pugatchconsilium

CHARTING THE COURSE TO SUSTAINABLE INNOVATION IN NEGLECTED DISEASES GLOBALLY

An "Optimization Model" for the Use of R&D Incentives –
September 2017

This report was commissioned by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). The views represented here are those of the authors only.

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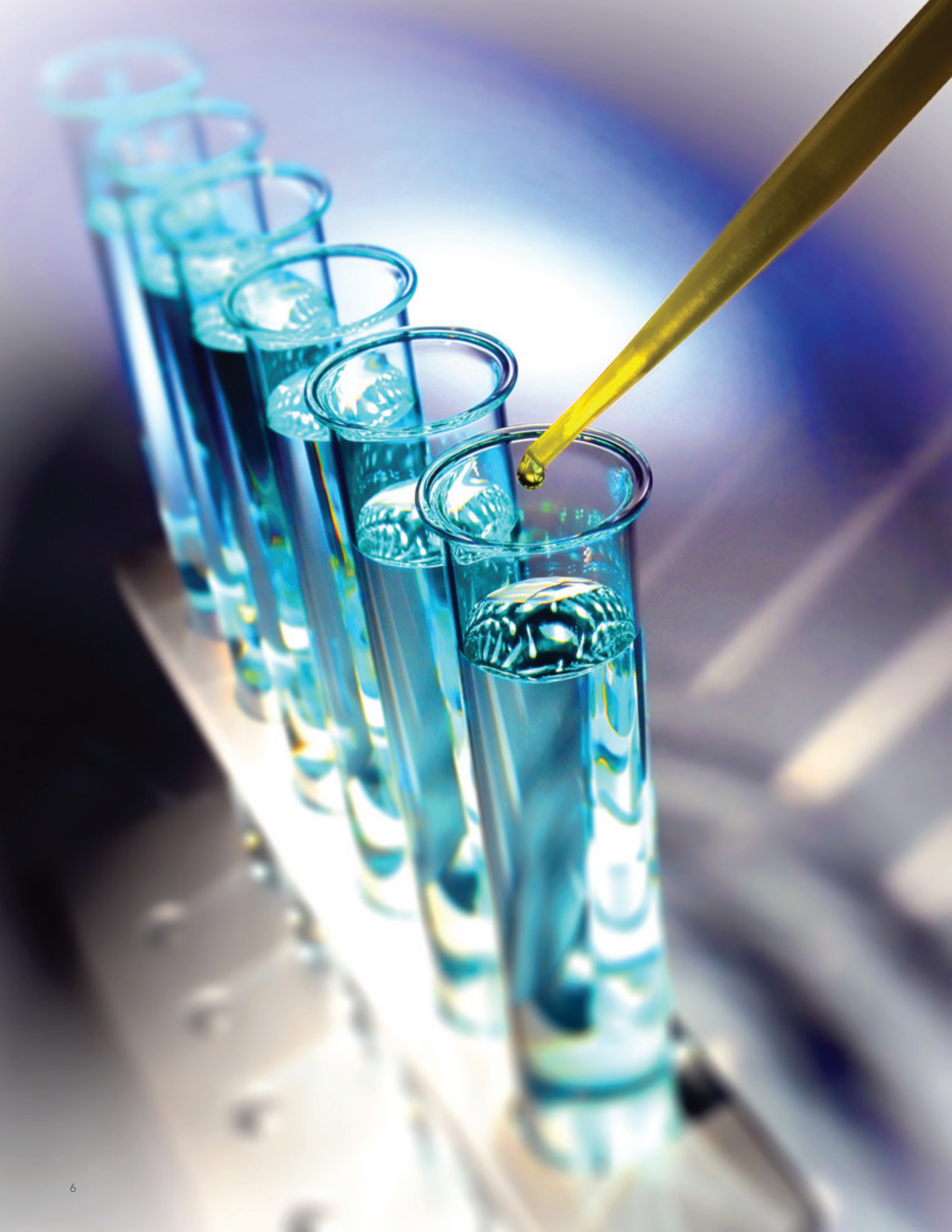


LIST OF ABBREVIATIONS

AMC	Advanced market commitment
AMR	Antimicrobial resistance
ARV	Antiretroviral drug
CEWG	WHO Consultative Expert Working Group on Research and Development: Financing and Coordination
CRO	Contract research organization
DNDi	Drugs for Neglected Diseases Initiative
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
G-FINDER	Global Funding of Innovation for Neglected Diseases
GHIT	Global Health Innovative Technology
GHIF	Global Health Innovation Fund
HAT	Human African Trypanosomiasis
HCV	Hepatitis C Virus
HIV/AIDS	Human immunodeficiency virus/Acquired immunodeficiency syndrome
IP	Intellectual Property
LMIC	Lower-middle-income country
LDC	Least developed country
MMV	Medicines for Malaria Venture
MNC	Multinational company
MPP	Medicines Patent Pool
NGO	Non-governmental organization
NIH	US National Institutes of Health
NIAID	US National Institute of Allergy and Infectious Diseases
NTD	Neglected and tropical diseases
PDP	Product Development Partnership
PHTI	Pediatric HIV Treatment Initiative (formed by UNITAID, DNDi and MPP)
PRI	Program Related Investments
PRV	Priority Review Voucher
R&D	Research and Development
SME	Small and Medium Enterprise
S&T	Science and Technology
TB	Tuberculosis
WHO	World Health Organization
TDR	UNICEF/UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases
WIPO	World Intellectual Property Organization

EXECUTIVE SUMMARY

In 2012 Pugatch Consilium authored *Assembling the pharmaceutical R&D puzzle for needs in the developing world*, which evaluated the opportunities and challenges associated with proposed initiatives aimed at stimulating research and development (R&D) of drugs, vaccines and diagnostics targeting neglected diseases (or diseases that primarily affect the developing world).

Five years on, the international context has evolved in terms of the expansion of international stewardship efforts and advances in R&D. At the same time, the challenges of new epidemics like the Ebola and Zika virus outbreaks and the growth of antimicrobial resistance (AMR) have buttressed a re-emergence of global discussions on innovative incentive strategies for neglected disease R&D, notably in the context of the recent UN High Level Panel on Access to Medicines. Though also wider in focus, the Panel's report (issued in September 2016) proposes use of many of the same R&D incentives and mechanisms aimed at "delinking" (or mitigating the cost of R&D and ensuring access to end products) that were examined in our 2012 study, as well as highlights additional proposals.

This study updates and expands the analysis from 2012 to evaluate newly proposed mechanisms against a "Blueprint for Success" as well as tracks progress made since then. Beyond this, there remains a need to move from a kind of "laundry list" of incentives and mechanisms to a more coherent and strategic "playbook" for leveraging these platforms that optimizes limited funds and R&D actors and in a rapid manner, in order to deliver new treatments when and where they are needed most. In this light, a third and core component of the study is the development of one potential model for optimizing the use of the different proposed R&D incentives and mechanisms in tandem with existing market-based incentives such that new R&D synergies are created.

1. Mapping ongoing efforts to meet R&D needs for neglected diseases: The Blueprint for Success

Eleven major proposed and existing R&D mechanisms are classified and examined in light of four crucial success factors for neglected disease R&D on the following page.

Mapping success factors of proposed R&D incentives and mechanisms for neglected diseases using the Blueprint for Success

	Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
	Is it sustainable and/ or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Grants	Public-philanthropic	Market-based, economic	Internal/cooperative or competitive model	IP retained unless donor sets IP or price conditions
	Depends on donor will; mostly ad-hoc	For early stage research	Top down identification of gaps	
R&D tax credits	Public	Market-based, economic	Internal/cooperative or competitive model	IP retained; market-based pricing
	Depends on political will, but established and scalable (proportional to costs)	More appealing to big entities	Applies to R&D generally	Via IP incentives or additional access scheme
Financial instruments/ Program Related Investments (PRIs)	Public-philanthropic	Market-based, economic	Internal/cooperative or competitive model	IP retained but IP and price conditions for select markets
	Dependent on donor will but deeper investment			
R&D prizes	Public-philanthropic	Non-market based, monetary	Crowdsourcing, competitive model	IP rights may not be retained
	Depends on donor will	Only for winners, amount set in advance	Top down identification of gaps	Depends greatly on success of previous factors
Advanced Market Commitments	Public-philanthropic	Market based, monetary	Internal/cooperative or competitive model	IP may be retained; price conditions/agreement
	Depends partially on donor/ partner will	Partially, does not necessarily cover full costs		
Extended or transferable IP rights/ exclusivity	N.A.	Market-based, economic	Internal/cooperative or competitive model	IP protection Market price
	Depends on political will	Depends on strength of IP environment		Enable innovative drug development and launch
International harmonization efforts	N.A.	Economic savings (easier procedures)	Any	IP protection; Market price
	Depends on political will			
Priority review vouchers	N.A.	Market-based (accelerate market benefits)	Any	IP protection Market price
	As long as regulatory resources available	Resources for R&D if voucher is sold	If review is adequately targeted	Drug faster to market
Collaborative research and data pooling/ sharing	Private (business), research entities	Economic savings (faster discovery), motivational	Cooperative (mostly private and public), crowdsourcing, in some cases open access and open source	IP ownership retained (except open source); Free licensing obligation to LDCs in some cases
	Dependent on data owner's will/ relatively limited operational cost			Dependent on type of arrangement
Patent pools	Private (business), public research entities	Motivational	Crowdsourcing, open access	Voluntary licenses, with potential limits on royalties, depending on forum
	Dependent on patent owner will	Only partially linked to early R&D phases	Potentially, if R&D is targeted	No guarantee of developing new products
PDPs	Private (business), public, philanthropic	Market-based, economic savings, motivational	Internal and open sources, Cooperative	Varies; IP and pricing conditions may be set
	Various funding sources but limited overall	Risk spreading, cost reduction	Pre-clinical through to registration/launch	PDP-specific arrangements

Financing-based incentive Regulatory incentive Operational incentive
Significant challenges Mixed or partial environment Relatively more promise in a given area

Source: Pugatch Consilium

Key findings from the Blueprint for Success

- **No single mechanism is a "silver bullet" for stimulating neglected disease R&D**
  New proposed R&D incentives and delinking mechanisms are most effective when applied in combination with other mechanisms, including existing market-based R&D incentives.

- **Financing-based mechanisms display the most significant limitations**
  Some mechanisms are simply not congruent with the level of funds needed for biomedical R&D, on top of being dependent on donor will and capacity. Certain mechanisms may be able to act in a bridging or "top up" function for existing R&D incentives. The utility of mechanisms that are more heavily defined or top-down appears to be limited to highly targeted circumstances.

- **Regulatory and operational mechanisms are taking on increasing relevance for addressing key gaps in neglected disease R&D**
  Regulatory and operational approaches for reducing R&D costs, linking partners and spreading risk appear to hold a great deal of promise for closing R&D gaps, particularly in the middle to later stages of the R&D cycle. As with financing-based instruments these approaches work best in combination but may entail relatively lower transaction costs.

- **IP maintains an integral role in R&D incentives and delinking mechanisms and in itself does not represent a barrier to access**
  IP rights are retained in varying degrees in many mechanisms, acting as platforms for commercialization and knowledge diffusion and incentives for engaging public and private R&D partners. Most importantly, for those mechanisms that target production of a tangible, complete treatment ready for launch, more often than not IP-based transactions play a crucial role. At the same time, removing IP (or requiring it be waived) does not necessarily ensure a given medicine will be accessible, and hence can represent a key barrier to making new treatments developed through R&D mechanisms available to patients.

2. Tracking progress in neglected disease R&D: The state of play and lessons learned on the ground

Reviewing a sample of empirical evidence on the level of actual R&D taking place it is clear that the rising tide of international efforts aimed at stimulating neglected disease R&D over the past two decades has paid off. Though data varies depending on how investment is measured, the past few years have been no exception, with unprecedented momentum in investment and collaboration on neglected disease R&D and expansion into new disease areas and unresolved needs. Recent years have also seen a surge in the role of the private sector, with the annual G-FINDER survey reporting that spending on neglected disease R&D by multinational companies and biotech SMEs has grown annually for the past four years. In turn, though still a small share of total R&D, translational R&D and clinical development of tangible neglected disease treatments, vaccines and diagnostics has risen and patients in developing countries are benefitting from advance access. Where possible these products are also being launched in market in the developing world.

Still, it goes without saying that much more is required to continue to close the R&D gaps for the developing world. Ensuring a higher rate of later phase clinical development and launch of products is essential. Expanding R&D efforts to cover more LDCs; remaining neglected diseases and populations; and new, looming challenges represent some of the top priorities.

3. A model for optimizing the use of R&D incentives and delinking mechanisms

To even more effectively leverage the investment and R&D instruments under discussion today, it is crucial to understand when and how R&D incentives and mechanisms aimed at neglected diseases might most effectively be applied. How specifically can R&D incentives and delinking mechanisms work in tandem with existing market-based incentives to create new synergies for neglected disease R&D? For instance, can PDPs lend additional operational or financial resources that facilitate existing clinical research efforts by research-based biopharmaceutical companies moving forward at a faster pace? Can voluntary patent pools and knowledge-sharing platforms enable wider licensing and use of IP rights to drive various pipelines – including, but not limited to, new, neglected disease applications?

This study presents a 3-layered model based on which R&D partners, governments, international institutions and other key stakeholders can optimize the use of incentives and mechanisms to effectively create momentum to advance R&D from discovery to full development and deliver novel treatments and technologies where they are needed most.

Layer 1: The R&D life-cycle perspective

In order to ensure that R&D actually takes place and that an end product is produced and made available, it is important that each mechanism be viewed not as a stand-alone solution but as an element of a sustainable framework that addresses all components of the R&D life-cycle. It therefore crucial to have a picture of which mechanisms stand out as enabling the early phases of R&D, which ones particularly focus on later stage development including clinical research, and finally those that mainly target registration, production and delivery.

- **Principle 1: Pre-defined and highly targeted funding mechanisms and collaborative innovation platforms mainly drive upstream research**
  Mechanisms providing highly targeted and pre-defined financial support as well as those providing non-financial support generally operate best in the upstream phase of the R&D process, including basic research and drug discovery as well as development in the laboratory. Certain mechanisms have a more proven track record for accelerating drug discovery and lead optimization and even early drug development, such as research grants and data sharing/pooling platforms like WIPO Re:Search and public-private "open labs".

- **Principle 2: Downstream R&D requires more flexible funding mechanisms and market-based platforms**
  Given the high costs of later stage drug development, scale-up, registration and launch of an actual product, mechanisms that are relatively less defined and limited in resources tend to support downstream R&D better than narrower mechanisms. Market-based incentives, including reducing regulatory costs and commercial or IP models that allow innovators to determine the focus and scale of investment, are particularly tailored for downstream R&D.

- **Principle 3: Models with a substantial market-based component remain the key incentive for clinical research**
  Who funds and carries out clinical trials – one of the most costly phases of the biopharmaceutical R&D life-cycle – still represents an important challenge in the neglected disease R&D puzzle. PDPs remain one of the few concrete platforms that focus specifically on clinical development by leveraging partnerships with industry, public and private actors and philanthropic entities. As a result, the research-based biopharmaceutical industry operating primarily on a market-based model continues to play a central role in enabling clinical research on neglected diseases. R&D mechanisms that complement, rather than seek to fully replace, the market-based model through additional funding, incentives and other resources stand the best chance of providing the necessary impetus for companies to invest in clinical research that would not have otherwise taken place or at a much more rapid pace.

Understanding where incentives and delinking mechanisms function best throughout the R&D life-cycle

	Research & discovery	*Preclinical development*	*Clinical development*		*Registration*	*Post-marketing & delivery*
Collaborative research	Enabling	Somewhat enabling				
Research data pooling/sharing	Enabling	Enabling	Somewhat enabling	Somewhat enabling		
Grants	Enabling	Enabling	Somewhat enabling			
Financial instruments/PRIs		Enabling	Somewhat enabling	Somewhat enabling	Somewhat enabling	Somewhat enabling
R&D prizes	Somewhat enabling	Enabling				Somewhat enabling
International regulatory harmonization			Somewhat enabling	Somewhat enabling	Enabling	
Priority review vouchers			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Advanced Market Commitments				Somewhat enabling	Enabling	Enabling
R&D tax credits			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Conventional market/IP-based model	Somewhat enabling	Somewhat enabling	Enabling	Enabling	Enabling	Enabling
Extended or transferable IP rights/exclusivity			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Patent pools				Somewhat enabling		Enabling
PDPs	Somewhat enabling	Enabling	Enabling	Enabling	Enabling	Enabling

Financing-based incentive Regulatory incentive Operational incentive

Source: Pugatch Consilium

- **Principle 4: IP rights are not antithetical to neglected disease R&D and delinking mechanisms**
  On top of the conventional IP-derived R&D model which runs across the R&D life-cycle, at each major stage IP-reliant models remain a relevant and even integral component in several R&D incentives and delinking mechanisms.

Layer 2: Maximizing the strengths of R&D players

It is also important to identify how to maximize the role of various R&D actors in using different R&D mechanisms and incentives. Which mechanisms best leverage each entity's natural capacity, existing incentive structure and ongoing R&D efforts? Grants, R&D prizes, data pooling and other collaborative research platforms tend to help activate R&D players that are focused primarily on basic research and drug discovery, including academic and research institutions and the open source community. Small and medium-sized biotechnology firms straddle both the upstream and downstream R&D phases and may benefit from the above mechanisms as well as financial instruments like equity and program-related investments and R&D tax credits. Downstream-related mechanisms like PDPs, patent pools, AMCs and regulatory streamlining, appear to best leverage the capacity and work of private entities – biotech firms as well as multinational research-based biopharmaceutical companies.

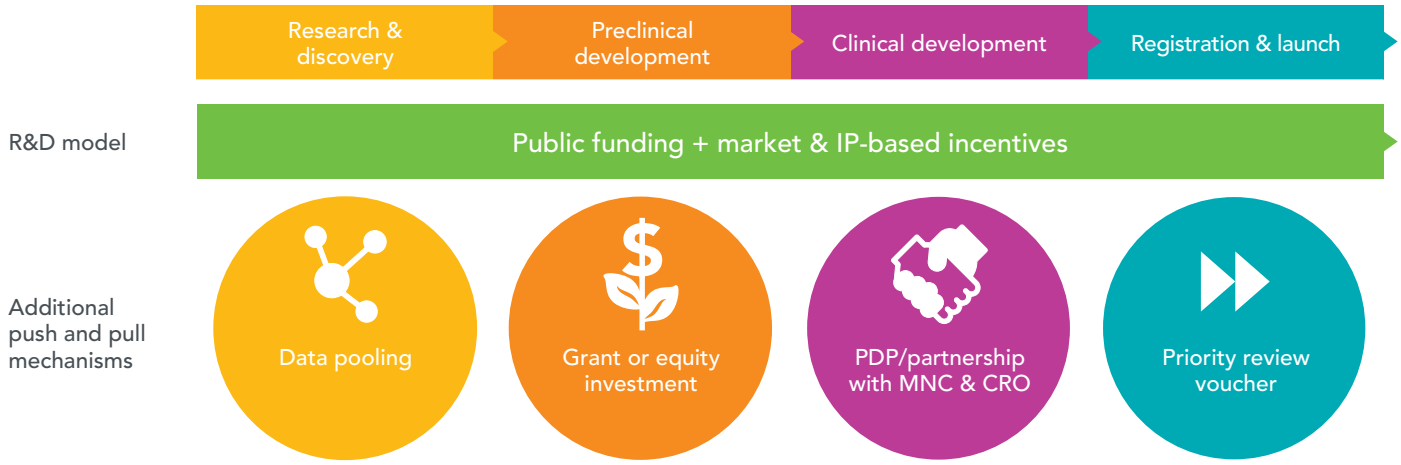
Layer 3: Ensuring alignment with the desired level of innovation

Finally, whether a given mechanism is appropriate depends on the specific R&D needs of the target disease, technology type and relevant population(s). While all are necessary, some mechanisms are more tailored to "quick wins" and others represent more long-haul endeavors. For example, some R&D gaps, such as development of vaccines for HIV and therapies for Type III diseases for which very little research is underway, require breakthrough products. Many of the push mechanisms driving upstream R&D inherently target novel drug R&D. Other areas require incremental improvements to established technologies, including for unmet needs of least developed countries like new fixed dose combination or pediatric formulations, improved delivery platforms and diagnostics. AMCs and patent pools are examples of mechanisms that may particularly target incremental innovations. Still other challenges necessitate sustainable manufacturing and delivery of existing drugs, which patent pools and supply chain initiatives (among other platforms) have sought to address.

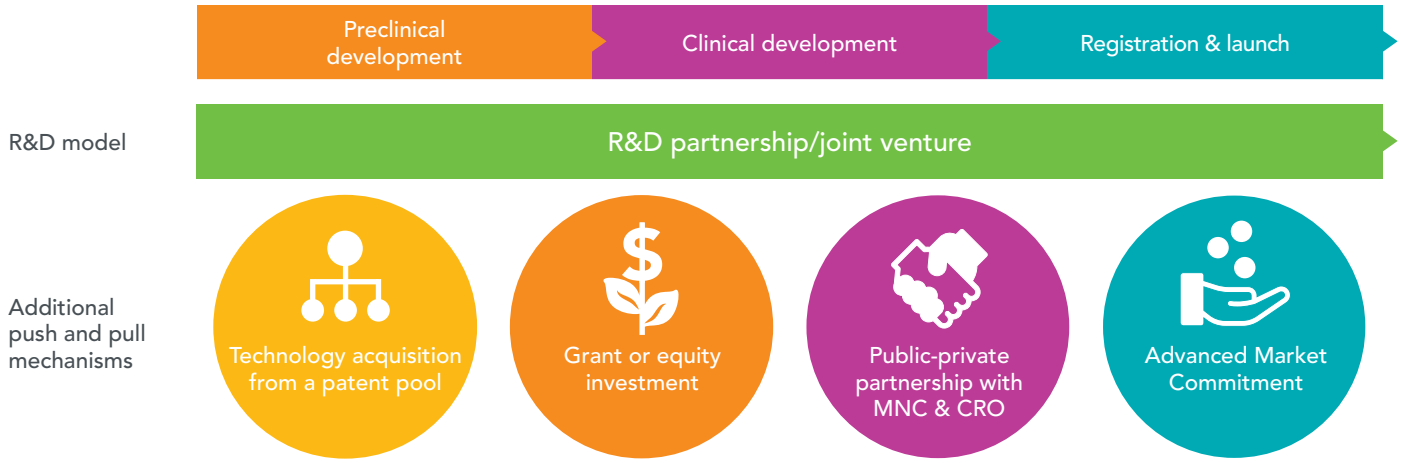
Putting it all together: Sample "mechanisms mixes"

The optimization model developed in this study depicts when, by whom and for what purpose different R&D incentives and delinking mechanisms might be used – in tandem with the existing biopharmaceutical R&D model – in order to effectively leverage the most suitable R&D partners at each phase of the process and achieve the desired outcome in a sustainable manner. Drawing on this model and recognizing that every disease area or gap faces its own particular circumstances, two potential combinations of mechanisms could include the following:

Potential R&D mechanisms mix for development of a breakthrough treatment



Potential R&D mechanisms mix for development of a reformulated/repurposed drug



Source: Pugatch Consilium


SERVICE
STATISTICAL DATA

INTRODUCTION

In 2012 Pugatch Consilium authored *Assembling the pharmaceutical R&D puzzle for needs in the developing world*, which evaluated the opportunities and challenges associated with proposed initiatives aimed at stimulating research and development (R&D) of drugs and other treatments targeting neglected diseases affecting the developing world.[1]

The report provided a preliminary assessment of various delinking mechanisms aimed at incentivizing R&D into neglected diseases against a set of success criteria, the Blueprint for Success. This matrix was aimed at providing a more coherent and practical framework for evaluating and scaling up future efforts.

Five years later, the international context has evolved in terms of the expansion of international stewardship efforts, rise of new challenges and growth of actual R&D. Following on from the 2012 report from the WHO Consultative Expert Working Group (CEWG) on Research and Development: Financing and Coordination and the ensuing work plan,[2] more coordinated priority setting for neglected disease R&D and greater application of R&D incentives is visible. As just one example, 2016 saw the launch of a Global Observatory on Health R&D,[3] with the WHO Advisory Committee on Health Research overseeing research priorities based on the database, including a focus on neglected diseases.[4]

At the same time, unmet needs in pressing areas have intensified, for instance around new epidemics like the Ebola and Zika virus outbreaks and the growth of antimicrobial resistance (AMR).[5] These have highlighted the importance of increased R&D coordination for global health emergencies and urgent investment in novel treatments, even among well-established diseases. In a positive sense, these developments have stimulated greater international coordination and investment in R&D. In the wake of the Ebola outbreak clinical development of anti-Ebola candidates has accelerated, and a first vaccine entered phase III trials in 2015.[6]

Though the issue on how to incentivize further neglected R&D efforts has remained high on the international agenda, the challenges of epidemics and AMR in particular have buttressed a re-emergence of global discussions on innovative incentive strategies for neglected disease R&D, notably in the context of the recent UN High Level Panel on Access to Medicines.[7] While wider in focus, the Panel's report (issued in September 2016) proposes use of many of the same R&D incentives and mechanisms aimed at "delinking" or mitigating the cost of R&D and ensuring access to end products that were examined in our 2012 study, as well as highlights newer proposals related to financial instruments, regulatory harmonization, open innovation platforms and data sharing consortiums.

Against this backdrop it is important to update and expand the analysis included in our 2012 study to incorporate newly proposed mechanisms as well as initial lessons learned about the success of more established R&D proposals. In parallel, there remains a need to move from a kind of "laundry list" of incentives and mechanisms to a more coherent and strategic "playbook" for exploring and leveraging these different platforms that optimizes limited funds and R&D actors and in a rapid manner, in order to deliver new treatments when and where they are needed most.

This report is divided into four sections. Section 1 sets the stage, outlining the evolving biopharmaceutical R&D model for neglected diseases – the fundamental components that remain at its core and the systemic gaps that exist in relation to neglected diseases and that proposed mechanisms seek to fill.

Section 2 develops an updated Blueprint for Success identifying four key success criteria and conditions that proposed mechanisms should display in order to fulfill these criteria. The section then uses the Blueprint to provide a set of concise

overviews of 11 key types of proposed incentives and mechanisms, including the manner in which they are expected to be used, systemic gaps they seek to fill and their main strengths and weaknesses vis-à-vis stimulating greater neglected disease R&D.

Section 3 supplements with hard evidence on actual R&D outcomes in terms of growth of the neglected disease pipeline globally as well as looking at a sample of the more established R&D proposals. The analysis underscores progress made over the past five years in terms of concrete R&D and which mechanisms, based on the data available thus far, have shown relatively greater promise to stimulate R&D.

Recognizing that no single mechanism is a silver bullet for securing neglected disease R&D, Section 4 presents one suggested model or scheme for optimizing the use of the different proposed R&D incentives and mechanisms in tandem with existing market-based incentives such that new synergies are created. The model is three-tiered, looking at combinations of mechanisms that capture the entire R&D life-cycle; leverage R&D entities most effectively; and target the appropriate level of innovation needed for a given disease, population or circumstance.

Methodological considerations and definitions

Neglected diseases

This report refers to the definition of neglected disease used by Policy Cures and the Bill and Melinda Gates Foundation in the G-FINDER survey:

…[D]iseases that have a higher incidence or different disease profile in developing countries. These factors have led to a lack of R&D investment in developing country-specific product development.[8]

The report also refers to the distinction between Type I, II and III diseases as defined by the WHO, in which 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, such as HIV and tuberculosis; and Type III diseases are those that are overwhelmingly or exclusively incident in developing countries.[9] A list of Type II and III neglected diseases considered in this report as well as their estimated global disease burden relative to the total is provided in Table 1. Unmet medical needs for Type I diseases, including rare diseases, fall outside the scope of this study.

Upstream and downstream R&D

Upstream R&D mainly comprises drug discovery, and generally includes the process of mapping diseases, isolating target points on these diseases, identifying "hit" molecules that are selective for a given target and potential for use in treatments, and transforming them into "lead series". Downstream R&D refers to the translation of drug discoveries into products and often includes licensing of promising lead compounds and platform technologies, optimizing them to develop actual drugs or vaccines and testing them in the laboratory and in patients in order to ensure their quality, safety and effectiveness.

Proposed and existing R&D incentives and mechanisms

In this study, the term "R&D incentives" and "R&D mechanisms" refer to all instruments that have either been proposed or are already implemented that seek to enhance innovators' return on investment even when market purchasing power is low and would not justify their spending and risk-taking. These instruments act as a complement to both the push (costs) and pull (prices) functions of the market and comprise delinking models as well as other incentives including market and commercial-based incentives.

Delinking mechanisms

The concept of delinking has continued to be part of the discussion on R&D incentives as a way to redress market failures and provide a more sustainable R&D model for neglected diseases. As mentioned in the 2012 study, "delinking" 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.

TABLE 1 Diseases considered as neglected in this report by disease type and global burden (in DALYs)

Disease	Type	Global disease burden (DALYs, 1000s, 2015)
Bacterial meningitis	II	23,267
Bacterial pneumonia	II	142,384
Cryptococcal meningitis	II	23,267
Dengue	II	2,613
Diarrheal diseases (e.g. rotavirus, E.coli, schigella, cholera, giardia, salmonella infections)	II	84,928
Hepatitis C	I/II	130
HIV/AIDS	II	62,759
Hookworm	II	1,756
Tuberculosis	II	56,037
Whipworm (trichuriasis)	II	543
Chagas disease	III	253
Leishmaniasis	III	1,357
Leprosy	III	489
Lymphatic filariasis	III	2,071
Malaria	III	38,520
Onchocerciasis (river blindness)	III	1,136
Schitosomiasis	III	3,514
Sleeping sickness (African Trypanosomiasis)	III	372
Trachoma	III	279
African viral haemorrhagic fever (including Ebola)	N.A.	N.A.
Buruli ulcer	N.A.	N.A.
Leptospirosis	N.A.	N.A.
Rheumatic fever	N.A.	N.A.
Roundworm (ascariasis)	N.A.	1,096
Strongyloidiasis & other intestinal roundworms	N.A.	N.A.
Tapeworm (cysticercosis)	N.A.	1,857

Source: WHO (2012), WHO Global Health Estimates 2015 Summary Tables


40/0.65
160/0.17

1 SETTING THE STAGE: UNDERLYING PRINCIPLES OF BIOPHARMACEUTICAL R&D AND GAPS IN NEGLECTED DISEASE R&D

As in the 2012 study, in order to understand the potential that different proposed R&D incentives and mechanisms have for success in neglected disease R&D – and to ensure they are optimized to actually secure new treatments – it is important to keep in perspective the biopharmaceutical R&D model.

Although, as this section will identify, different systemic challenges exist in relation to neglected disease R&D, the fundamental elements and principles of the model remain integral to neglected disease R&D. In addition, while today R&D strategies and the roles of different R&D actors are becoming much more fluid and collaborative – for neglected diseases and for the biomedical field more generally – nevertheless the underlying process of and elements needed for drug discovery and development and the costs involved must still be recognized and integrated into new strategies for neglected disease R&D.

1.1 Ticking all of the boxes? Understanding the fundamental costs and elements of biopharmaceutical R&D for neglected diseases

The entire biopharmaceutical R&D process surrounding the creation of a new drug is a very involved and a financially risk process, with significant resources invested. The development of innovative medicines takes some 10-15 years on average.[10] Concurrently, though estimates vary depending on the circumstances the average cost of bringing an innovative drug from discovery and development to patients (including failures) is constantly rising, by some estimates upwards of USD2 billion.[11] On average between 5,000 to 10,000 compounds need to be screened for a drug to enter clinical trials, and only few of those undergoing clinical testing result in an approved medicine. Laboratory and clinical testing can go on for decades, absorbing the majority of R&D costs. In particular, the testing of drug candidates in human volunteers via clinical trials prior to regulatory approval, which is divided into three main phases, represents an undertaking of 6-7 years per drug candidate, or between 55% and 75% of the total R&D process.[12] Costs of clinical trials are known to have doubled in the past decade.[13] Given the high costs of development, only around a third of approved medicines return revenues that match or exceed R&D costs. Figure 1 outlines the time and investment typically required for each stage of the biopharmaceutical R&D process.

FIGURE 1 The biopharmaceutical R&D process and timeline

Research and discovery

Scientists attempt to isolate new chemical or biological entities using advanced screening and synthesising techniques.

Pre-clinical development

Initial safety tests and assessment studies, such as toxicology, are performed on animals.

Clinical development

Phase I Initial phase tests a drug candidate in 20-100 healthy volunteers to assess how the body processes it and what side effects manifest themselves. A drug must show a minimum level of safety in order to move to the next phase of studies.

Phase II Examines a drug candidate's effectiveness in treating a targeted disease relative to other existing drugs or to a placebo. It explores whether the candidate acts against the disease and if it causes any adverse reactions in patients, and how this measures up to existing treatments. Studies involve 100 to 500 volunteers, all of whom experience the targeted disease or condition.

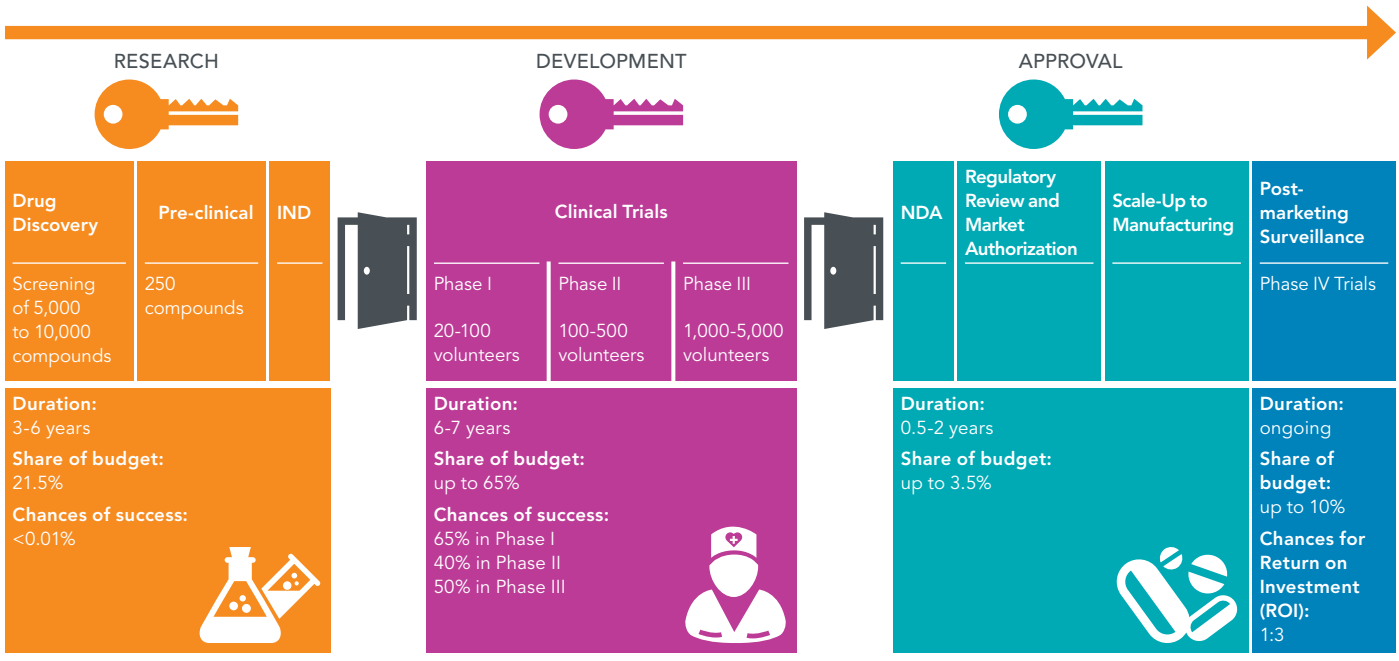
Phase III If the candidate is proven safe and effective in the first two phases, the study is shifted to a far larger scale, from 1,000 to 5,000 subjects. Studies test the safety and effectiveness of the drug candidate in different populations and conditions. This phase generates a large amount of data on the candidate in order to understand as clearly as possible the safety risks associated with the drug and to identify the right dosage and mode of use. Due to the scale of operations, Phase 3 studies are the most costly and time-consuming trials.

Registration

Results of pre-clinical and clinical studies and proof of meeting international standards are submitted to drug regulatory authorities for their review.

Post-marketing study

Biopharmaceutical companies must submit a plan for on-going monitoring and study of the drug as part of its approval for marketing. These studies are intended to safeguard larger scale use of the drug by monitoring any adverse effects that become evident as well as identifying what appears to be the most appropriate and effective manner of use. Post marketing studies typically provide the largest amount of evidence on a drug relative to data gathered in earlier phases.



Source: Pugatch Consilium; adapted from PhRMA (2013) and Nature (2010)

With this framework and process in mind, biopharmaceutical R&D also relies on several key elements to drive forward the R&D life-cycle. These include:

- **Robust scientific and technological life science capabilities and infrastructure**
  Elements often identified are a sufficient quantity of highly-skilled biomedical professionals and researchers; scientific infrastructure; the presence of research clusters; technology transfer frameworks and financial support for R&D, including both public and private investment.

- **Facilitative regulatory and clinical environments**
  These include clinical standards and regulatory requirements that establish adequate levels of quality and safety for biopharmaceutical products.

- **Effective exclusivity periods derived from intellectual property (IP) rights**
  The market exclusivity period provided by IP rights (including patents and regulatory data protection) and additional incentives for the production of orphan drugs give drug manufacturers the protection needed to recoup R&D investments. As such, market exclusivity 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.[14]

- **Market incentives and frameworks for the launch of products**
  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 releases additional resources for addressing public health needs by reducing the prices of medicines and also allows innovators to focus on the next generation of medicines, including new health technologies and improvements to existing ones.

The process and elements described in this sub-section have been successfully implemented over the last several decades to produce a steady stream of new drugs and health technologies, despite increasing costs and risks of R&D.

1.2 Systemic gaps in the biopharmaceutical R&D process for neglected diseases

Yet, when it comes to neglected diseases there are several systemic roadblocks in the R&D model that arise when seeking to develop new treatments and technologies. These gaps should be addressed in order to create an effective forward pathway.

Upstream gaps: Insufficient dedication to basic research efforts aimed at neglected diseases

Public research institutions, universities, hospitals, biotechnology firms and other organizations have limited incentives and financial resources to invest in neglected disease research, with the bulk of basic research directed towards domestic health priorities in developed markets. As a result, without additional dedicated funding, key elements of drug discovery are missing for neglected diseases.

Downstream gaps: Inadequate financial and commercial incentives for translational and clinical development

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 authorization and manufacturing the final product. Though the later stage pipeline is growing, the costs of bringing promising candidates through full development, clinical testing and registration remain some of the biggest bottlenecks in neglected disease R&D.

In addition, developing and least developed countries face particular challenges that may require modifications or reformulations of existing treatments, including cultural norms and climate-related or environmental limitations (such as high temperatures, infrequent health visits, level of sanitation, etc).

The possibility that even if developed, these drugs may still not be accessible to populations in developing countries

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.[15] 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,[16] work to fill this gap to some extent, but are insufficient methods on their own.

Beyond the issue of price, developing countries face a number of other barriers to the ability to adequately access needed medicines, particularly new and improved therapies, including limited access to health care and necessary infrastructure and technologies; inadequate financing for health and medicines; local costs that drive up the price of medicines such as taxes and tariffs; gaps in procurement and supply chain frameworks; regulatory deficiencies; and socio-cultural norms and lack of awareness of opportunities to obtain care.[17] International and national efforts to reduce these types of barriers include the global public-private partnership, the NTD Supply Chain

TABLE 2 Key systemic roadblocks for neglected disease R&D

R&D Stage	Research and discovery	Preclinical development	Clinical development	Registration	Postmarketing & delivery
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 analysis

Forum, which contributes to improving delivery of neglected disease medicines to developing countries, including in relation to customs clearance and warehousing.[18]

Table 2 provides a summary of key gaps in relation to neglected disease R&D across the biopharmaceutical R&D cycle and how they impact innovation needed for these diseases.

Even in a context of these systemic challenges vis-à-vis neglected disease R&D, the inherent parameters of biopharmaceutical R&D remain in place and the key enabling elements of the process continue to be well equipped to handle key aspects of the R&D process for treatments aimed at neglected diseases. Yet, in order to truly address the unmet needs in developing countries for treatments aimed at neglected diseases and on a sustainable basis, it is necessary to supplement market-based incentives with a wide range of different push and pull mechanisms, which the next section will map in more detail.

2 MAPPING ONGOING EFFORTS TO MEET R&D NEEDS FOR NEGLECTED DISEASES: OVERVIEWS OF KEY R&D INCENTIVES AND DELINKING MECHANISMS

R&D incentives and delinking mechanisms have evolved over the years in response to systemic gaps in R&D for neglected diseases. In the past few years, some models have grown from start-up initiatives to mature and established platforms for neglected disease innovation that, in some cases, have expanded the neglected disease research landscape.

At the same time, new models for funding and enabling the process of neglected disease R&D have been proposed. Yet, for all proposed mechanisms there is a need to understand whether and to what extent they fulfill the conditions required to bridge the gaps identified in the previous section. Section 2 will compare a number of existing and proposed R&D incentives and mechanisms on a like-for-like basis to see how well each of them fit into the R&D puzzle for neglected diseases, shedding light on their strengths and weaknesses by measuring them against key success factors. As a backdrop, the section will first outline these success factors.

2.1 The updated Blueprint for Success: A grid for benchmarking strengths and weaknesses of existing and proposed platforms

Building on the scheme used in our 2012 study, a Blueprint for Success of incentives and mechanisms for neglected disease R&D should comprise at least four factors:

1. Availability of needed "inputs" to R&D

First, each mechanism involves the provision of financial or in-kind support (such as data or assets, operational support or streamlining of regulatory processes) from various partners that may be leveraged to fill in gaps in neglected disease R&D incentives or otherwise ease the process. Ideally, the funding or other inputs can be sustained over the long term and be applied to a growing range of diseases and circumstances. All partners providing inputs, particularly financial, face some form of constraints that affect their ability to provide a steady and growing supply for neglected disease R&D, though certain mechanisms are shaped such that provision of a needed R&D input is more finite and less reliable than others. Given the inherent limits to available inputs, especially when it comes to funding, one wider component of global R&D efforts has been to consider the creation of various international funds for neglected disease R&D, including in the recent UN High Level Panel.[19] The proposals take a wide range of formats and engage different actors but the basic idea is to pool international funds and deliver them to R&D actors using many of the proposed R&D incentives discussed in this section. Thus far, most of these initiatives remain in the proposal and scoping stages.[20]

2. Incentives for participation

Beyond being sustainable and scalable, funding or other R&D inputs provided within a given mechanism should adequately incentivize R&D actors to participate. The clearer and wider the advantage to R&D actors is, the greater their level of participation (and potentially, additional investment). These incentives may act as push mechanisms, generally provided in advance of R&D, or pull mechanisms, made available once the R&D is conducted (and for some, end products are actually produced). In many cases, they complement or leverage existing market-based incentives. Having said that, pre-defined or limited rewards tend to be less effective than broader incentives, though they may be sufficient if targeted to an appropriate type of R&D and R&D actor (see section 4 for further discussion).

3. Research paradigm and focus

Third, in order to maximize use of R&D inputs, proposed mechanisms should capitalize on synergies among different R&D actors and should be targeted towards a defined gap in the R&D process in relation to neglected diseases. Proposed R&D mechanisms tend to fall on a spectrum of openness and sharing (from crowdsourcing to defined data/asset pools to exclusive arrangements). Though, as mentioned, neglected disease R&D inherently requires more collaborative innovation, various levels of collaboration are relevant depending on the circumstances and R&D context. Crucially, given that this report is focused on R&D and innovation for neglected diseases, the mechanisms should target a bottleneck related to R&D specifically, and not wider, related issues.

4. Ability to generate actual innovation and make it available to patients

Finally, R&D mechanisms should be assessed based on their ability to generate actual development of new treatments that can be accessed by patients in developing countries. This entails both the potential of a given mechanism to lead to a tangible product (either directly or as part of a combination of mechanisms) – which is the primary prerequisite for accessing treatments – as well as additional efforts to facilitate access and/or remove barriers. While most if not all proposed mechanisms seek to improve access to medicines by catalyzing R&D efforts for unmet needs, some specifically focus on bringing innovative treatments through the development stage to make them available to patients. Many may include specific IP and pricing arrangements (and in some cases, donations) addressing affordability of treatments in endemic countries, as long as they do not undermine the incentives in place to develop the medicines in the first place.[21] Some mechanisms also involve complementary efforts aimed at capacity building, regulatory and clinical trial policy reform and supply chain improvements.[22]

Table 3 summarizes these success factors and the key elements of each incentive or mechanism that are examined and classified.

TABLE 3 Updated "Blueprint for Success": Key success factors for R&D incentives and delinking mechanisms

Area	Features examined and classified	Success factor
1. Availability of needed R&D inputs	Private, public (national and international) or philanthropic	Enjoys sustained funding over the long-term Funding can be expanded to other mechanisms or scaled up to meet growing demand
2. Incentives for participation	Direct financial (market or non-market based), indirect financial (savings) or non-financial motivation	Effectively mitigates costs and risks of relevant R&D activities Identifies incentives of various R&D actors (based on the type of R&D inputs provided and the environment in which each operates) and targets them accordingly
3. Research paradigm and focus	Competitive, collaborative, open source or open innovation	Identifies and tackles systemic gaps in the R&D process
4. Ability to generate actual innovation and make it available to patients	IP and pricing arrangement Non-pricing access support	Successfully leads to creation of an end product, milestone in the R&D process, or supporting technology Facilitates removing barriers to access, without undermining incentives to develop the innovation in the first place

Source: Pugatch Consilium

2.2 Assessing R&D incentives and delinking mechanisms against the Blueprint for Success

This sub-section provides an overview and analysis of 11 key R&D incentives and mechanisms against the above Blueprint for Success to better understand how they fit into the R&D puzzle for neglected diseases and what are main the strengths and weaknesses of each. Though not a comprehensive list, the incentives and mechanisms examined in this section comprise many that have been discussed in international forums and initiatives – both those that have been implemented and those that are still in the proposal stage. The mechanisms selected for analysis in this section also reflect an effort to capture the main types of incentive models considered today, from direct funding to regulatory and operational R&D "enablers" including data sharing, on-the-ground support and regulatory streamlining. Table 4 outlines the mechanisms considered in this section.

In the following pages, each overview provides a brief description of the R&D incentive or mechanism and how it is applied today in relation to neglected disease R&D. The overviews also outline key strengths and weaknesses of each mechanism vis-à-vis the Blueprint for Success, which are summarized in a table, particularly the final row which is colored coded based on the relative promise of a mechanism to address a given success factor: red refers to there being significant challenges; yellow to a mixed or partial environment; and green to the mechanism having relatively more promise in a given area.

TABLE 4 Overview of R&D incentives and delinking mechanisms

Incentive/Mechanism	Definition
FINANCING-BASED MECHANISMS 	
Research grants	Additional funding in advance of R&D aimed at specific research outcomes
Financial instruments/Program Related Investments (PRIs)	Financial investments that, although they may generate income, are made primarily to accomplish charitable purposes
R&D prizes	End prizes: Pre-defined payments to R&D entities in lieu of sales; conditional on achieving a particular outcome Milestone prizes: Reward for reaching specified milestones in the R&D process
Advance Market Commitments	Agreements to develop and supply a product in exchange for a temporary purchase guarantee
R&D tax credits	Direct contribution to research entities in order to promote R&D in specific research areas by increasing returns to R&D in these areas
REGULATORY MECHANISMS 	
Extended or transferable IP rights	Possibility to extend market exclusivity for a product developed to fight a neglected disease, or apply the extension to another top-selling product by the same innovator
Priority review vouchers	Right granted to neglected disease innovators to receive priority review of another of its products that would not otherwise qualify for faster approval
International regulatory harmonization efforts	Harmonization of national regulatory standards for approval of R&D and products in line with international standards, leading to reduced red tape and uncertainty
OPERATIONAL MECHANISMS 	
Collaborative research and data pooling	Data pooling/sharing: Platforms for licensing or sharing research data and know-how among R&D actors Open innovation: Practice of opening up proprietary data and research facilities to external researchers Open source/crowdsourcing: Platforms for wider contributions from independent researchers
Patent pooling	Platforms for the cross-licensing of intellectual property for use in R&D
PDPs	Public private partnerships involving a combination of grant funding, partnering and operational support focused on product development

Source: Pugatch Consilium

Research grants

Description and use

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 and widespread mechanisms for basic scientific research. The US National Institutes of Health (NIH) continues to allocate more than 80% of its budget through grants.[23]

A significant portion of R&D investment into neglected diseases – an estimated 72% of the total – occurs through grants,[24] most of which goes directly to researchers and innovators. Around 20% is channeled through PDPs.[25] Science and technology agencies, most notably the NIH, finance three quarters of these grants, and the rest mainly comes from philanthropic donors.[26]

Grants are regarded as seed money to help kick-start – not sustain – innovation. In order to enhance their effectiveness and aid in sustained funding once the grant runs out, they are increasingly coupled with collaborative research or co-funding requirements.[27]

Strengths and weaknesses

✔ Grants are versatile; they can finance actual R&D as well as other related activities, including training and development of personnel specializing in neglected diseases. Where they fund R&D itself, grants mainly cover early phase research.

✔ Grants may also target development activities.[28] This is the case of the Global Health Innovative Technology (GHIT) Fund, a public-private-non-profit joint undertaking established in 2013 by the Japanese Government, six Japanese pharmaceutical companies, and the Gates Foundation, joined in 2015 by the Wellcome Trust.[29] As of December 2016, most of its grants were allocated to pre-clinical and clinical development activities (USD28 million USD33million respectively),[30] supporting 6 clinical trials in Uganda, Tanzania, Ivory Coast, Burkina Faso, Peru and Bolivia, with two additional trials set for 2017.[31]

✘ Traditionally, donors designate the topics of grants, meaning that the capacity of grants to address R&D needs largely depends on an effective need assessment process in their design phase. Some grant schemes have addressed this shortcoming by allowing researchers more space to define their research focus. This is the case of Grants4Targets, Bayer's open innovation initiative, that provide financial support to test hypotheses on novel targets received by external contributors.[32]

✘ 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.

✘ In terms of its complementarity to market-based incentives, some donors make their grants conditional on specific access arrangements. For instance, in the case of the GHIT, patents resulting from R&D efforts must be licensed royalty-free to users operating in least developed and lower income countries (with possible ad hoc arrangements for developing countries), and profit can be made only on products sold in developed countries.[33]

TABLE 5 Blueprint for Success: Grants

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Public or philanthropic donors	Financial and market-based economic reward from product revenues	Both internal or collaborative research efforts such as consortia can be financed	Delivery/pricing arrangements for specific countries
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Finance projects of a limited timeframe; continuity is not ensured	For innovators (the risk of failure is borne by the donor); amount set ex-ante	Top-down identification of gaps	Varies

■ Significant challenges ■ Mixed or partial environment ■ Relatively more promise in a given area

Financial instruments and program-related investments

Description and use

Complementing grant-making, resources are increasingly allocated to alternative funding instruments such as equity stakes, loans and guarantees. These instruments – notably used by foundations in partnership with biotech firms – draw on private sector expertise to encourage market-based investments as well as leverage – to varying degrees – the charitable rather than financial goals of investors. They can also be referred to as "program-related investments" (PRI) and benefit from special tax provisions in the US.[34]

Notably, PRIs stimulate private-sector innovation in high-potential, high-risk technologies, often at a very early stage, that would have difficulty attracting strictly commercial investors. The Gates Foundation, considered to be the largest PRI investor, committed USD167 million in 14 health R&D PRIs from 2009 to 2016. Although not focused on profit, in some cases PRIs have managed to generate large returns.[35] The Global Health Investment Fund (GHIF), a social impact public-private investment fund set up in 2012, supports development of new or improved technologies through preferred equity investments and mezzanine loans, as well as project financing.[36]

Investees are chosen for their capacity to respond to a specific R&D need identified by the investor often by enlarging their research focus to neglected disease areas. Successful examples include investment of "dual market" technologies, such as the Gates Foundation's equity investment in Kymab, a British start-up, which funded a vaccine program parallel to those Kymab had carried out in other therapeutic areas.[37]

Strengths and weaknesses

✔ Compared to grants, financial instruments like equity investments and PRIs are deeper, more sustainable investments that build on a strong relationship between investors and investees. They award greater commercial flexibility and wider rights to the investor, such as a validating power in the R&D entities' main decisions and claims on their assets if they do not respect the term of the investment or go bankrupt. In return, they also require increased commitment from the investors to align their objectives with the ones of other investors.

✔ In terms of addressing R&D gaps and facilitating access, while equity investments apply mainly to early R&D phases, late stage development support is also emerging.

✘ PRIs and equity investments are dependent on the attractiveness and potential of a given program. To reduce risks and improve the quality of business models or technologies before investment is made, some investors make their investment decision conditional on successful meeting of milestones. This is notably the case of PATH's experimental investment program for social enterprise start-ups.[38] PRIs are also often coupled with grants to support project sustainability.

✘ In some cases investors may place conditions on market access, such as requirements for "charitable" access.[39] If the investee fails to adhere to such commitments he can be obliged to buy shares back. Alternatively, the foundation could obtain the IPR necessary to take the project forward with another partner.[40] Similarly, the Gates Foundation's Global Access commitments require that final products are provided at an affordable price to LDCs and sometimes, to developing countries.

TABLE 6 Blueprint for Success: Financial instruments and PRIs

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Philanthropic investors and collaborative (public-private) funds	Market-based economic reward	Both internal or collaborative research efforts such as consortia; but most often single biotech start-ups	Often legally binding charitable commitments
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on investor will; can increase project credibility and chances of additional funding	Deeper and longer-term investment than grants	Relatively effective in aligning investors and investees' agenda	Supports product development

Mixed or partial environment Relatively more promise in a given area

R&D tax credits

Description and use

R&D tax breaks allow companies to offset a portion of their expenditures on R&D for neglected diseases against their tax liabilities. Increasingly, R&D tax schemes apply to research outputs and not only inputs.[41] So-called "patent box" (or "innovation box") schemes provide a lower tax rate on income from patents (or from other IP) generated from R&D efforts.

Tax credits to increase R&D efforts into unmet medical needs have been implemented in a few contexts with mixed success. Tax credits for orphan drugs as part of a wider incentive package, with extended exclusivity, are regarded as an appealing pull factor,[42] and have registered positive outcomes in the US scheme offering 50% credit of qualified clinical trial costs.[43] However, in other instances tax credits have proved insufficient on their own to provide enough funding and guarantee of return for R&D entities. The 20-40% tax credit for drug and vaccines development for tuberculosis, malaria and HIV/AIDS offered by the UK's Vaccine Research Relief scheme had a low uptake and has been dropped as of 2017.[44]

Strengths and weaknesses

- ✔ Compared to direct funding programs, they can be implemented with modest administrative costs both for public authorities and beneficiaries compared to direct funding programs.
- ✔ Also, they are available to a broader range of innovators and can often leverage the capacity of different companies to assess which products are truly most promising to meet the need of neglected diseases.
- ✔ They are not conditional on results and are awarded after R&D investments have been made.
- ✘ Tax credits use national public funds and their sustainability depends on political will to pursue the objective for which they are intended.
- ✘ Although refundable tax credit mechanisms have been devised to address the lack of offsetting revenues by start-up biotech companies,[45] they may remain more appealing for big companies who have the resources to manage fiscal planning and absorb the time delay in receiving savings.

TABLE 7 Blueprint for Success: R&D tax credits

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Public funds	Market-based economic rewards	Both internal or collaborative research efforts such as consortia can be financed	Not foreseen
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on political will	Partially (after investment takes place); more appealing to big companies	More open ended in terms of innovators and targeted R&D	Supports product development Supply not directly addressed

Mixed or partial environment Relatively more promise in a given area

R&D prizes

Description and use

R&D prizes provide financial rewards to research entities for achieving a pre-defined outcome, whether an end product or a milestone commitment. They are mostly considered for generating investment in new and relatively unexplored areas or attracting attention to a specific goal or technology. While innovation prizes have been applied successfully to fields such as aerospace and green energy, their applicability to biopharmaceutical R&D is limited.

Though most are in the initial stages, as Table 8 shows biopharmaceutical R&D prizes are mainly intended as voluntary schemes that complement market-based rewards and allow winners to retain the IP rights over their products. Most biopharmaceutical prizes launched recently deal with diagnostic tests tackling the issue of antimicrobial resistance. More established prizes covering medical R&D more generally aim to strengthen R&D processes and enable R&D actors without directly funding a specific R&D effort, such as selecting research ideas that could translate into a biomedical startup or overcoming barriers to patient participation in clinical trials.[46]

The utility of R&D prizes for the development of actual medicines and other therapies remains unproven. Few hard results have issued from biomedical prizes, with several not receiving valid proposals, outpaced by unexpected developments in R&D, or in the initial stages.[47]

TABLE 8 R&D prizes aimed at biomedical R&D

		Disease/ Research focus		Design option			Participation		Selectivity		Approach to IP rights	
		Unmet medical needs	Beyond neglected diseases	End prize	Interim prize	Open source dividend	Mandatory	Voluntary	Single (or few) winner	Multiple winners	Replaces IP	Maintains IP
Implemented	EC prizes on better use of antibiotics and vaccines	X		X				X	X			X
	UK Longitude Prize on AMR	X		X				X	X			X
	US AMR Diagnostic Challenge	X		X	X			X		X		X
	Prize4Life ALS prizes	X		X	X			X	X			X
	SUDEP institute challenge		X	X	X			X	X			X
	Archon Genomics XPRIZE		X	X				X	X			X
Proposed	Medical Innovation Prize and Prize Fund for HIV/AIDS (Sanders bills)	X	X	X	X	X	X			X	X	
	Health Impact Fund	X	X	X	X	X		X		X	X	
	TB Diagnostic Prize Fund and Chagas Prize Disease Fund	X		X	X	X		X	X		X	
	Global Health Innovation Quotient Prize	X			X			X	X			X
	HIV Prize Fund	X		X				X		X	X	

Source: Pugatch Consilium analysis

Strengths and weaknesses

✔ While prizes alone may not provide the necessary incentives or financial capabilities to fully develop and produce medicines for use in developing countries, they may be able to act in parallel to existing market-based incentives as push mechanisms.

✘ Under the prize model - particularly end prizes – only one (or a few) successful innovator is awarded.

✘ Even for the "winner" there is still no guarantee that the prize amount will cover costs of development sufficiently.

✘ In addition, the top-down approach needed for larger schemes, where program administrators decide the prize topics and scale, can make it relatively difficult to properly target R&D needs.

TABLE 9 Blueprint for Success: R&D prizes

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Philanthropic, private and public donors	Monetary rewards that complement market-based profits (and in few proposals, replace them)	Crowdsourcing of solutions: contribution open to wider public Competitive: contributors compete with each other to win the prize	Prize winner retains IP
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on donor will and not proportional to investment (i.e. not scalable)	End prizes: risk entirely borne by innovator; Milestone prizes: better mitigate risks	Smaller prizes address specific technical questions of the R&D pipeline. Proposed large schemes have a more top-down approach	Development and supply not generally addressed

■ Significant challenges ■ Mixed or partial environment

Advance Market/Purchase Commitments (AMCs)

Description and use

Under an AMC or other type of supply and purchase guarantee, donors make a financial commitment to fully or partially finance the purchase of treatments meeting pre-established criteria at a specified price, if and when they are developed. For example, a USD5 million AMC announced in January 2016 is aimed at aiding Merck with taking its Ebola vaccine through approval and WHO pre-qualification, even as international epidemic focus has shifted to the Zika virus.[48] GAVI has agreed in advance to purchase the Ebola vaccine – the most advanced Ebola candidate[49] – once it is ready for licensing.[50] The candidate is expected to submitted for market approval in 2017, and has secured fast-track review by both EMA and FDA. UNICEF is reportedly in the process of launching an AMC for newly developed vaccines and diagnostic materials for Zika virus, on the basis of a Zika virus Vaccine Target Product Profile.[51]

Strengths and weaknesses

✔ AMCs replicate or mimic demand, thereby creating a sufficiently large expected market for a given product where none exists and can potentially strengthen incentives to invest in late stage development, registration, manufacturing and launch of that product. The specified price and quantity of drugs to be purchased at the price determine the size of market that would be generated under an AMC.

✔ Similar to a market-based situation, firms compete to bring products to market quickly and develop better products to gain market share. The commercial reward of market-based revenues rather than a predefined compensation allows innovators to choose the most effective course for R&D and launch. According to a 2015 impact evaluation,[52] the PneumoAMC helped encourage the development of other programs for pneumococcal conjugate vaccines (PCVs).[53] It also spurred incremental innovation to address cold-chain challenges and further reduce the cost of production.[54]

✔ AMCs support both short and long term access to treatments by ensuring their actual development as well as supporting adequate and affordable supply, with price decreasing with time and a very small contribution required from endemic countries.

✘ 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. In the case of the GAVI-run pilot PneumoAMC, from 2017 the price was reduced from USD3.5 to USD3.05,[55] and purchases have been financed by GAVI with a USD20 cents per dose from recipient countries.

TABLE 10 Blueprint for Success: Advanced Market Commitments

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Philanthropic and public donors	Replicates market incentives and competition	Both internal or collaborative research efforts such as consortia can be financed	Commitment that, once purchases of the pre-determined drugs at the agreed prize have been made, producers either drop the price to a lower level or license their technology to other manufacturers
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on political will and proportional to investment (i.e. not necessarily scalable)	Focus mainly on late-stage R&D and launch	R&D focus established by research entities, mainly biopharmaceutical companies	Enable the production and generally, the supply and distribution, of affordable end products to low and middle income countries

Mixed or partial environment Relatively more promise in a given area

Extended or transferable IP rights

Description and use

Extended IP rights addressing neglected disease R&D provide an additional period of exclusivity for an approved product, which can include a product not targeting neglected diseases. One proposed application consists of waiving IP rights for neglected disease drugs and in turn transferring the extension to another drug from the same innovator, potentially a "blockbuster" drug ('transferable IP rights').

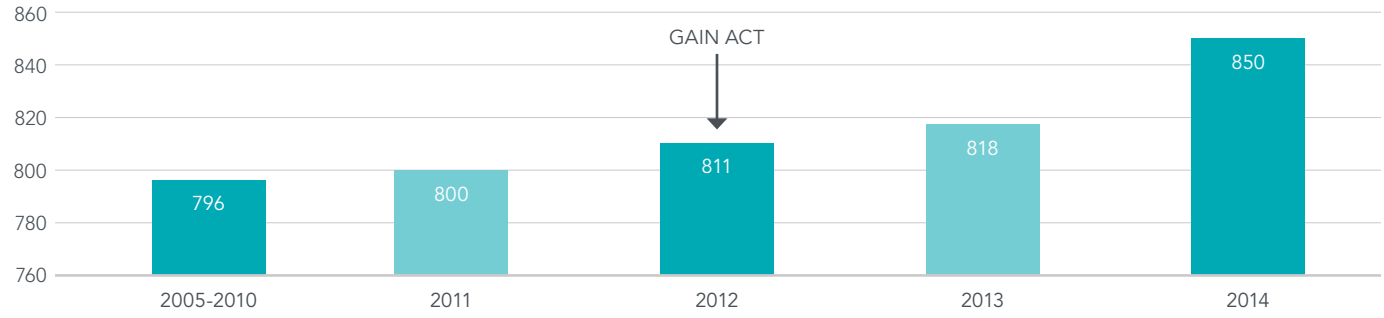
While the idea that IP rights be transferred to a different drug in the same company's portfolio has not yet been implemented, extended market exclusivity has been applied in the US for two other categories of drugs with similarly limited markets: orphan drugs and antibiotics.[56] Under the 1983 Orphan Drug Act, developers of treatments for designated orphan drugs qualify for a package of incentives, notably a seven year period of marketing exclusivity following marketing approval in addition to fast-track procedure for FDA registration and a 50% tax credit on the cost of clinical trials undertaken in the US.[57] By many accounts, the Orphan Drug Act has resulted in greater availability of products for rare diseases, increasingly filling the gap of these unmet medical needs, with more than 500 drugs approved since the Orphan Drug Act was passed.[58]

Along the same lines, the Generating Antibiotics Incentives Now (GAIN) Act adopted in 2012 seeks to increase the commercial value to manufacturers of antibiotics primarily deemed for the US market by extending the term of market protection granted by FDA to innovator drugs.[59] Antibiotics intended for 21 pathogens can be designated as "Qualified Infectious Disease Products",[60] which provides for priority review and 5 years of additional exclusive marketing rights upon approval. As Figure 2 shows, a positive trend is visible in the number of antibiotic clinical trials registered in the NIH's Clinicaltrials.org database since the GAIN legislation was launched. These two positive examples point to the potential of extended market exclusivity as a pull incentive to stimulate market forces in areas where they were previously insufficient.

Strengths and weaknesses

- ✔ As a regulatory and market-based measure, extended or transferrable IP rights entail only marginal up-front costs, and could be implemented with relative ease should there be political will to do so.
- ✔ In addition, they allow for bottom-up identification of R&D needs and solutions by innovators themselves, and carry limited risks for both innovators and public decision-makers.
- ✔ Extended or transferrable IP rights mainly target incentives of biopharmaceutical companies and hence directly mitigate mainly downstream R&D costs and risks.
- ✘ Extended or transferrable IP rights have not yet been applied to neglected diseases as such.
- ✘ They could potentially delay generic competition on designated drugs, though not necessarily.

FIGURE 2 Clinical trials on antibiotics by year, global (based on year first received)



Source: Pugatch Consilium analysis based on Clinicaltrials.gov

TABLE 11 Blueprint for Success: Extended or transferrable IP rights

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
No direct funds needed (regulatory measure)	Market-based (Increased revenues by giving innovators more time to recoup investment costs)	Products developed using other incentives can benefit ex post	IP protection; no specific arrangement
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on political will to ensure continuity of scheme	Risks borne by innovators: rewards depend on strength of IP environment	Bottom-up identification of R&D needs	Enable innovative drug development and launch

Mixed or partial environment Relatively more promise in a given area

Priority Review Vouchers (PRV)

Description and use

PRV and other voucher schemes reward manufacturers that develop a new drug for neglected diseases with a regulatory voucher that can be redeemed for priority review of a separate or future medicine, such as a blockbuster.

Since 2007, the US has granted PRVs to innovators who obtain marketing approval from the FDA for a product that treats or prevents one of the 22 FDA-defined neglected tropical diseases.[61] Vouchers entitle them to receive priority review of one of their other products, reducing approval time by approximately 4 months,[62] or, alternatively to sell the voucher to another company.[63] If used, they increase returns on innovators' wider pipelines through earlier market entrance than would otherwise occur, and allowing innovators to start recouping costs sooner. If sold, they provide additional revenue in a lump-sum amount that can partially or fully cover R&D costs. In 2014, Knight Therapeutics, Inc. reportedly sold for USD125 million a PRV for the leishmaniasis treatment miltefosine, for which it invested USD12 million.[64] Four vouchers have been issued to date for neglected diseases and an additional nine vouchers for related program to promote approval of drugs for rare pediatric diseases have been awarded, including on a vaccines for epidemic cholera.[65] PRVs across the board, including those for tropical diseases and rare pediatric diseases, are being sold at increasingly higher prices, with prices 2-3 times higher in 2015-16 compared to the sales price for vouchers sold in 2014.[66] The 2016 Cures Act required the comptroller general to report on the impact and effectiveness of existing PRV programs in addressing unmet medical need before 2020.[67]

Strengths and weaknesses

- ✔ PRVs are dependent on the political will of the authority that implements them, but do not imply additional direct costs for governments, since voucher holder fees cover the cost of additional resources required to guarantee speedier review.
- ✔ In addition, although intended to enlarge the number of products approved for tropical diseases with incidence in the United States, the FDA review as part of the PRV could also help establish treatments that primarily affect developing countries and accelerate market approval and launch in these countries.[68]
- ✘ For their part, while having advantages PRVs also involve risks for innovators, with no guarantee the neglected disease candidate will make it to the market approval stage.
- ✘ Thus far, PRVs mainly target new chemical entities that represent either a fully new treatment or a significant improvement compared with marketed products, and thus may not be applicable where a reformulation or re-purposing of existing products is needed.
- ✘ It is also unclear how PRVs would be used for follow-on products in a given therapeutic or disease area (or where competing products already exist or are under development).[69] These uncertainties affect incentives for investment by innovators.[70]

TABLE 12 Blueprint for Success: Priority Review Vouchers

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
No direct funds needed (regulatory measure)	Market-based; Increased revenues of potentially blockbuster products	Both internal or collaborative research efforts such as consortia can be financed	IP protection; no specific arrangement
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
May be dependent on political will of public authorities	If sold, provide financial resources to cover R&D costs; if used, greater risk to lose advantage if review results in a negative decision	Bottom-up identification of R&D needs	Speeds up development and approval of neglected disease treatments; accelerates access to blockbuster drugs in developed countries; does not directly target supply

Mixed or partial environment Relatively more promise in a given area

International regulatory harmonization and capacity building efforts

Description and use

International harmonization efforts include a range of initiatives aimed at identifying global standards, definitions and disease prioritization and working with national authorities to implement these standards. On-going efforts to spur mutual recognition for regulatory approvals in LMICs notably include the African Medicines Regulatory Harmonization Program.[71] This initiative addresses problems related to highly variable regulatory capacities, different requirements and formats, lack of clear guidelines and timelines and limited leverage of reference evaluations such as WHO prequalification, with the ultimate goal of establishing an African Medicine Agency.[72] An example of clinical trial procedure harmonization is provided by the WHO African Vaccine Regulatory Forum (AVAREF),[73] a network of ethics committees and national medicines regulatory authorities of African countries aimed at strengthening ethics and regulatory capacity for clinical trials for vaccines.[74] AVAREF facilitated regulatory and ethical examination of an Ebola efficacy vaccine trial in Guinea and overcame the difficulty of limited data available on the candidate. Since 2016 it has expanded its scope to all medical products.[75]

Strengths and weaknesses

✔ Increased harmonization of clinical and approval phase procedures has the potential to accelerate the development process of health technologies targeting developing countries' needs, particularly in the clinical trial phases as well as registration and launch. It does so by facilitating information review and sharing among drug regulatory authorities.

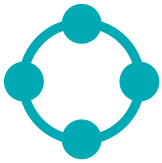
✔ Beyond reducing approval delays, it ensures compliance with higher quality standards and lowers development costs by avoiding duplication of testing and reporting carried out during R&D.

✘ International regulatory harmonization may require some investment of government resources and a potential lag time to integrate into existing national regulatory processes.

TABLE 13 Blueprint for Success: International regulatory harmonization efforts

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
No direct funds needed (regulatory measure)	Faster regulatory processes; lower R&D costs associated with preparation of registration dossier	Products developed under different research structured can benefit; particularly useful to facilitate collaborative efforts	IP protection; no specific arrangement
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on political will to ensure continuity of efforts	Higher standards in line with international norms reduces costs of development	Addresses resources and incentives needed for registration	Better regulation improves availability of quality products and makes them more readily available; does not directly target supply

Mixed or partial environment Relatively more promise in a given area



Collaborative research and data sharing/pooling mechanisms

Description and use

Collaborative research comprises a number of overlapping concepts and platforms. The concept of crowdsourcing, i.e. looking outward to engage external actors to provide innovation, is increasingly under consideration in the realm of biomedical innovation, including open research and "open source" models where results and even the research process are in the public domain.[76] Examples include AstraZeneca Open Innovation,[77] Bayer's Grants4Targets and Grants4Indications,[78] and Lilly's Open Innovation Drug Discovery.[79]

Intrinsically similar, the concept of open innovation refers to the efforts by research institutes and biopharmaceutical companies to incorporate external innovation or to share data and assets through partnerships with external R&D actors in order to invigorate internal research activities.[80] This type of collaboration includes both exclusive partnerships and formal pooling of data among a defined group of innovators, often matching R&D work-streams of academia and SMEs with the relevant assets, associated know-how and general expertise and resources of larger companies. Two examples of data sharing platforms are WIPO Re:Search (for more discussion, see section 3) and the Malaria and Pathogens Boxes, which grant wide access to 400+ compounds with known activity against malaria and neglected diseases respectively.[81]

Strengths and weaknesses

✔ Through aggregating data and enabling matching of assets and knowledge with interested R&D actors, collaborative innovation platforms mainly fill gaps in the early research pipeline in terms of basic research and screening of potential compounds for neglected diseases, enabling translational R&D.

✔ The cost of collaboration as such is limited to the data management and governance structure of the data sharing platforms and partnership facilitators, though more resources are needed to move promising compounds forward into development.

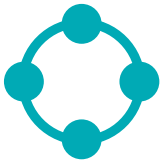
✘ Few examples cover pre-clinical or clinical development, though there are key exceptions. For instance, in June 2016 the FDA approved the first clinical trial evaluating a Zika virus vaccine in humans, just 4 months after the WHO declared the Zika epidemic a public health emergency. The drug was developed by US manufacturer Inovio Pharmaceuticals and a South Korean company, GeneOne Life Science, with collaboration from US and Canadian academic institutions.[82] In addition a few data pooling initiatives also target sharing of clinical data on a voluntary basis,[83] with meta-analysis pooled thus far reportedly supporting new efforts to improve dosage and administration of malaria treatments.[84]

✘ In some collaborative innovation platforms R&D actors must comply with various conditions, such as making the data publicly available or ensuring the end product is licensed on a non-exclusive basis.[85]

TABLE 14 Blueprint for Success: Collaborative innovation and data sharing platforms

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Private companies and public research entities/universities	Indirect/increase access to research data that may serve as base materials for further research and accelerate drug discovery and delivery	Both internal or collaborative research efforts such as consortia can be financed	IP retained; possible obligation to disclose research outcome (open access)
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Funding not a crucial element (although data sharing infrastructure needed)	Reduce time of screening and delivering projects; Spread costs across different R&D players	Research focus is often, though not always, decided by innovators	Development and supply not addressed

Mixed or partial environment Relatively more promise in a given area



Patent pools

Description and use

Patent pooling has traditionally been used as a means of facilitating product development in technology sectors, particularly where different entities own large numbers of patents that need to be utilized in the research process. This is based on the idea that patent pools are able to provide a cost-effective "one-stop shop" for licensing several patents on essential technologies at once, especially for NGOs and local firms.

In relation to biomedical R&D and particularly neglected diseases patent pools are fairly limited but two major platforms, the Pool for Open Innovation against Neglected Tropical Diseases (POINT), now incorporated into WIPO Re:Search, and the Medicines Patent Pool (MPP), have been utilized increasing over the past several years. Funded by UNITAID, the MPP aims to facilitate access to existing treatments through price competition (producing generics) and improving delivery of therapies for HIV and (since 2015-16) hepatitis C and tuberculosis.[86] As Table 5 indicates, during its first five years of operation the MPP has largely focused on voluntary royalty-free licenses for generic production of 12 priority ARVs (with 5 of these for pediatric use).[87] The MPP also provides technical and project management support to its 12 generic partners for the development of APIs and new formulations aimed at easing administration of medicines in resource-poor settings and improving efficacy.[88] In 2015-16 the MMP expanded its mandate to Hepatitis C (HCV) and tuberculosis. A first license for a direct-acting antiviral was granted by Bristol-Myers Squibb in 2015 and since licensed by 7 generic manufacturers.[89] Sub-licensees can also use the product to develop new fixed-dose combinations and receive a technology transfer package (i.e. chemical and product information, as well as regulatory and safety documents) to accelerate registration and production processes, though most have not availed of the package.[90]

The one exception to this pattern highlighted in Table 15 is a recent move to license a compound still under development, specifically to jump-start clinical development of an antibiotic candidate that showed promise in early stage trials and became stalled. In November 2016 the MPP concluded a license with the John Hopkins University on the antibiotic sutezolid, also the first TB-related license.[91] The patent covers the combination of sutezolid with other TB compounds, and grants exclusive rights to the MPP to sub-license it royalty-free for developing and selling products in countries where it is patent-protected. A Phase IIb trial has reportedly been under development since 2013 but with no clear sponsor apart from the NIH financing the production of the drug.[92]

Strengths and weaknesses

- ✔ Any qualified drug manufacturer interested in using a patent can obtain the relevant license by agreeing to the licensing obligation (and geographical limitation) imposed by the donors.
- ✔ Patent pools have recently begun to be applied to clinical development of a neglected disease candidate (though the crucial question of funding for actual trials and development is not necessarily addressed).
- ✘ Thus far, patent pools have had a fairly narrow application; they have primarily been used for generic production and only in a few cases for actual drug development.
- ✘ The use of patent pool to fill in R&D gaps is mainly limited to situations where cross-cutting product patents affect development of related products, notably new formulations.

TABLE 15 Medicines Patent Pool licenses concluded as of January 2017 by R&D phase

Date	Licensed product	Disease	Owner	R&D Phase	Main target
	Darunavir (ARV)	HIV	US NIH	Post approval	Scale up generic production
September 2010	Valganciclovir (Price agreement)	HIV	Roche	Post approval	90% price reduction and tech transfer to scale up generic production; increase access
2011 (amended in 2014 and 2015 to expand supply of two ARVs)	Combination of TDF/FTC with efavirenz (EFV)	HIV	Gilead Sciences	Post approval	Scale up generic production
April 2013	Abacavir pediatric	HIV	ViiV Healthcare	Post approval	Scale up generic production
December 2013	Atazanavir (ATV)	HIV	BMS	Post approval	Scale up generic production
December 2013	Dolutegravir (ARV) paediatrics and adults	HIV	ViiV Healthcare	Post approval (recently approved)	Accelerate and scale up generic production
April 2014	Lopinavir (LPV), ritonavir (r)	HIV	AbbVie	Post approval	
December 2014 (amended in 2015 to expand supply)	Enofovir, emtricitabine, cobicistat, elvitegravir, and the Quad (a combination of the four ARVs)	HIV	Gilead Sciences	Phase III trial, except for emtricitabine approved	Accelerate and scale up generic production
July 2015	Raltegravir paediatrics	HIV	MSD	Post approval	Scale up generic production
February 2015	Solid Drug Nanoparticle Technology	HIV	Liverpool University	Post approval	Accelerate the development of WHO-recommended ARVs as nanomedicines
April 2015	Daclatasvir (DCV)	HCV	MSD	Post approval	Scale up generic production
November 2015	Lopinavir (LPV), ritonavir (r)	HIV	AbbVie	Post approval	Scale up generic production
December 2016	Sutezolid	TB	John Hopkins University	Phase II trial	Accelerate drug development

Source: Pugatch Consilium, adapted from MPP (2017)

TABLE 16 Blueprint for Success: Patent pools

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Patents provided by companies, public research entities and universities	Lack of market returns that would justify further development; ideological motivation	Upstream research pattern not affected	Royalty-free licenses on a non-profit basis for LDCs; licenses to other developing countries are negotiated on a case-by-case basis
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Royalty-free licenses ensure relatively long-standing commitment; but thus far limited mainly to generic and incremental innovation	Mostly mitigates the cost of manufacturing generic drugs; and reduces transaction costs of incremental innovation by putting patents in one place	Generally not targeted at specific needs of development process; supports particular unmet needs like pediatric populations	May allow price competition

■ Mixed or partial environment

Product Development Partnerships (PDPs)

Description and use

PDPs operate as virtual coordinators of various R&D actors, in particular bridging public and private research entities with philanthropic and public funding, that together can deliver ingredients, technologies and clinical and manufacturing operations. Most PDPs for neglected diseases are non-profit organizations that pool funding from various donors – with a high dependence on funding from the Gates Foundation[93] – and spread it throughout the pipeline to different partners. PDPs receive 15% of total funding for neglected diseases. However, if the NIH is excluded, the share of funds received rise to 39%.[94] Three PDPs – PATH, Medicines for Malaria Venture (MMV) and TB Alliance – collectively receive almost half of all funding to PDPs (USD256 million).[95] In terms of disease focus, the "big three", HIV/AIDS, TB and malaria, continue to receive the highest attention and resources, but the range of focus and specialization in certain neglected diseases has grown significantly over the past 5-10 years. For instance, DNDi, which receives the fourth highest share of funding globally among PDPs has a broad portfolio, with a heavy focus on parasitic and filarial diseases along with more established disease areas.

It addition, it is worth noting that although overlap exists, PDPs have generally developed a specific focus and/or expertise that make their efforts widely complementary. Table 17 gives an overview of the focus and scope of actions of the main PDPs.

TABLE 17 Focus and scope of action of major PDPs targeting neglected diseases

PDPs[96]	Disease focus	Main health technologies	Number of partners
Medicine for Malaria Venture	Malaria	Drugs	400+[97]
Program for Appropriate Technology in Health (PATH)	HIV, malaria, TB, diarrheal diseases and pneumonia	Vaccines/drugs/diagnostics	2000+
Global Alliance for TB Drug Development (TB Alliance)	TB	Drugs	27 drug developer partners,[98] 12 donors,[99] 40 clinical trial sites[100]
International AIDS Vaccine Initiative (IAVI)	HIV	Vaccines	100+[101]
DNDi	Malaria and other parasitic diseases, pediatric HIV Hepatitis C, mycetoma, filarial diseases	Various	250+[102]
Aeras	TB vaccine	Vaccines	100+ global partners (of which 40 major funders and academic institutions)[103]
Innovative Vector Control Consortium (IVCC)	Vector-born diseases	Insecticides	6 private companies, 6 funders and 5 trial sites[104]
International Partnership for Microbicides (IPM)	HIV	Prevention products	25 (13 civil society platforms, 5 private companies, 7 clinical research centers)[105] plus various other products development partners
Foundation for Innovative New Diagnostics (FIND)	HIV, TB, Malaria, Hepatitis C, Buruli Ulcer, parasitic diseases	Diagnostics	185 (of which 46 private companies)[106]
International Vaccine Institute (IVI)	Cholera, enteric fever, dengue, MERS-CoV	Vaccines	6 manufacturers, 3 research institute (not exhaustive list)[107]
Infectious Disease Research Institute (IDRI)	Core: TB, leishmaniasis, leprosy Malaria and other parasitic diseases, including Zika, filarial diseases, pandemic influenza, HIV/AIDS[108]	Vaccines, diagnostics, drugs and adjuvants	125[109] (of which 50 in the US)
CONRAD	HIV and STDs	Prevention products[110]	14 partners (of which 3 private companies)[111]
European Vaccine Initiative (EVI)	Parasitic diseases including Zika, HIV, influenza, TB	Vaccines	33 (mostly CMO, CRO, pharma)
Tuberculosis Vaccine Initiative (TBVI)	TB	Vaccines	38 research entities

Source: Pugatch Consilium analysis

Strengths and weaknesses

- ✔ PDPs provide a platform for integrating the owners of a wide range of inputs into the product development process, such that a single company or entity does not bear the full cost and risk of R&D.
- ✔ 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 programs to carry them out.
- ✔ 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 incentivizing participation in PDPs. 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 utilized for tuberculosis combination therapies). They may also be interested in its application to more commercial research programs.
- ✘ Large operation, requiring a number of partners and donors and some coordination costs.

Intellectual property rights and PDPs

IP rights continue to represent a key platform for partner engagement, compensation and management within PDPs.[112] At the research stage, PDPs often operate using agreements with their partners that allow them to generate IP in exchange for ensuring access to the research outcomes. In the case of academic research, IP rights are either co-owned or fully assigned to PDPs, with royalties generating funding to be reinvested into the PDP R&D pipeline. Private partners usually retain their IP but commit, as is, for instance, the case for the MMV, to license it with worldwide royalty-free licenses.

During the development phase, patenting of assets is an important way of growing value and attracting private partners to bring candidates through clinical development and registration. For example in 2015 the MMV licensed drug candidate DDD107498 to Merck Serono, developed with the University of Dundee. According to the agreement, the company is charged with development and registration, and the MMV will contribute with its disease-specific knowledge and grant access to public and private sector networks in malaria-endemic countries. As another example, AF156, a novel class of antimalarial molecules developed by a public-private consortium, has been licensed to Novartis in 2016 to enter Phase III trials.

As a general rule, PDP access arrangements often limit the geographical coverage of patents to guarantee access in endemic countries, and protection is primarily sought in wealthier countries that share the disease burden, or for possible different indications in case of Type III diseases. In 2009, Novartis and MMV introduced Novartis's Coartem Dispersible, the first artemisinin-based combination (ACT) formulation developed for children with malaria. As of 2016, more than 300 million doses had been delivered without profit to 50 endemic countries, mainly in Africa, at a price of USD0.38.

TABLE 18 Blueprint for Success: PDPs

Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
Funding >90% from philanthropic/aid agencies; Data/technology provided by private partners	Market-based, economic savings, ideological motivation	Virtual R&D organization, networking different partners	Typically exclusive or non exclusive royalty-free licenses of end products to LDCs
Is it sustainable and/or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Dependent on donor will and capacity	Funding and risks spread among multiple players; Cost reduced by avoiding duplication and maximizing resource allocation	Combines expertise to tackle pre-clinical to launch	Enables innovative drug development and launch Access to end product according to specific arrangements

■ Mixed or partial environment ■ Relatively more promise in a given area

2.3 Section summary

The following table summarizes the 11 R&D incentives and mechanisms examined in this section using the Blueprint for Success.

TABLE 19 Summarizing success factors of proposed and implemented R&D incentives and mechanisms for neglected diseases in light of the Blueprint for Success

	Source and availability of needed R&D inputs	Incentives for participation	Research paradigm and focus	Ability to generate actual innovation and make it available to patients
	Is it sustainable and/ or scalable?	**Do they mitigate costs and risks of R&D?**	**Does it address R&D gaps?**	**Is access facilitated?**
Grants	Public-philanthropic	Market-based, economic	Internal/cooperative or competitive model	IP retained unless donor sets IP or price conditions
	Depends on donor will; mostly ad-hoc	For early stage research	Top down identification of gaps	
R&D tax credits	Public	Market-based, economic	Internal/cooperative or competitive model	IP retained; market-based pricing
	Depends on political will, but established and scalable (proportional to costs)	More appealing to big entities	Applies to R&D generally	Via IP incentives or additional access scheme
Financial instruments/ Program Related Investments (PRIs)	Public-philanthropic	Market-based, economic	Internal/cooperative or competitive model	IP retained but IP and price conditions for select markets
	Dependent on donor will but deeper investment			
R&D prizes	Public-philanthropic	Non-market based, monetary	Crowdsourcing, competitive model	IP rights may not be retained
	Depends on donor will	Only for winners, amount set in advance	Top down identification of gaps	Depends greatly on success of previous factors
Advanced Market Commitments	Public-philanthropic	Market based, monetary	Internal/cooperative or competitive model	IP may be retained; price conditions/agreement
	Depends partially on donor/ partner will	Partially, does not necessarily cover full costs		
Extended or transferable IP rights/ exclusivity	N.A.	Market-based, economic	Internal/cooperative or competitive model	IP protection Market price
	Depends on political will	Depends on strength of IP environment		Enable innovative drug development and launch
International harmonization efforts	N.A.	Economic savings (easier procedures)	Any	IP protection; Market price
	Depends on political will			
Priority review vouchers	N.A.	Market-based (accelerate market benefits)	Any	IP protection Market price
	As long as regulatory resources available	Resources for R&D if voucher is sold	If review is adequately targeted	Drug faster to market
Collaborative research and data pooling/ sharing	Private (business), research entities	Economic savings (faster discovery), motivational	Cooperative (mostly private and public), crowdsourcing, in some cases open access and open source	IP ownership retained (except open source); Free licensing obligation to LDCs in some cases
	Dependent on data owner's will/ relatively limited operational cost			Dependent on type of arrangement
Patent pools	Private (business), public research entities	Motivational	Crowdsourcing, open access	Voluntary licenses, with potential limits on royalties, depending on forum
	Dependent on patent owner will	Only partially linked to early R&D phases	Potentially, if R&D is targeted	No guarantee of developing new products
PDPs	Private (business), public, philanthropic	Market-based, economic savings, motivational	Internal and open sources, Cooperative	Varies; IP and pricing conditions may be set
	Various funding sources but limited overall	Risk spreading, cost reduction	Pre-clinical through to registration/launch	PDP-specific arrangements

Financing-based incentive Regulatory incentive Operational incentive
Significant challenges Mixed or partial environment Relatively more promise in a given area

Source: Pugatch Consilium

Table 19 highlights the following key findings on the potential success of R&D incentives and delinking mechanisms for neglected diseases:

- **No single mechanism is a "silver bullet" for stimulating neglected disease R&D**
  Generally speaking, new proposed R&D incentives and delinking mechanisms are most effective when applied in combination with other mechanisms, including existing market-based R&D incentives. Still, in light of the Blueprint for Success, some mechanisms seem to better address key factors of success, including overcoming costs and risks associated with neglected disease R&D and having wider application and scalability.

- **Financing-based mechanisms display the most significant limitations**
  A number are simply not congruent with the level of funds needed for biomedical R&D, on top of being dependent on donor will and capacity. Certain mechanisms, such as equity investments, grants, R&D tax credits and Advanced Market Commitments, may be able to act in a bridging or "top up" function for existing R&D incentives. Those mechanisms that are more heavily defined or top-down, including R&D prizes, are more likely to be used in a highly targeted manner.

- **Regulatory and operational mechanisms are taking on increasing relevance for addressing key gaps in neglected disease R&D**
  Regulatory and operational approaches for reducing R&D costs, linking partners and spreading risk appear to hold a great deal of promise for closing R&D gaps, particularly in the mid to later stages of the R&D cycle. As with financing-based instruments these approaches, including regulatory streamlining, extended or transferable exclusivity, voluntary data and asset sharing and Product Development Partnerships, work best in combination but entail relatively lower transaction costs.

- **IP maintains an integral role in R&D incentives and delinking mechanisms and in itself does not represent a barrier to access**
  IP rights are retained in varying degrees in many mechanisms, acting as platforms for commercialization and knowledge diffusion and incentives for engaging key R&D partners like biotech SMEs and research-based biopharmaceutical companies. Most importantly, for those mechanisms that target production of a tangible, complete treatment (including full clinical development, market approval and launch), more often than not IP-based transactions play a crucial role. Moreover, removing IP (requiring it be waived) does not necessarily ensure a given medicine will be accessible, and hence can represent a key barrier to making new treatments developed through R&D mechanisms available to patients.

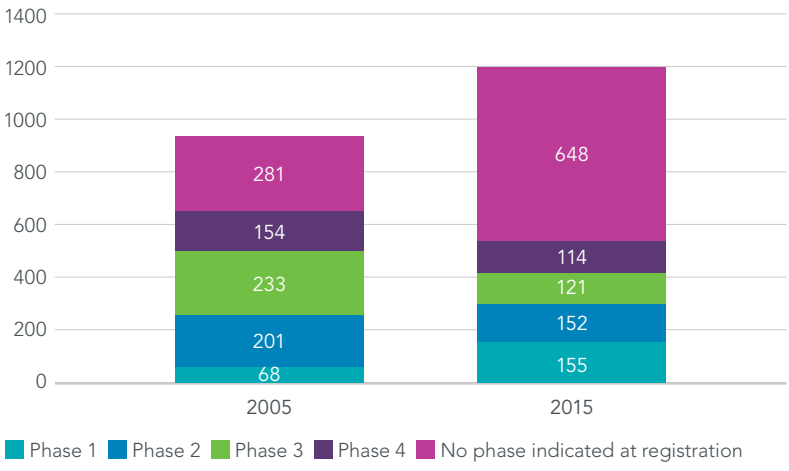
These findings will be fleshed out in more detail in section 4, taking into consideration the following discussion on what can be learned about the success on the ground of relatively established R&D mechanisms for neglected diseases.

3 TRACKING PROGRESS IN NEGLECTED DISEASE R&D: THE STATE OF PLAY AND LESSONS LEARNED ON THE GROUND

More than twenty years since the international community first made a concerted effort to address the gap in R&D for diseases primarily affecting the developing world, the scale and the scope of global collaboration aimed at filling in this gap has grown enormously.

For instance, though it remains a limited portion of total investment in biomedical R&D (at around 2%), annual spending on neglected disease R&D (including Ebola and related viruses) has reached at least USD3 billion as of 2015, representing an annual rise of around 13% particularly on the back of significant investment in Ebola-related R&D.[113] Though public sector funding is trending downward, recent years have seen a surge in the role of the private sector, with the annual G-FINDER survey reporting that spending on neglected disease R&D by multinational companies and biotech SMEs has grown annually for the past four years.[114]

FIGURE 3 Change in annual rate of clinical trials for neglected diseases by phase: 2005 vs. 2015



Source: Pugatch Consilium analysis based on Clinicaltrials.gov (2017)

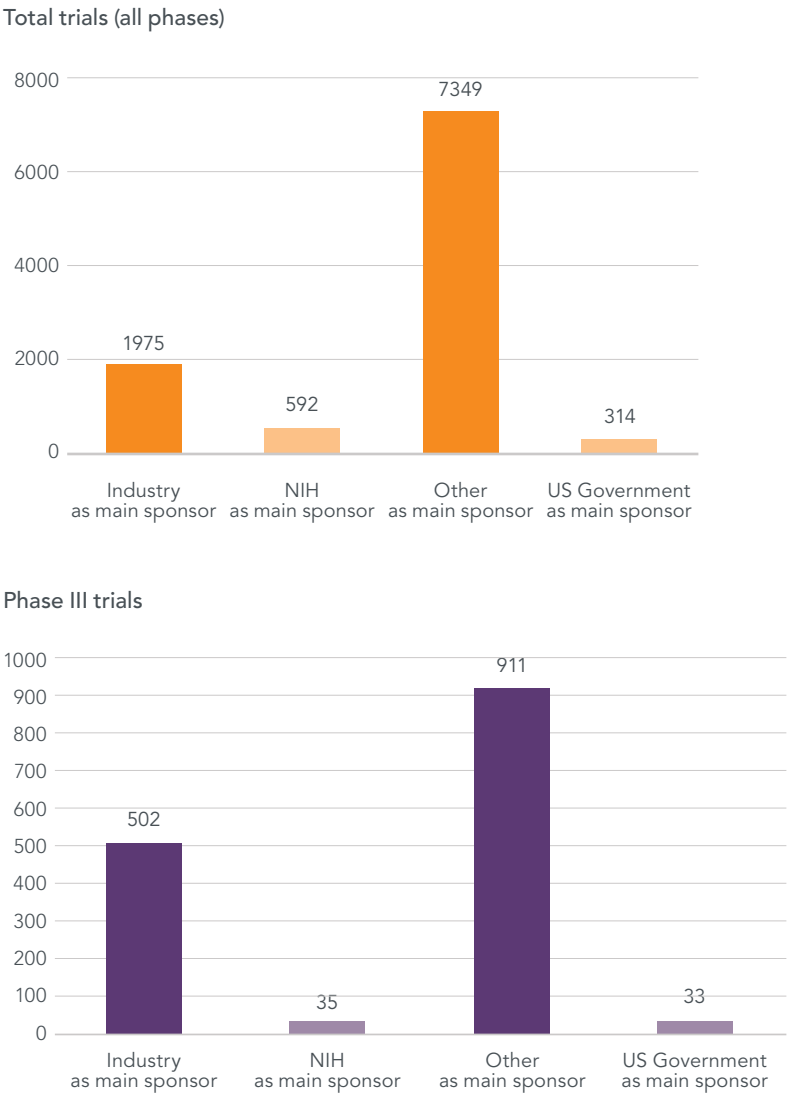
In light of ongoing progress in securing funding as well as use of non-financial instruments, it is worth briefly considering what achievements have been made in terms of tangible R&D generally and what we can learn about the effectiveness on the ground of specific R&D mechanisms. While many mechanisms remain in the proposal stage, a number have been implemented for several years, and following a review of the state of play of neglected disease R&D generally, this section will examine available evidence on how they have (or have not) contributed to the neglected disease pipeline.

3.1 The evolution of the neglected disease R&D landscape

No doubt, the R&D landscape for neglected diseases has improved over the last decade. In terms of R&D activity one indicator of the amount of biopharmaceutical R&D being conducted in the area of neglected diseases is the level of clinical research taking place. Global clinical trial registries provide a picture of the number, type and phase of clinical trials on neglected diseases in the developing world. One such resource is the US National Institutes of Health's Clinicaltrials.gov database, which provides comprehensive, in-depth data on global clinical research.[115]

Looking at data from Clinicaltrials.gov on clinical trials first registered between 2005 and 2015 for all types of interventions on a set of 19 neglected diseases,[116] Figure 3 indicates that the annual rate of new clinical trials grew by nearly 30% (from 937 to 1190 trials) from 2005 to 2015. Importantly, the rise in neglected disease trials has been significant in the early phases of clinical research, which

FIGURE 4 Funders of neglected disease clinical trials, trials funded as main sponsor, 2005-2015



Source: Pugatch Consilium analysis based on Clinicaltrials.gov (2017)

*"Other" comprises research institutes, universities, foundations, non-US public authorities and PDPs

test drug safety in a small number of volunteers and which are indicative of a growing pipeline in neglected disease R&D. Having said that, many of these trials do not progress to more wide scale testing and development of new drugs (not to speak of regulatory review and delivery of these drugs en masse). In fact, while the annual rate of Phase I trials more than doubled (from 68 to 155) during the period, both Phase II and Phase III trials decreased (notably Phase III trials dropped from 233 in 2005 to 121 in 2015).

Looking at priority diseases among clinical trials on neglected diseases, around two thirds of total trials that took place between 2005 and 2015 target HIV, and roughly 80% of trials cover the "big three": HIV, malaria and TB.[117] Some neglected diseases continue to play a very marginal role in the R&D pipeline, as in the case of leprosy or trachoma, while others, such as sleeping sickness and Chagas disease (which are targeted by certain initiatives in particular, like DNDi), have witnessed a notable increase over the last five years.

Developing countries themselves have become more active hosts of clinical trials targeting neglected diseases. Trials in developing countries have grown both generally and for neglected diseases.[118] This means that developing countries now benefit from a higher rate of advance access to experimental treatments, which can literally revolutionize existing treatments available (or make treatments available for the first time). Clinical trials also enable capacity building and technology transfer in local communities.[119] Still, neglected disease clinical trials taking place in least developed countries represent a very small portion, with the exception of malaria. Even in this case, only 60% of trials are located in LDCs despite 90% of deaths occurring in Sub-Saharan Africa alone.[120] As a result, the benefits described above are felt at much lower rate among some of the countries that need them most, and remain an important gap.

As with neglected disease R&D more generally, public sector actors play a significant role in sponsoring clinical trials on neglected diseases, with philanthropic entities also funding an important share. As Figure 4 shows, many small organisations such as research institutes and universities, often within partnerships, fund the largest share of clinical trials, each of them covering a handful of studies. However, looking more closely at the third phase of clinical research only, which comprise the largest, most costly and time-consuming trials – and in a number of ways the deciding factor for whether a promising treatment becomes a fully fledged drug – the private sector (the biopharmaceutical industry in particular) plays an integral role. Indeed, based on the share of

TABLE 20 Sample of products targeting neglected diseases (excluding HIV and Hepatitis C) approved since 2005

Product name	Year	R&D type	Disease	Developer
CYD-TDV (Dengvaxia)	2015	Vaccine	Dengue	Sanofi Pasteur
Delamanid (Deltyba)	2014	Medicine	TB	Otsuka
Para-aminosalicylic acid (Granupas)	2014	Medicine	TB	Lucane Pharma
Rifapentine and isonihazid combination	2014[121]	Medicine	TB	Centers for Disease Control and Prevention/Sanofi
Diethylcarbamazine – DEC	2013 (WHO prequalified)	Medicine	Lymphatic filariasis	Eisai
Bedaquiline (Sirturo)	2012	Medicine	TB	Janssen
Artesunate-Mefloquine Fixed Dose Combination –ASMQ FDC	2012 (WHO prequalified)	Medicine	Malaria	DNDi/Farmanguinhos/Cipla
Arterolane maleate-piperaquine phosphate (Synriam)	2012	Medicine	Malaria	Ranbaxy (Daiichi Sankyo)
Pyronaridine and artesunate, Fixed Dose Combination (Pyramax)	2012 (WHO prequalified)	Medicine	Malaria	MMV/Shin Poong Pharmaceuticals
Piperaquine tetraphosphate -dihydroartemisinin (Euratesim)	2011	Medicine	Malaria	MMV/Sigma-Tau
Miltefosine (Impavido)	2011 (WHO Essential Medicines List)	Medicine	Leishmaniasis	Zentaris (sold to Paladin Labs in 2008)/TDR
Paediatric formulation of benznidazole	2011	Medicine	Chagas	LAFEPE/DNDi
Sodium Stibogluconate and Paromomycin combination – SSG & PM	2011	Medicine	Leishmaniasis	DNDi
Nifurtimox oral and Eflornithine IV combination	2009 (WHO Essential Medicines List)	Medicine	Sleeping sickness (HAT)	Epicentre/MSF/DNDi/ Swiss TPH/TDR/Sanofi/ Bayer HealthCare
Pediatric Artemether and lumefantrine combination (Coartem) Dispersible	2009	Medicine	Malaria	Novartis/MMV
Artesunate and Amodiaquine Fixed Dose Combination (Winthrop)	2007	Medicine	Malaria	Sanofi/DNDi
Rotarix	2006	Vaccine	Rotavirus	GSK
RotaTeq	2006	Vaccine	Rotavirus	Merck & Co
Paromomycin IM	2006	Medicine	Leishmaniasis	Institute for One World Health

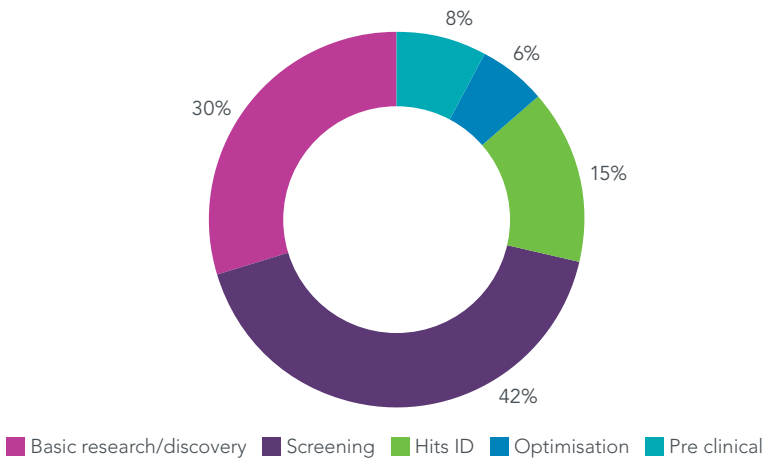
Source: WHO Global Observatory on Health R&D; EMA (2016), IFPMA (2014), DNDi (2016)

Phase III trials with industry as a main sponsor (as shown in Figure 4) it can be said that at least a third of Phase III trials would not take place without an industry partner and funding.

Looking at R&D outputs from another angle, at product approvals, the number of fully developed treatments is growing incrementally. One study registered an increase of product registrations in the period between 2000 and 2011 compared to the two previous decades, although this figure overall remained a limited percentage of total approvals (around 5%).[122] A number reflect important reformulations and extension of indications of existing treatments (and in some ways, the "low hanging fruit"), with just some new chemical entities. Table 20 provides a sample of approved products for neglected diseases from various sources, including the WHO Global Observatory on Health R&D and the European Medicines Agency.

Altogether, it is clear that the growth of spending and non-financial efforts directed towards neglected disease R&D is paying off both in terms of the rate of clinical trial activity as well as new product approvals. Having said that, much more is needed to truly fill in the gaps and unmet health needs that the developing world faces today.

FIGURE 5 Distribution of WIPO Re:Search collaborations by upstream R&D stage, as of 2016



Source: Pugatch Consilium, adapted from BVGH (2017)[123]

3.2 Capturing impact of R&D incentives and initiatives: Case examples

Upstream R&D: Open innovation platforms

Platforms encouraging "open innovation" and R&D collaborations based on voluntary licensing or sharing of data have been particularly valuable in the early phases of drug development for neglected diseases, facilitating access to databases and driving upstream partnerships. A prime example is WIPO Re:Search, a public-private partnership and IP-based initiative launched in 2011 under the aegis of the UN.[124] The overall objective of WIPO Re:Search is to stimulate partnerships and create a new market for underutilized assets with potential use for neglected disease R&D.

During the five years of operation, the WIPO Re:Search consortium has more than tripled its members, attracting participation from various multinational biopharmaceutical companies, biotech firms and universities, and overall demonstrated its proof of concept, i.e. that IP rights are conducive to greater neglected disease R&D.[125] Through the Partnership Hub this initiative connects the biopharmaceutical industry's assets and resources to qualified academic and nonprofit researchers with novel product discovery or development ideas.[126] As of January 2017, 108 collaborations had been created,[127] mostly in the basic research/discovery and screening phases.[128] By focusing on early stage research, with some collaboration reaching pre-clinical development, data sharing platforms like WIPO Re:Search may also prove complementary to PDPs who in turn manage product development, and to which candidate drugs can be transferred.[129]

WIPO Re:Search collaborations bring together a wide range of innovators and target various levels of innovation, from brand new products to repurposing of existing products.[130] For instance, research-based biopharmaceutical company MSD made available to the University of California a selection of statin analogs, a commercially successful group of drugs developed to reduce elevated cholesterol levels with potential to work as inhibitor of schistosomes.[131] MSD researchers have also provided support in interpreting results from the compound screening led by the university.[132]

In another case, Pfizer supported the efforts of a US SME to repurpose one of its compounds for treating dengue fever. The company, 60 Degree Pharmaceuticals, received access to Pfizer's confidential investigator's brochure and used the data to design its Phase Ib/IIa trial, currently ongoing in Singapore.[133]

Almost three out of four partnerships bring together research entities from developed countries.[134] While capacity building activities such as training and "in-kind" donation take place, a 2015 WIPO Re:Search external review identified room for improvement in the capacity to catalyse research efforts from developing countries' institutions.[135] Positively, in 2016 a greater number of collaborations between two entities from low-to-middle income countries were reportedly launched than during the five previous years together.[136] Expansion of the WIPO Re:Search initiative is also expected to bring about increasing capacity building activities and delivery programs.[137]

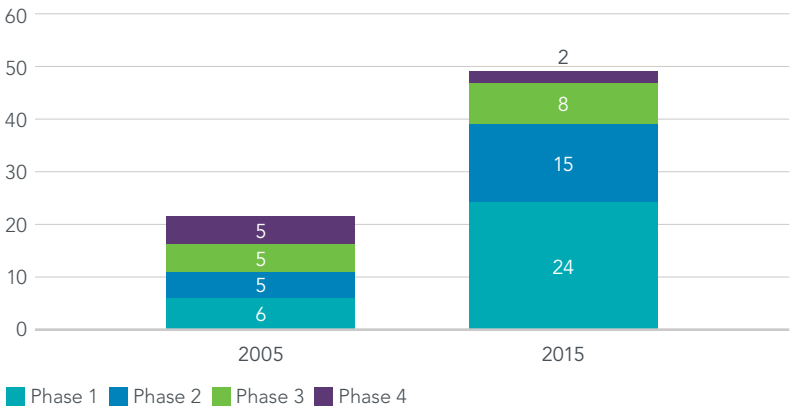
Downstream R&D: PDPs

PDPs have contributed to populating pipelines and delivering products, mostly through incremental innovation. For example, almost empty in the 1990s, today the global anti-malaria portfolio contains over 40 projects in preclinical or clinical phases (with nearly half initiated since 2010).[139] PDPs have been instrumental in this progress; the large majority of these projects have resulted from partnerships between the aforementioned MMV and biopharmaceutical companies. In particular, PDPs have contributed to bringing breakthrough products to market. Since its creation in 2003, DNDi has delivered six new treatments.[140] As another example, a partnership between GlaxoSmithKline Biologicals (GSK) and the PATH Malaria Vaccine Initiative (MVI) yielded the RTS,S/ASO1 malaria vaccine.[141]

In addition, clinical trials for which a PDP is registered as a sponsor more than doubled over the last decade, from 21 in 2005 to 53 in 2015 (as seen in Figure 6). The most remarkable increase took place in Phase I and II trials. Among the most active PDPs in terms of sponsoring clinical trials are PATH (53), Medicines for Malaria Venture (50), Aeras (49) and DNDi (40).

PDPs are also playing an important role in engaging and integrating R&D actors, such as biotechnology companies and universities, in wider partnerships. As of 2012, 40% of products for neglected diseases in development by biotechnology companies had a PDP partner.[142] Looking at it from another angle, in the case of malaria and TB PDPs have managed to increasingly leverage resources from partners. As Figure 7 shows, the share of trials sponsored by PDPs out of total trials for these two diseases increased since 2008, despite PDPs' share of funding declining since that year.[143] Involvement of PDPs in a larger number of trials suggests increased efforts to partner and distribute costs and risks across other funders.

FIGURE 6 Clinical trials for neglected diseases sponsored by PDPs and registered in Clinicaltrials.gov, 2005 and 2015, by phase[138]



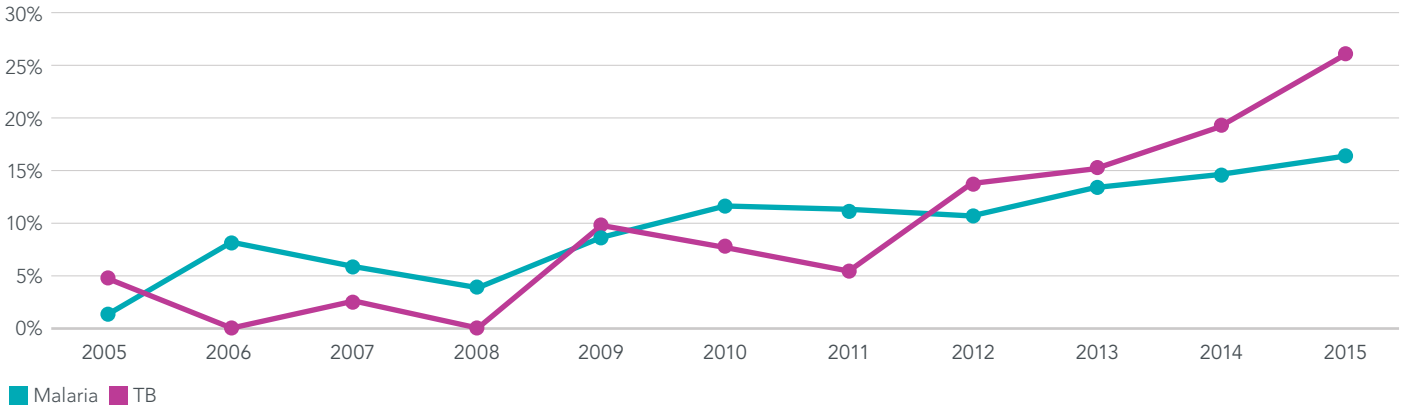
Source: Pugatch Consilium based on clinicaltrials.gov

Incremental innovation: Patent pools

While mainly applied to license patents for the production of generic drugs (as mentioned),[144] the application of patent pools to the biopharmaceutical field has also supported some important advances in incremental innovation for neglected diseases. The Medicines Patent Pool (MPP) remains the primary example of patent pooling for neglected diseases.

The MPP has primarily focused on HIV, providing licenses for most of the priority ARVs and has

FIGURE 7 Share of PDP-sponsored trials out of total trials: Focus on malaria and TB



Source: Pugatch Consilium analysis; Clinicaltrials.gov (2017)

TABLE 21 Sample of recent R&D outputs delivered by PDPs

PDPs	Clinical trials	Products approved	Delivery	Other
Program for Appropriate Technology in Health (PATH)	Most advanced malaria vaccine candidate in phase III[145] and potentially the first vaccine against a human parasite 7 vaccine candidates against pneumonia and diarrheal disease[146] Phase I trial for a new rotavirus drug	Japanese encephalitis vaccine[147] Paromomycin intramuscular injection Vaccine vial monitors SoloShot SILCS Diapraghm	MenAfriVac meningitis vaccine delivered to over 235 million people;[148] production of semisintetic artemisinin for sustainable production of antimalarian;[149] river blindness diagnostic test; rapid Strip test for malaria	Center for Vaccine Innovation and access pooling vaccine experts[150] Innovative electronic data system for real-time data to improve the quality of malaria case management[151]
Medicine for Malaria Venture	9 molecules in development to solve the challenges of drug resistance and treatment adherence[152]	4 antimalarial products approved (latest pediatric formulation Piramax – pinoradinine artesunade)	Over 250 million courses of Coartem dispersable given to children 52.9 million vials of artesin injection against severe malaria distributed	230 malaria boxes distributed to researchers Established a network of clinical trial sites in malaria- endemic countries
Drugs for Neglected Diseases Initiatives (DNDi)	Development of advanced oral candidate for HAT completed in 2016; partnership with Sanofi[153] Development of a NCE (Fexinidazole)	Launch of new combination treatment for sleeping sickness;[154] and 5 new formulations (ASAQ and ASMQ for malaria, SSG&PM for VL in Africa, a pediatric dosage of benznidazole for Chagas, a combination VL treatment for Asia)[155]	6 implementation projects to give access to new treatment developed	3 regional disease-specific clinical trial platforms NTD Drug Discovery Booster project to speed up compounds identification with 5 pharmaceutical companies
Global Alliance for TB Drug Development (TB Alliance)	nixTB clinical trial first trial to study an XDR-TB drug regimen with minimal pre-existing resistance[156] Phase 2b trial testing a novel regimen (including 2 NCEs)[157] to reduce treatment	2 approved pediatric formulations[158]	Partnerships with national actors for access to new formulations[159]	School-based curriculum, educational materials on TB[160]

Source: Pugatch Consilium based on PDP websites and yearly reports

expanded the number of countries where formulations can be sold. All licenses include the possibility of combining products into appropriate fixed-dose combinations or developing adapted pediatric formulations.[161] As Table 22 indicates, development of nearly half of the priority formulations and products identified by the Pediatric Antiretroviral Drug Optimization group had been initiated as of 2015, with a lag time on average of 2-3 years from availability of the license through the MPP. These were carried out mainly in partnership with DNDi and UNITAID through the Pediatric HIV Treatment Initiative. Having said that there is still a long way to go to leverage available compounds for pediatric formulations of ARVs.[162] All key pediatric HIV medicines under IP protection have been pooled (and their formulations permitted for sale in the countries where 98% of children with HIV live),[163] yet of 45 HIV treatment formulations available in 2015, just 8 were adapted for children needs.[164]

As mentioned the MPP has also recently broken new ground by licensing a compound still under development with potential for TB treatment in combination with other drugs. The aim is to bring the product through Phase IIb clinical development and on, though use of the license toward this end is still in the early stages.[165]

3.3 Section summary

Reviewing a sample of empirical evidence on the level of actual R&D taking place it is clear that the rising tide of international efforts over the past two decades has paid off. Though data varies depending on how investment is measured, the evidence discussed in this section suggest that the past few years have been no exception, with unprecedented momentum in investment and collaboration on neglected disease R&D and expansion into new disease areas and unresolved needs. Though still a small share of total R&D, translational R&D and clinical development of tangible neglected disease treatments, vaccines and diagnostics has risen and patients in developing countries are benefitting from advance access. Where possible these products are also being launched in market in the developing world.

Still, it goes without saying that much more is required to continue to close the R&D gaps for the developing world. Ensuring a higher rate of later phase clinical development and launch of products is essential. Expanding R&D efforts to cover more LDCs; remaining neglected diseases and populations; and new, looming challenges represent some of the top priorities. To better leverage the investment and instruments under discussion today, it is crucial to understand when and how R&D incentives and mechanisms aimed at neglected diseases might most effectively be applied.

TABLE 22 Development status of priority pediatric HIV formulations and products as of 2015

Priority pediatric formulations and products (as per PADO2)	Licensed to MPP	Development started by MPP licensees (as of 2015)
ABC/3TC/LPV/r	2013 (ABC), 2014 (LPV)	Pediatric HIV Treatment Initiative (PHTI)
LPV/r	2014	-
ABC/3TC/EFV		PHTI project
DRV/r	(Patent holder supports PHTI)[166]	PHTI project
RAL	2015	-
ATV/r	2013	-
DTG/XTC/TAF	2014 (DTG, TAF)	-
DTG	2014	-

Source: Pugatch Consilium based on Fernando Pascual and Sandeep Juneja (MPP)[167] and MPP Progress Report 2010-2015

4 A MODEL FOR OPTIMIZING THE USE OF R&D INCENTIVES AND DELINKING MECHANISMS FOR NEGLECTED DISEASES

Of the R&D and delinking mechanisms analyzed in the previous sections of this study, none alone can fill the gaps in R&D incentives and address unmet needs in the area of neglected diseases. The Blueprint for Success developed in section 2 highlights the strengths and weaknesses of each mechanism and the degree to which each address key gaps in R&D incentives, including both push and pull angles.

The impact analysis in section 3 supplements with hard evidence on outcomes generally and from major, established mechanisms, underscoring which, based on the data available thus far, have shown relatively greater promise to stimulate R&D and which, less. In other words, some mechanisms are more likely to be successful in driving real advances in neglected disease R&D than others.

Yet, by this standard a number of existing and proposed mechanisms show promise. How and in what manner should they be applied in order to most effectively fill in gaps in R&D incentives?

Perhaps even more importantly, how can R&D incentives and delinking mechanisms work in tandem with existing market-based incentives to create new synergies for neglected disease R&D? For instance, can PDPs lend additional operational or financial resources that facilitate existing clinical research efforts by research-based biopharmaceutical companies moving forward at a faster pace? Can voluntary patent pools and knowledge-sharing platforms enable wider licensing and use of IP rights to drive various pipelines – including, but not limited to, new, neglected disease applications?

The need to build on the specific strengths of both push and pull mechanisms through hybrid strategies (including more conventional market-based incentives such as IP rights and other commercial incentives) is already accepted.[168] What is less clear and what this section seeks to address is, is there a concrete scheme – a strategic playbook – based on which R&D partners, governments, international institutions and other key stakeholders can optimize the use of incentives and mechanisms to effectively create momentum to advance R&D from discovery to full development and deliver novel treatments and technologies where they are needed most?

This section presents a multi-layered model for optimizing the use of R&D incentives and delinking mechanisms within different contexts. Various angles could be examined, but this model looks at the following three layers or perspectives:

1. The R&D life cycle

This layer looks at which area(s) of the R&D process a given mechanism is most effectively applied.

2. R&D players

This layer examines which mechanism(s) different R&D entities should focus their efforts on. In what areas should they position themselves to deliver the greatest benefit in terms of advancing neglected disease R&D?

3. Level of innovation

This layer explores how a given mechanism should be used in terms of the type or degree of needed innovation (in terms of a given disease, population, etc) it supports, recognizing that different levels of innovation require varying degrees of investment and therefore different sets of incentives.

4.1 Layer 1: The R&D life-cycle perspective

In order to ensure that R&D actually takes place and that an end product is produced and made available, it is important that each incentive and delinking mechanism be viewed not as a stand-alone solution but as an element of a sustainable,

long-term framework that together addresses all components of the R&D life-cycle. Some incentives can be short-term or targeted catalysts for certain components of the R&D process, but do not necessarily support R&D beyond the targeted area or phase. It therefore crucial to have a picture of which mechanisms stand out as functioning well in the early phases of R&D (research and discovery as well as pre-clinical development), which ones particularly focus on later stage development including clinical research, and finally those that mainly target registration, production and delivery.

TABLE 23 Understanding where incentives and delinking mechanisms function best throughout the R&D life-cycle

	Research & discovery	*Preclinical development*	*Clinical development*		*Registration*	*Post-marketing & delivery*
Collaborative research	Enabling	Somewhat enabling				
Research data pooling/sharing	Enabling	Enabling	Somewhat enabling	Somewhat enabling		
Grants	Enabling	Enabling	Somewhat enabling			
Financial instruments/PRIs		Enabling	Somewhat enabling	Somewhat enabling	Somewhat enabling	Somewhat enabling
R&D prizes	Somewhat enabling	Enabling				Somewhat enabling
International regulatory harmonization			Somewhat enabling	Somewhat enabling	Enabling	
Priority review vouchers			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Advanced Market Commitments				Somewhat enabling	Enabling	Enabling
R&D tax credits			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Conventional market/IP-based model	Somewhat enabling	Somewhat enabling	Enabling	Enabling	Enabling	Enabling
Extended or transferable IP rights/exclusivity			Somewhat enabling	Somewhat enabling	Enabling	Enabling
Patent pools				Somewhat enabling		Enabling
PDPs	Somewhat enabling	Enabling	Enabling	Enabling	Enabling	Enabling

Financing-based incentive Regulatory incentive Operational incentive

Source: Pugatch Consilium

Principle 1: Pre-defined and highly targeted funding mechanisms and open innovation platforms mainly drive upstream research

Mechanisms providing highly targeted and pre-defined financial support – whether acting as a push or pull mechanism – generally operate best in the upstream phase of the R&D process, including basic research and drug discovery as well as development in the laboratory. Certain mechanisms have a more proven track record for accelerating drug discovery and lead optimization and even early drug development, such as research grants and data and know-how sharing/pooling platforms like WIPO Re:Search and different industry-sponsored 'open labs'. Also, financial instruments, like equity investments and program related investment, that mainly target research projects (there are also PRIs for other phases) are promising for translational research and overcoming the so-called "valley of death" between drug discovery and product development. R&D tax credits can also be considered to fall in this category; though they are more open-ended than other mechanisms and may also impact other stages of R&D they have tended to function best stimulating early drug development rather than late development.

Other targeted mechanisms are not yet launched, remain mostly under discussion with little tangible activity or only show promise under limited circumstances. For example, R&D prizes are most useful where the way forward, for instance in terms of treatment or diagnosis of a given disease, is not clear and more non-traditional approaches are needed, and have therefore generally tackled specific research questions to advance early development phases of medicines and diagnostic tools. Crowdsourcing models are typically focused on the discovery phase up to clinical development but remain mostly conceptual and thus far have a limited application, to some extent because of a lack of a financial element that can support moving forward with development of a compound once it is identified.

Principle 2: Downstream R&D requires more open-ended funding mechanisms and market-based platforms

Given the high costs of later stage drug development, scale-up, registration and launch of an actual product, mechanisms that are relatively less defined and limited in resources tend to support downstream R&D better than narrower mechanisms. Market-based incentives, including reduction or transfer of regulatory costs as well as IP-based models that allow R&D entities to determine focus and scale of investment, are particularly tailored for downstream R&D. Many such mechanisms are pull mechanisms that function best when the prospect of a complete and approved product is more established, including priority review vouchers, extended or transferable market exclusivity and AMCs. These types of pull mechanisms can generally provide necessary additional financial and resource-based incentives to enable the last phases of development. Broadly speaking, the extent and pulling force of these models depends on their size. Relatively smaller commitments, such as AMCs, can mostly support scale up of the supply of drugs for which development is already largely complete, whereas wider incentives or larger commitments involving funding, know-how and operational support, such as PDPs, patent pools (to the extent they are applied to novel drug development) and additional exclusivity, could expand the pulling effect to the clinical development phases.

Principle 3: A full or partial market-based model remains the key incentive for clinical research

Who funds and carries out clinical trials – as mentioned, one of the most costly phases of the biopharmaceutical R&D life-cycle – still represents an important challenge in the neglected disease R&D puzzle. As Table 23 indicates, few mechanisms and incentives effectively cover the clinical phases (and particularly not in a scalable manner). PDPs remain one of the few major platforms that focus specifically on clinical development by leveraging partnerships with industry, local public and private actors and non-profits. Under certain circumstances, such as epidemics or other situations requiring extremely urgent accelerated development of drugs or vaccines, sufficient

resources are made available and combined to enable clinical testing of promising candidates (for instance in the case of the Ebola virus). In addition, on a limited basis grants can reduce the investment required of biopharmaceutical companies by adding direct funding for trials as well as sponsoring R&D and regulatory capacity building for local actors.[169]

As a result, R&D incentives and delinking mechanisms targeting clinical research mainly complement the existing market-based model of clinical development. In other words, the research-based biopharmaceutical industry operating primarily on a market-based model continues to play a central role in incentivizing clinical research. R&D mechanisms that complement, rather than seek to fully replace, the market-based model through additional funding, incentives and other resources stand the best chance of providing the necessary impetus for companies to invest in clinical research that would not have otherwise taken place or at a much more rapid pace.

Principle 4: IP rights are not antithetical to neglected disease R&D and delinking mechanisms

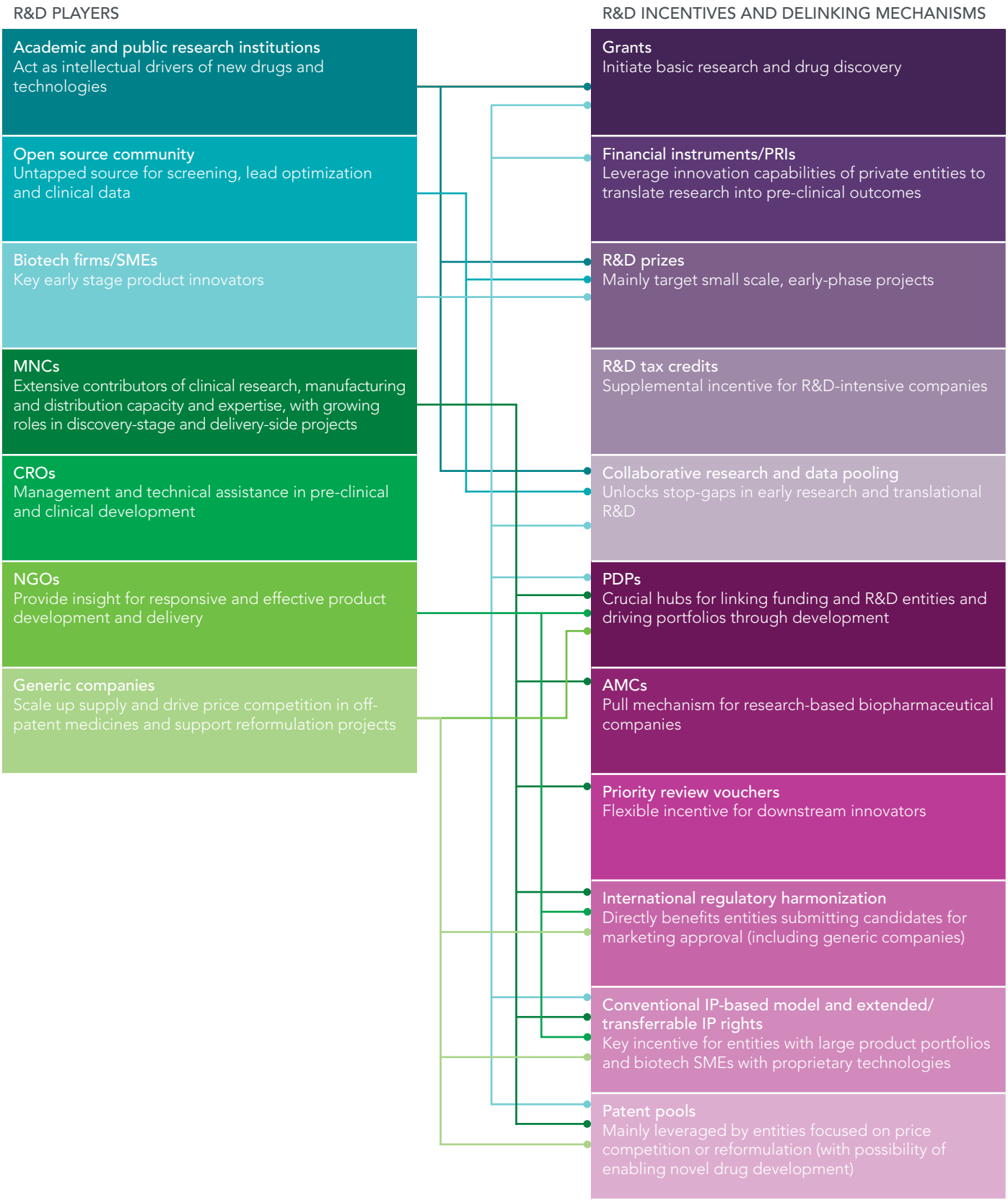
In a similar vein, looking at the spread of R&D incentives and delinking mechanisms across the R&D life-cycle in Table 23, it appears that on top of the conventional IP-derived R&D model which runs across the R&D life-cycle, at each major stage IP-reliant models remain a relevant and even integral component in several R&D incentives and delinking mechanisms. Open innovation and research and patent pooling platforms often rest on licensing of assets (whether exclusive or non-exclusive) for knowledge diffusion aimed at stimulating upstream research. As outlined in section 2, many PDPs also utilize proprietary models for R&D partnerships and collaborations. Moreover, in various mechanisms, R&D entities are able to retain IP on compounds developed within a given mechanism, even if there are sometimes limitations on how it is exercised vis-à-vis certain countries or situations.

4.2 Layer 2: Maximizing the strengths of key R&D players

On top of understanding where in the R&D life-cycle each mechanism or incentive can be most effectively applied it is also important to identify how to maximize the role of different R&D actors in using these mechanisms and incentives. Which mechanisms are best used by academic or public research entities and which by private entities? Which mechanisms leverage each entity's natural capacity, existing incentive structure and ongoing R&D efforts best?

As Figure 8 indicates mechanisms aimed at upstream R&D tend to activate R&D players that are focused primarily on drug discovery and translational R&D. In turn, downstream-related mechanisms best leverage the capacity and work of private entities, including multinational research-based biopharmaceutical companies and biotech firms. The following sub-section outlines the way in which different mechanisms align with the strengths and focuses of key R&D players in neglected disease R&D.

FIGURE 8 Aligning R&D mechanisms and incentives with key R&D players



4.3 Layer 3: Ensuring alignment with the desired level of innovation

Finally, it is crucial to consider mechanisms against the desired outcome of a given area of neglected disease R&D. Whether a given mechanism is appropriate depends on the specific R&D needs of the target disease, technology type (drug, vaccine or diagnostic) and relevant population(s). For example, some R&D gaps require breakthrough products, others modifications or incremental improvements to established technologies and still others sustainable manufacturing and delivery of existing drugs. Of course, this is not a hard and fast division. In fact, taking global R&D together many disease portfolios focus in parallel on short-term, "quick wins" like reformulating an already marketed drug for a certain population and longer-term R&D efforts focused on therapies that come at the disease from a completely new angle.

For example, there is, no doubt, a need to feed neglected disease pipelines with breakthrough discoveries, such as development of vaccines for HIV and therapies for Type III diseases for which very little research is underway. Many of the push mechanisms driving upstream R&D inherently target novel drug R&D.

Other mechanisms, such as AMCs and (when it comes to R&D) patent pools, have thus far been used mainly to stimulate incremental innovation. Incremental innovation plays a crucial role in tackling unmet needs of LDCs and maximizing the use of resources by targeting reformulation or repurposing of existing drugs for use in neglected diseases. While a relatively large market exists for new HIV treatments, unmet medical needs of LDCs relate to new fixed doses combination or pediatric formulations. In the case of tuberculosis, improved delivery platforms and diagnostics are among the most compelling research needs (and the Medicines Patent Pool has sought to address these needs for the past several years).[170]

Finally, mechanisms enabling scale-up production of existing vaccines and drugs, including generics, are also crucial for addressing unmet health needs around neglected diseases in developing and least developed countries. Production and distribution of existing rotavirus vaccines has enabled great progress towards diarrhea prevention in infants.[171] In addition, despite a growing interest in reformulation and recently in end stage novel drug development, in large part the MPP and concept of patent pooling for neglected diseases more generally has focused on acquiring voluntary licenses for on-patent HIV medicines for generic production in LDCs.

4.4 Putting it all together: Sample "mechanism mixes"

What the model developed in this section depicts is when, by whom and for what purpose to use different R&D incentives and delinking mechanisms – in tandem with the existing biopharmaceutical R&D model – in order to effectively leverage the most suitable R&D partners at each phase of the process and achieve the desired outcome in a sustainable manner. Drawing on this model, various combination of mechanisms may be considered.

For instance, with the aim of developing a breakthrough treatment, one approach could be to:

1) Combine data pooling with a financial-based mechanism such as grants or equity investments that together act as push mechanisms for funding and enabling upstream R&D; followed by

2) Leveraging the drug discovery capabilities of academic programs and the translational capacity of biotech firms for preclinical development; followed by

3) A PDP partnering with a research-based biopharmaceutical company and CRO, along with local partners, for the clinical development phase; and

4) Use of a priority review voucher for an MNC-led registration of the drug.

For reformulating or repurposing of an existing treatment for a new indication or area, one approach might be to use patent pooling to acquire a protected technology needed to alter the existing drug and an AMC to stimulate extension of clinical trials to this indication/formulation as well as production and delivery to countries in need.

It goes without saying that every disease area and gap in neglected disease R&D faces its own particular set of circumstances and there is need for a nuanced approach to address each. Having said that, the model or strategic playbook of "moves" developed in this section for different general situations is one proposal for optimizing application of the many R&D incentives and mechanisms under discussion today with the hope of generating new synergies and continuing to intensify progress toward addressing gaps in neglected disease R&D.

FIGURE 9 Potential mechanisms mix #1: Combination of R&D incentives and delinking mechanisms to support development of a breakthrough treatment

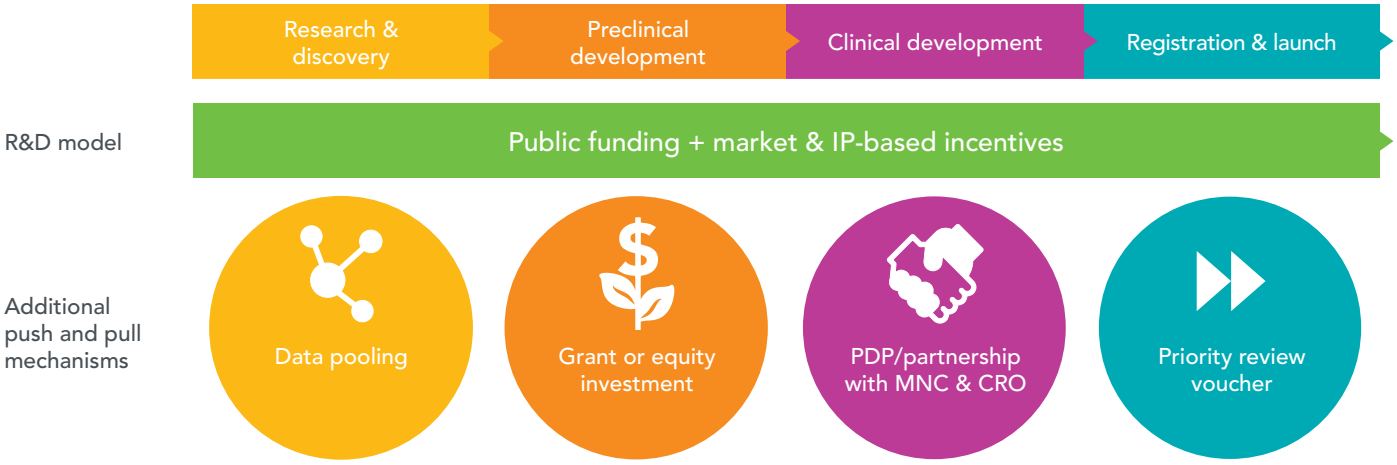
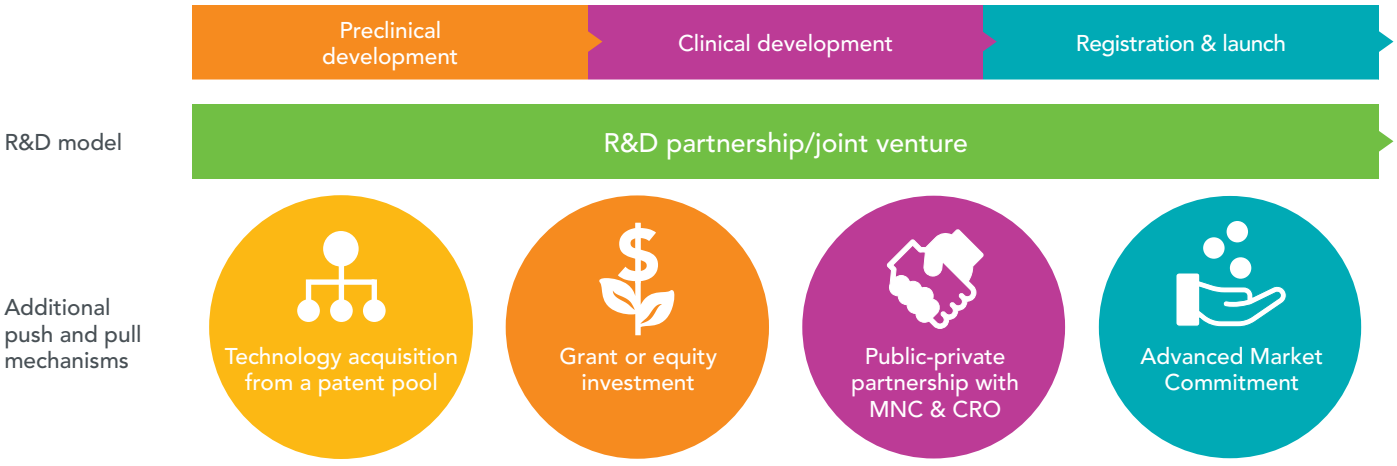


FIGURE 10 Potential mechanisms mix #2: Combination of R&D incentives and delinking mechanisms to support development of a reformulated or repurposed drug



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