	Still in proposal stage, therefore no evidence to suggest it will accurately target systemic gaps
Mitigation of cost and risk of relevant R&D	NA	Still in proposal stage
Leveraging of capabilities of partners to translate research into clinical outcomes	NA	Still in proposal stage
Sustainability of R&D funding for specific disease areas	✗	Not reasonable to assume political will for sufficient international commitment to meet funding needs
Effective access to end product	✓	Key principle of treaty; depends on mechanisms implemented
Compatibility with other mechanisms	✗	Depends on mechanisms implemented; may erode mechanisms aimed at access, e.g. AMCs and manufacturer pricing programmes

Source: Pugatch Consilium (2012)