HEALTH PRODUCT RESEARCH & DEVELOPMENT FUND: A PROPOSAL FOR FINANCING AND OPERATION

Special Programme for Research and Training in Tropical Diseases (TDR)

World Health Organization

TDR For research on diseases of poverty
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Particular care was taken to ensure that a broad range of perspectives were captured, including different clusters and units within WHO, organizations undertaking R&D, regulatory agencies, funding bodies, intergovernmental organizations, nongovernmental organizations (NGOs), health and other ministries. These inputs have greatly contributed to the development of the approach outlined in this report. We very much appreciate the time and experience people shared.

We would also like to thank the Swiss Agency for Development and Cooperation for helping to fund this study and the resulting analysis and options presented. The contents of this report are the sole responsibility of TDR and can in no way be taken to reflect the views of the Swiss Agency for Development and Cooperation.

And the management of the portfolio of funded R&D projects. The principle aim of the financial mechanism is to support the development of health products that are accessible and affordable to the populations that need them. As requested by the World Health Assembly, the options presented in this report utilize existing mechanisms.

PREFACE

Despite the funding of over US$ 3.4 billion reported by the 2015 G-Finder to support research and development (R&D) of new products for neglected diseases, R&D pipelines are still limited for products treating diseases primarily targeting low- and middle-income countries (LMICs), compared to products with higher market values.

Through the decision by the World Health Assembly (WHA67(15)),[1] the Special Programme for Research and Training in Tropical Diseases (TDR)[2] was asked by the Director-General of the World Health Organization (WHO) to explore the possibility of using TDR's existing governance mechanism to host a pooled fund, raised by the WHO, to support R&D for Type III and Type II diseases and the specific R&D needs of developing countries in relation to Type I diseases.

I am pleased to share with you a report detailing work that was undertaken with analytic support from McKinsey & Company. The work focused on the following:

1. developing for the first time, a financial model for a health product R&D Fund for Type III and II diseases;
2. preparing a TDR-based Scientific Working Group (SWG) for the management of R&D project portfolios and a sustainable health product R&D Fund; and
3. designing a compendium of target product profiles (TPPs) for these neglected diseases to assist the work of the SWG and provide a global picture of health product needs for these disease areas.

We are grateful to the Government of Switzerland for funding these exploratory studies and would also like to extend our gratitude to the many interviewees who kindly provided their insights, experiences and advice.

As you will see in the report, in order to accelerate and fill the gaps in the R&D pipeline for diseases primarily affecting LMICs, the following issues needed to be considered:

- a fund of sufficient scale (e.g. reaching US$ 100 million annually over a 10-year period) should be set up;
- the fund's project portfolio should be varied by including both short-term repurposing and longer-term discovery efforts;
- the fund must be operated transparently, with clear objectives and non-political, evidence-based decision-making processes; and
- the fund must have a methodology for accepting "new" funders and maximizing leverage.

Based on its extensive experience in developing and managing a wide-range of project portfolios and a pooled fund, TDR is confident that, if requested, it could establish a transparent and efficient governance mechanism to manage the pooled fund and to assist in accelerating the development of diagnostics, vaccines and treatments.

John Reeder

Director
Special Programme for Research and Training in
Tropical Diseases (TDR)

1. For the decision see: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_DIV3-en.pdf (accessed 10 February 2016).
2. TDR website: http://www.who.int/tdr/about/en/ (accessed 28 January 2016).

FOREWORD

This report is an important milestone in the World Health Organization's commitments to support the development of a more equitable system of health research and development (R&D). It is the first attempt to provide an analysis of the current R&D landscape for diseases of poverty, and to propose how to de-link the cost of these products from their research and development.

A mere 1% of the new chemical compounds registered between 2000 and 2011 were approved for diseases of poverty,[3] even though these diseases make up 11% of the disease burden.[4] Recognizing this gap, members of the World Health Assembly asked the Director-General, Margaret Chan, to pursue this work. Following a review of existing mechanisms to support R&D, the Special Programme for Research and Training (TDR) was identified as the best organization to provide a proposal on how to finance and operationalize this critical work.

This report provides a new tool that TDR has developed that can estimate the minimum development costs and timeline for R&D from preclinical through Phase III trials. It also provides a suggested structure for the management of a pooled fund that would support projects coming out of global priorities that meet the greatest public health needs.

The proposed fund structure would be set up to ensure that any new treatments or diagnostic tools developed are affordable, accessible, acceptable and available to the countries that need them.

We believe this report provides thoughtful analysis on how to create a new and fairer R&D system for diseases without a commercial market. It offers all Member States of the World Health Organization the opportunity to become involved – identifying those priorities, funding those priorities, and sharing the benefits of both better health and stronger development for all.

Professor Hannah Akuffo

TDR Joint Coordinating Board Chair

Dr Ren Minghui

Assistant Director-General
HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases/TDR Special Programme Coordinator,
World Health Organization

3. Pedrique B, et. al., The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. Lancet GH. 2013;1:e371–9.
4. Murray CJL, et. al., Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 2012; 380: 2197–223.

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ABBREVIATIONS

BMGF	Bill and Melinda Gates Foundation
CMC	Chemistry, manufacturing and control
COI	Conflicts of interest
DALY	Disability-adjusted life year
DFID	Department for International Development of the United Kingdom
DND*i*	Drugs for Neglected Diseases *initiative*
Dx	Diagnostic
FDA	Food and Drug Administration of the United States
FIND	Foundation for Innovative New Diagnostics
GAVI	Gavi, the Vaccine Alliance
GHIF	Global Health Investment Fund
GHIT Fund	Global Health Innovative Technology Fund
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
GPH	Global public health
HIV/AIDS	Human immunodeficiency virus / acquired immunodeficiency syndrome
IAVI	International AIDS Vaccine Initiative
IP	Intellectual property
JCB	Joint Coordinating Board of TDR
KPI	Key performance indicator
LMIC	Low- and middle-income country[5]
MMV	Medicines for Malaria Venture
NCE	New chemical entity
NGO	Nongovernmental organization
NIH	National Institutes of Health of the United States
NTD	Neglected tropical disease
P2I model	Portfolio-To-Impact model of TDR
PDP	Product development partnership
R&D	Research and development
Rx	Drug/treatment
SAGE	Strategic Advisory Group of Experts on Immunization
STAC	Strategic Technical Advisory Committee of TDR
SWG	Scientific Working Group
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
Vx	Vaccine
WHA	World Health Assembly
WHO	World Health Organization

5. As defined by the World Bank.

EXECUTIVE SUMMARY

Research and development (R&D) for health products normally focuses on diseases with a commercial market in high-income countries. R&D is still limited for several, if not most, diseases defined by the World Health Organization (WHO) as Type III and II diseases:

- **Type I diseases:** are incident in both rich and poor countries with large numbers of vulnerable populations in each;
- **Type II diseases:** are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries;
- **Type III diseases:** are those that are overwhelmingly or exclusively incident in developing countries.[6]

Furthermore, there is little coordination between funders on disease priorities for existing funding, meaning that individual efforts are sometimes fragmented. The World Health Assembly (WHA) asked the Director General, through the Special Programme for Research and Training in Tropical Diseases (TDR), to explore how a new fund, raised by WHO, would assist in giving impetus to R&D for these diseases in order to eventually lead to new health products (diagnostics, vaccines and treatments). This report outlines the outcomes of the preparatory studies conducted to explore financing mechanisms, including options for the fund's creation and key operational considerations.

There are funding bottlenecks for R&D throughout the development pipeline for Type III and II diseases, in particular with respect to translational research and expensive phase III clinical trials. R&D financing needs differ by disease, with diagnostics most critical for some diseases and new treatments or vaccines for others. WHO is currently developing a broad WHO Prioritization Mechanism to set priorities based on data collected by the WHO Global Observatory on Health Research and Development (R&D). It should be noted that the exact structure and mandate of the WHO Prioritization Mechanism had not been defined during the preparation of the report. However, the financing and downstream coordination mechanism described in this report will be applicable in putting into operation any priorities set by the WHO Prioritization Mechanism.

Financing and coordination mechanisms would help to address some of the most critical funding bottlenecks and shortages. These mechanisms could perform three main roles.

1. **An operational priority setting mechanism** could unite diverse stakeholders to effectively focus on the most critical unmet needs in the R&D of health products, as identified by the WHO Prioritization Mechanism.
2. **An active coordinating mechanism** could include the creation of a new forum to convene donors, making global R&D activities and funding needs more transparent. Larger donors are unlikely to relinquish control of their independent funding decisions, making formal coordination challenging. However, such a forum could ensure identification of critical R&D gaps and agree on how those areas could be funded. This would provide a formal mechanism for discussion, establish collaboration among funders, and give a "base" level for funding for projects that could benefit from other funders becoming involved.
3. **A direct fund** could help address some of the most critical R&D financing needs for Type III and II diseases. The potential of various fund sizes to launch new health products by 2030 was investigated. The results indicate that, in the long run, an annual disbursement of US$ 100 million or more would have the possibility of funding a portfolio of the most promising and innovative product development projects, which could overcome some of the larger gaps. This is instead of focusing solely on relatively low-cost activities such as drug reformulation or repurposing. The fund could also address the financing needs outlined below.
   - It should be constituted with "new" money, as opposed to redistributing money that is already available to public health researchers and developers.
   - The convening power of WHO could help to access such new funds, but care would have to be taken to ensure efficient and transparent processes.

6. http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf, accessed 26 January 2016. See also Annex 1.

- Building on experience acquired from product development partnerships (PDPs), public-private R&D initiatives, other funds and the private sector, the fund should have a diversified portfolio of projects and enable targeted partnerships along the projects' development paths. The portfolio should include projects that could provide shorter-term projects (development of repurposing drugs or improved point-of-care diagnostics using existing platforms) as well as longer-term discovery efforts.

Regardless of which option is ultimately chosen for the R&D financing mechanism, it will be critical to provide a set-up and process that enables transparent, objective and non-political decision-making. To ensure this, a Scientific Working Group (SWG) would be convened and managed by TDR, as per its usual operating framework governed by three bodies: the Joint Coordinating Board (JCB), the Standing Committee, and the Scientific and Technical Advisory Committee (STAC). The SWG would be responsible for: the management of the health product projects portfolio, including detailed analyses of the R&D landscape; the identification of project types with high feasibility and impact potential; the development of calls for proposals; the monitoring and evaluation of projects; and the financing recommendations of selected projects.

Together with a world-class knowledge of infectious diseases, SWG members should have experience in:

- leading product development;
- assessing risks;
- making challenging portfolio decisions, from feasibility evaluation of chemistry, manufacturing and controls (CMC)[7] to clinical trials;
- evaluating regulatory compliance and providing regulatory guidance;
- working in health systems in low- and middle- income countries (LMICs);
- financing or developing businesses, including being able to assess projects' potential to deliver health impacts and their probability of success, and assess teams' capacities and experience;
- evaluating potential health impact and values from health economists' point of views.

This core SWG could be supplemented by expert groups, such as legal and intellectual property (IP) experts, and disease and product specialists from the individual priority disease areas set by the WHO Prioritization Mechanism. Depending on the status of a funded project, the SWG would consider endorsing the use of specific incentive mechanisms (such as grant-funded push mechanisms), or proposing purchase commitment pull mechanisms to the WHA through the JCB. The ideal SWG operational mechanism would depend on how priorities are set by the WHO Prioritization Mechanism but the SWG could decide in real-time how to prioritize and put into operation the different types of projects. Depending on the availability and/or suitability of target product profiles (TPPs), the SWG would establish or finalize TPPs or candidate product profiles. The SWG would also determine the critical decision point from a funding prospective and plan in advance for engagement around important inflection points based on a key stage-gate process. The SWG's decision-making on the portfolio could be assisted by using toolkits, such as a compendium of TPPs and a framework for prioritizing projects or guiding investment decisions.

Key recommendations based on the above observations are outlined below.

1. A fund of sufficient scale (e.g. incremental increase starting at US$ 10–15 million up to US$ 100 million disbursed annually over a 10-year period) should be set up to support health product R&D in Type III and II diseases.
2. The fund's portfolio of projects (e.g. gradual increase in number of funded projects starting from 5–7 projects per year to an average of 35–40 projects) should be balanced between short-term repurposing and longer-term discovery efforts.
3. The fund should have transparent, objective and non-political decision-making processes.
4. The fund should be able to access "new" sources of funding.

This report is structured in four sections. First, the report summarizes the current R&D landscape for Type III and II diseases.[8] Then, it presents options for setting up a R&D financing mechanism. It also provides guidance on how to operate this mechanism, including setting up the SWG. Finally, it reviews the set of tools that would assist the SWG in decision-making and portfolio management. Developing countries' special R&D needs for Type I diseases was not investigated, but the Financial Mechanism presented in this report would still be applicable as this broadly falls under the need to repurpose existing health products.

Although the studies were conducted at the WHA's request to the Director-General to prepare for discussions to consider establishing a global product development fund and to understand how it could be put into operation, the outcomes outlined in this report could find wider adoption and assistance in filling the R&D pipeline gaps for diseases of poverty or to fulfil other unmet needs, such as the development of new antibiotics to combat antimicrobial resistance or to prepare for potential pandemic outbreaks.

7. The importance of evaluating the quality of chemical starting points was underscored by the experts involved in the Global Health Innovative Technology (GHIT) Fund in their recent publication: Katsuno K. et al. Hit and lead criteria in drug discovery for infectious diseases of the developing world. Nat Rev Drug Discov. 2015;14:751–8. Although this report covers the investigations from preclinical to phase III studies, further investigations may be required to investigate cost, time and attrition rates required in early-stage research and discovery phase, including hit discovery, target validation, assay development, lead generation and lead optimization.
8. Due to time constraints, the focus of this report is on Type III and II diseases.

1

BACKGROUND

Diseases that primarily affect low- and middle-income countries (LMICs) are still a major cause of mortality, disability and poverty *(1–3)*. The World Health Organization (WHO) defines such diseases as Type III ("overwhelmingly or exclusively incident in developing countries") and Type II ("incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries") *(4)*. (See also Annex 1).

These diseases are often referred to as neglected diseases or diseases of poverty. They consist mainly of infectious and parasitic diseases, but also include some nutritional deficiencies, maternal and neonatal conditions, respiratory infections, sensory organ diseases, cardiovascular diseases and digestive diseases *(4)*. These diseases are often characterized by market failure, where the commercial potential for drugs, vaccines and diagnostics is too small to spur sufficient product development activity *(5–6)*. Although they represent a high proportion of the disease burden in LMICs, a limited number of new treatments, only four[9] out of 336 new chemical entities (NCEs) registered between 2000 and 2011 were developed and approved for these diseases *(3)*. In 2009, approximately US$ 2.4 billion, among a global total of US$ 240 billion[10] in annual health R&D investment, was allocated to neglected diseases *(7)*. Although governments, philanthropists and industries invested over US$ 3.3 billion on R&D for 35 neglected diseases in 2014, it is unclear whether funding will continue to fill the pipeline gaps for those diseases *(8)*. Furthermore there are no universally agreed funding priorities. Taking the above into account, there is a call for change in approaches to stimulate product development to reduce the Type III and II disease burden in LMICs.

Recognizing this problem and the recommendations of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) *(9)*, the World Health Assembly (WHA) requested WHO to establish the WHO Global Observatory on Health R&D, and to convene an open-ended meeting of Member States prior to the Sixty-ninth WHA *(10)*. The WHO Global Observatory on Health R&D aims to collect data, in terms of types of health R&D being conducted, where, by whom and how, timeline and funding needs. Data will be used to assist in identifying gaps and selecting global priorities for R&D in diseases of poverty. The WHA further requested the Director-General to direct TDR to explore how a financial mechanism with voluntary contributions could be established for product R&D for Type III and II diseases, and the specific R&D needs of developing countries in relation to Type I diseases.[11]

Following this request, TDR commissioned three studies[12] to assist in providing background information for developing a financial mechanism and for rolling out a product development fund. These included: (a) the design of a financial model for a sustainable health product R&D fund; (b) the preparation of a TDR-based Scientific Working Group (SWG) to manage R&D project portfolios and a sustainable health product R&D fund; and (c) the design of a compendium of target product profiles (TPPs) *(11–13)*. It should be noted that global priority setting and fundraising are outside TDR's mandate.

The guiding principles for the work were to:

- design the fund around the heterogeneous nature of diseases;
- identify best practices with respect to the organizational and operational set-up of other relevant initiatives, e.g. Global Health Investment Fund (GHIF), Global Health Innovative Technology (GHIT) Fund, Drugs for Neglected Diseases Initiative (DND*i*), Medicines for Malaria Venture (MMV), etc.;
- engage diverse stakeholders playing crucial roles across the public health "value chain" in the design;
- reflect the nuanced incentives to potential recipients and/or to the global health community in the design; and
- integrate best practices in portfolio management and funding decisions from philanthropic donors and the private sector.

This report summarizes the work performed under this mandate and aims to:

- provide a brief overview of current R&D activity in Type III and II diseases;[13]
- outline options for a flexible financial mechanism for health product R&D, including sample product portfolios for each option;
- describe possible governance, and downstream coordination and operating models for the financial mechanism, including the set-up of a SWG; and
- provide a set of tools that the SWG could use for the fund's operations and portfolio management.

9. Excludes new chemical entities and treatment paradigm developed for HIV/AIDS.
10. Purchasing power parity-adjusted.
11. Incident in both rich and poor countries, with large numbers of vulnerable populations in each (4).
12. Studies were conducted from September to December 2015.
13. Due to time constraints, the studies focused on Type III and II diseases.

2

METHODOLOGY

This report represents the findings of a structured analytical review and assessment of global R&D financing needs and opportunities, complemented by stakeholder interviews. This analysis was structured into four key themes. An overview of the methods used under each theme is provided below.

1. The analysis of the R&D landscape for Type III and II diseases was based on multiple data sources, including: WHO and external publications and reports *(14)*; academic literature *(15)*; the Pharmaprojects clinical development database *(16)*; and stakeholder interviews.

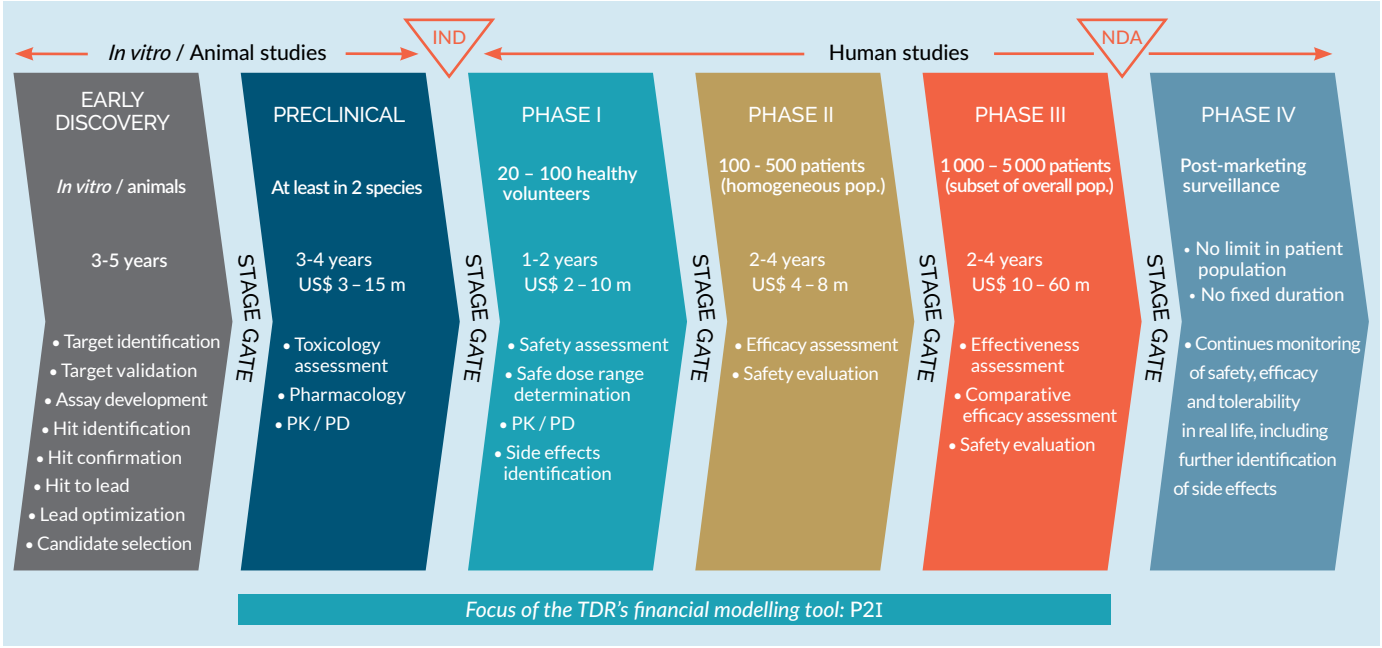
2. Options for the financial mechanism were discussed and evaluated in an interactive workshop with more than 20 participants from across WHO and TDR. This discussion was guided by inputs from the broader group of stakeholders interviewed before the workshop.

3. A financial and health impact model, named the Portfolio-To-Impact Model (P2I model) was developed specifically for this study to analyse and visualize how different funding options would assist in reducing R&D gaps and to bring new products to market for diseases of poverty. The P2I model was also designed to estimate the health impact of new interventions launched (in terms of global disease burden reduction, or disability-adjusted life years – DALYs – averted as well as lives saved) and the associated economic benefit. The model was based on assumptions specific to diseases of poverty for development costs, attrition rates and cycle times of each development phase (from preclinical to phase III) (See Fig. 2.1), with major determinants of the development challenge for each product. Specific assumptions were developed for each product archetype from diagnostics, vaccines and biologicals to drugs (see Fig. 2.2). The assumptions were based on a bottom-up analysis of clinical trial costs and a review of over 25 000 development candidates for attrition rates and cycle times *(16)*. These assumptions were further refined and validated based on academic literature *(17, 18)*, industry publications *(19)* and consultations with several PDPs, biopharmaceutical and diagnostic industry players and major donor organizations. At a high level, the model considers user inputs as well as cost, probability of success and cycle time assumptions to calculate expected launches, total costs and future pipeline snapshots (see Fig. 2.3). Although developed specifically for use with Type III and II diseases, the P2I model is flexible and robust enough that it can also be used in the context of emergency preparedness or antimicrobial resistance (AMR). However, further guidance should be determined by the WHO Prioritization Mechanism to deal with specific R&D needs for developing countries in relation to Type I diseases.

4. The governance and operating model options were based on benchmark analysis of over 15 analogous development organizations spanning the public, private and social sectors. Interviews with WHO and TDR governance experts and external stakeholders guided the tailoring of the financial mechanism as well as its governance model. The operating model recommendations were also steered by best practices in private sector portfolio management and by insights gathered from interviewees from other funder organizations.

   To supplement the above analyses, over 130 stakeholders from approximately 80 organizations, representing a cross-section of the global R&D landscape, were interviewed to gather external perspectives, validate emerging findings and inform the final recommendations. Fig. 2.4 gives a breakdown of the different stakeholders interviewed. The list of stakeholders is given in Annex 2.

FIG. 2.1 THE DRUG DEVELOPMENT PROCESS



IND: investigational new drug application; NDA: new drug application; m: million; PK: pharmacokinetics (absorption, distribution, metabolism, excretion); PD: pharmacodynamics; pop.: population; P2I: Portfolio-to-Impact.
Sources: PAREXEL *(19)*; Hughes et al. *(20)*; Paul et al. *(21)*; DiMasi et al. *(22)*.

FIG. 2.2 INTERVENTION ARCHETYPES

	ARCHETYPES		DESCRIPTION	EXAMPLES
NEW VACCINE	1	Simple	Platform has been used to develop other vaccines	Hepatitis A, Hepatitis B, polio
	2	Complex	Requires completely novel approach/no platform; no existing research exists	Pneumococcal conjugate vaccine (PCV), Meningitis B
NEW CHEMICAL ENTITY (NCE)	3	Simple	Validated target/mechanism of action	Primaquine
	4	Innovative	Novel target/mechanism of action, with understanding of disease pathogenesis	Ibrutinib
	5	Complex	Novel target/mechanism of action without understanding of disease pathogenesis	Imatinib
REPURPOSED DRUG [a]	6	Simple	Drug has sufficient safety data to start development in Phase II	Azithromycin (trachoma), doxycycline
	7	Complex	Drug requires some Phase I clinical trials to verify safety in humans	Moxidectin
NEW BIOLOGIC [b]	8	Simple	Validated target/mechanism of action	IL-17 antibody (autoimmune diseases)
	9	Complex	Novel target/mechanism of action	Natalizumab
DIAGNOSTIC	10	Assay development	Development of a diagnostic assay	Lateral flow tests, qualitative and quantitative molecular tests, etc.
	11	Simple technical platform development	Development of a technological platform that enhances current technology	Hypersensitive malaria rapid diagnostic test (RDT)

[a] Includes reformulations and combination therapies.
[b] Does not include biosimilars.

FIG. 2.3 CONCEPTUAL OVERVIEW OF FINANCIAL MODEL

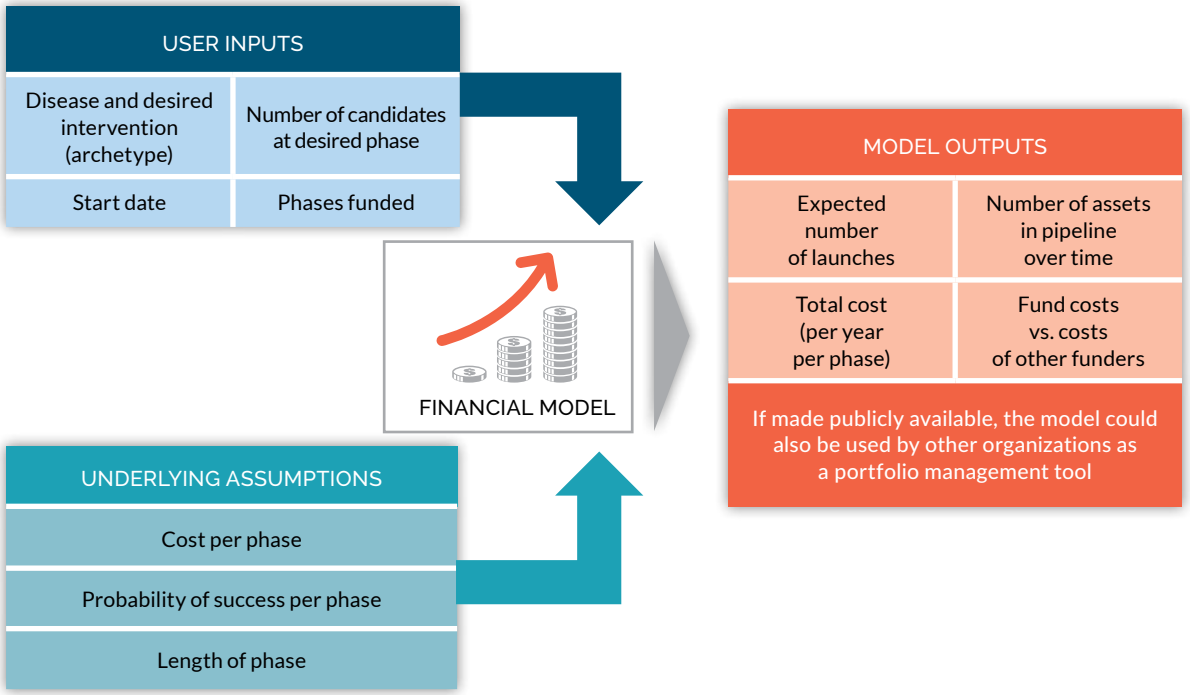
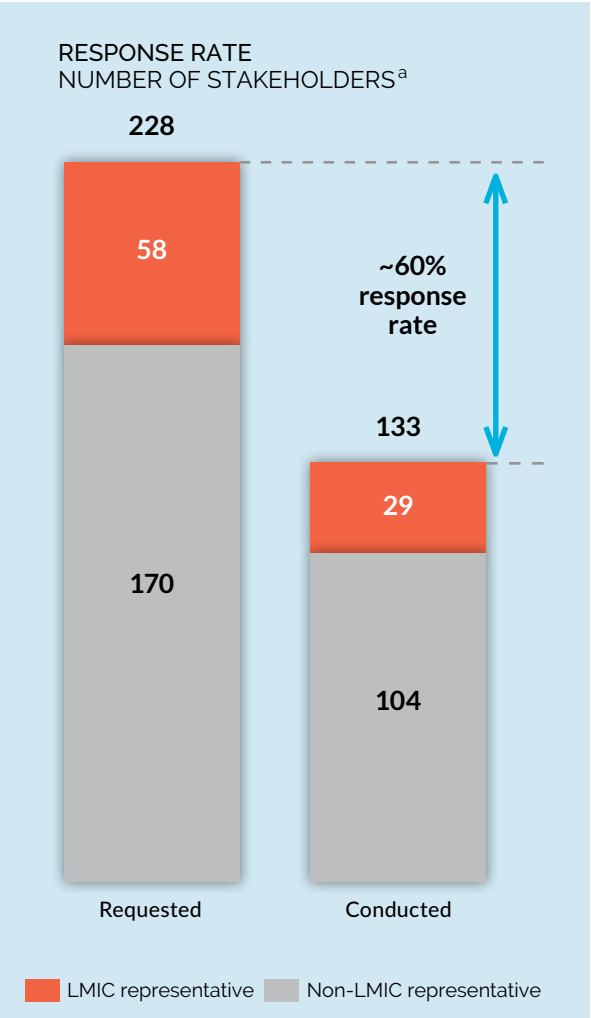
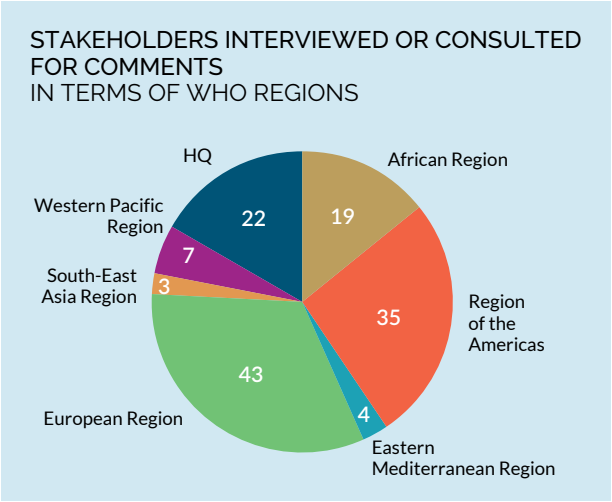
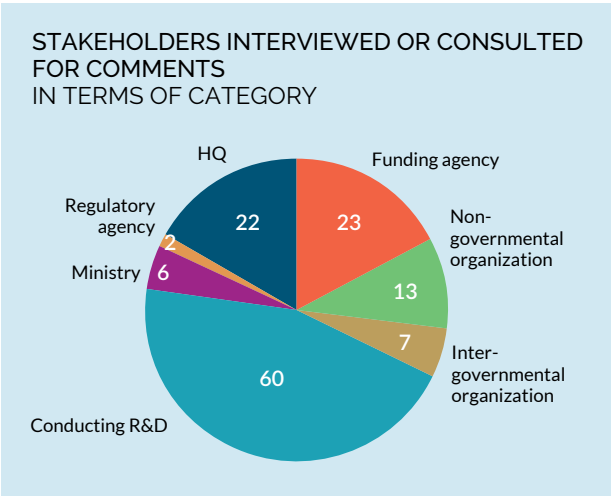


FIG. 2.4 STAKEHOLDER INTERVIEW ANALYSIS







HQ: Headquarters; LMIC: low- and middle-income country; R&D: research and development.

[a] The list of stakeholders is given in Annex 2.

3

OVERVIEW OF CURRENT R&D LANDSCAPE IN TYPE III AND II DISEASES

The review of the R&D landscape centres on three key analyses: a comparison of burden of disease with level of investment; an analysis of the pipeline per disease; and the collection of emerging themes from stakeholder interviews.

This section focuses on Type III and II diseases, acknowledging, however, that there are also unmet R&D needs in Type I diseases specific to LMICs. This landscape analysis supplements the G-Finder reports *(14)*[14] by expanding the analysis to all Type III and II diseases and investigating the treatment and vaccine R&D pipelines for each disease.

This analysis is not intended to identify specific unmet needs for each disease, or specific disease areas for a financial mechanism to prioritize. Rather it:

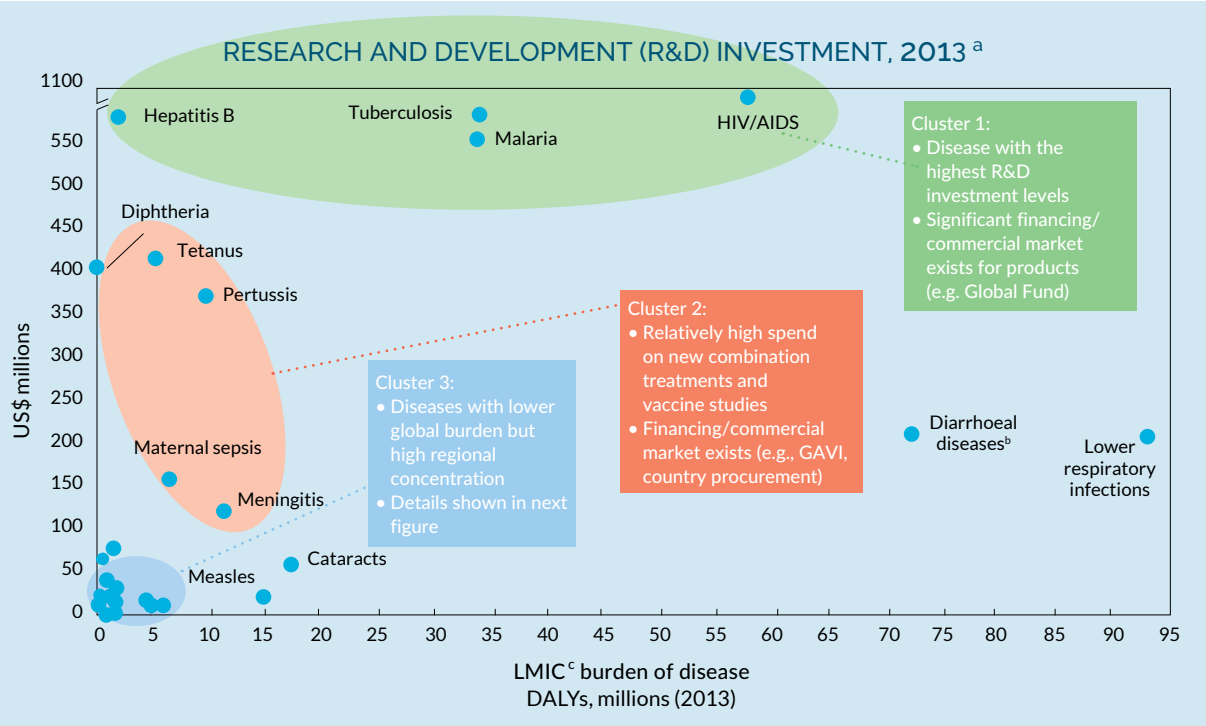
- develops realistic working assumptions for potential focus areas the WHO Prioritization Mechanism may set in order to test various options for the financial mechanism; and
- helps define example scenarios with which to compare different financial mechanism options.

The mapping of the special R&D needs of developing countries for Type I diseases was not within the scope of this report, but the financial model described would still be applicable as this broadly falls under the need to repurpose existing health products with the exception of the development of biosimilars.

The first step of the R&D landscape analysis is to understand the intensity of R&D investment relative to the burden of disease, shown in Fig. 3.1. A closer view of Cluster 3 diseases with seemingly lower global burden but with high regional concentration is shown in Fig. 3.2. The data in these analyses were generated by combining publicly available information *(14–16)* with the cost assumptions developed for the P2I model which will be published in 2016.

14. The G-Finder 2015 report had not been published at the time the financial model was developed. It should also be noted that unlike the G-Finder report, the landscape analysis covers all Type III and II diseases regardless of the need for new products.

FIG. 3.1 COMPARISON OF DISEASE BURDEN WITH INVESTMENT LEVEL



DALYs: disability-adjusted life years; GAVI: Gavi, the Vaccine Alliance; Global Fund: Global Fund to Fight AIDS, Tuberculosis and Malaria; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome.

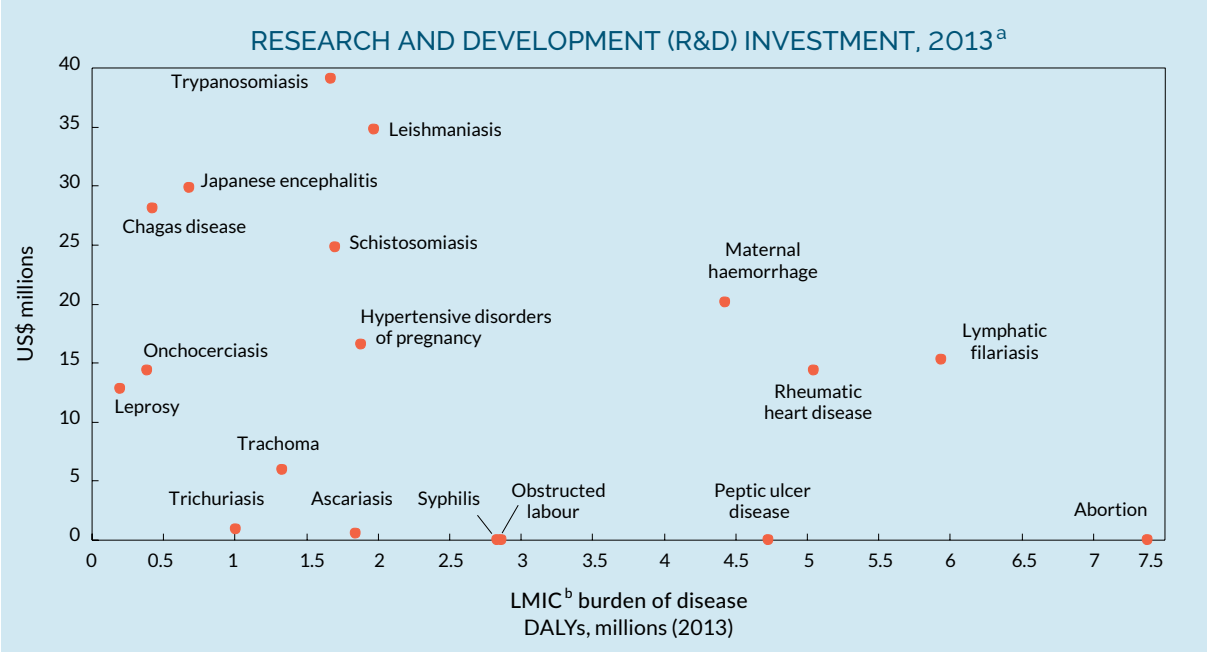
[a] R&D investment figures reflect 2014 G-Finder data where applicable; for all other diseases, R&D investment figures were estimated based on available pipeline information and cost assumptions by phase from TDR's financial model; excludes diseases requiring surgical/nutritional interventions.

[b] Includes rotavirus, *Shigella*, cholera, enterotoxigenic/enteroaggregative *Escherichia coli* (ETEC/EAggEC), *cryptosporidium*, *Gziardia* and others.

[c] World Bank Classification.

Sources: data derived from WHO Global Burden of Disease estimates (2012); G-Finder database (2014); TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016); Pharmaprojects data analysis (2015).

FIG. 3.2 ADDITIONAL DETAIL ON DISEASES SHOWN IN CLUSTER 3 FROM FIG. 3.1



DALYs: disability-adjusted life years; LMIC: low- and middle-income country.

[a] R&D investment figures reflect 2014 G-Finder data where applicable; for all other diseases, R&D investment figures were estimated based on available pipeline information and cost assumptions by phase from TDR's financial model.

[b] World Bank Classification.

Sources: data derived from WHO Global Burden of Disease estimates (2012); G-Finder database (2014); TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016); Pharmaprojects data analysis (2015).

The second analysis reviews the pipeline for each of the Type III and II diseases. This was done by cross-referencing the Pharmaprojects pipeline database *(16)* with individual diseases (Figs. 3.3, 3.4). The pipeline analyses corroborated many of the hypotheses that initially prompted this investigation. Importantly, there is significant variety within the clinical development pipelines for Type III and II diseases.

Diseases, such as malaria, tetanus, HIV/AIDS, tuberculosis (TB) and hepatitis B, have larger pipelines than truly "neglected" diseases, such as trichuriasis, rheumatic heart disease, or ascariasis, which have very few assets under development.

FIG. 3.3 DEVELOPMENT PIPELINE FOR TYPE III DISEASES FOR TREATMENTS AND VACCINES

TYPE III DISEASES [a]	NO. OF LAUNCHED PRODUCTS (Rx / Vx)	NO. OF PRECLINICAL TREATMENTS	NO. OF TREATMENTS IN DEVELOPMENT	PIPELINE IN CLINICAL DEVELOPMENT	NO. OF PRECLINICAL VACCINES	NO. OF VACCINES IN DEVELOPMENT	PIPELINE IN CLINICAL DEVELOPMENT
Malaria	(17 / 0)	45	6 7 7 20	31%	22	3 4 1 8	27%
Pertussis	(0 / 53)	1		0	9	4 3 6 2 15	63%
Tetanus	(6 / 57)	1		0	10	3 2 7 2 14	58%
Diphtheria	(0 / 55)	0		--	9	3 2 7 2 14	61%
Leishmaniasis	(6 / 0)	19	2 2 7 11	37%	1	1	50%
Schistosomiasis	(1 / 0)	5	1 2 5 8	62%	0		--
Onchocerciasis	(1 / 0)	5	3 2 5	50%	0		--
Chagas disease	(2 / 0)	12	1 2 1 4	25%	1		0
Ascariasis	(9 / 0)	1	1 3 4	80%	0		--
Lymphatic filariasis	(0 / 0)	6	3	33%	0		--
Measles	(2 / 7)	0	1	100%	4	1 1 2	33%
Trypanosomiasis	(2 / 0)	8	1 1 2	20%	0		--
Trachoma	(3 / 0)	2	1 1 2	50%	0		--
Hypertensive dis. of pregnancy	(0 / 0)	0	1 1 2	100%	0		--
Maternal haemorrhage	(8 / 0)	2	1	33%	0		--
Japanese encephalitis	(0 / 7)	2		0	5		0
Other diseases (3) [b]	(7 / 2)	0		--	0		--
TOTAL	**(64 / 181)**	**109**	**63**	**37%**	**61**	**54**	**50%**

Phase I Phase II
Phase III Registered

[a] Ordered based on total number of Rx and Vx projects in the pipeline.
[b] Includes leprosy, abortion and syphilis .
-- : no assets in either pipeline.
Source: Pharmaprojects data analysis (2015).

Key takeaways:

- Malaria has a relatively "rich" pipeline driven by a high level of donor focus and a successful product development partnership (PDP) effort over the last 15 years.
- Diphtheria-tetanus-pertussis (DTP) vaccine has a large number of launched products and current research is in follow-on vaccine combinations and improvements (e.g. Hexavalent, aP vs. wP research).
- Malaria and DTP also have significant markets; the malaria market is attributable to large procurers, e.g. Global Fund, and DTP antigens are in every immunization schedule globally, with significant support from GAVI.
- Seven vaccines against Japanese encephalitis (JE) have been launched (market creation assisted by GAVI).
- All other Type III diseases have relatively less pipeline activity or mostly preclinical research, which highlights the need for incentivizing research through early funding.

FIG. 3.4 DEVELOPMENT PIPELINE FOR TYPE II DISEASES FOR TREATMENTS AND VACCINES

TYPE II DISEASES [a]	NO. OF LAUNCHED PRODUCTS (Rx / Vx)	NO. OF PRECLINICAL TREATMENTS	NO. OF TREATMENTS IN DEVELOPMENT	PIPELINE IN CLINICAL DEVELOPMENT	NO. OF PRECLINICAL VACCINES	NO. OF VACCINES IN DEVELOPMENT	PIPELINE IN CLINICAL DEVELOPMENT
HIV/AIDS	(52 / 0)	57	17 24 14 6 61	52%	33	28 21 2 1 52	61%
Hepatitis B	(56 / 47)	46	1 14 7 1 23	33%	23	8 4 3 2 17	43%
Tuberculosis (TB)	(9 / 2)	37	4 1 9 1 15	29%	20	5 10 1 16	44%
Lower respiratory infections	(52 / 1)	20	8 15 6 2 31	61%	0	2 2	100%
Maternal sepsis	(19 / 0)	25	4 7 3 1 15	38%	0	1 1	100%
Dengue	(0 / 0)	21	5 5	19%	12	3 2 1 6	33%
Meningitis	(5 / 18)	0		--	17	1 3 5 9	35%
Upper resp. infections	(37 / 0)	7	2 3 4 9	56%	0		--
Cataracts	(12 / 0)	2	4 3 1 8	80%	0		--
Rheumatic heart disease	(8 / 0)	0	4 4	100%	0	1 1 2	100%
Trichuriasis	(9 / 0)	1	1 3 4	80%	0		--
Hookworm disease	(9 / 0)	1	1 3 4	80%	0		--
Diarrhoeal diseases	(16 / 1)	3	2 2	40%	2		0
All other diseases (4) [b]	(13 / 0)	2	1 1	33%	0		--
TOTAL	**(297 / 69)**	**222**	**182**	**45%**	**107**	**105**	**50%**

Phase I Phase II
Phase III Registered

HIV/AIDs: human immunodeficiency virus/acquired immunodeficiency syndrome.

[a] Ordered based on total number of Rx and Vx projects in the pipeline.

[b] Includes iron-deficiency anemia, peptic ulcer disease, obstructed labor, birth asphyxia and birth trauma.

-- : no assets in either pipeline.

Source: Pharmaprojects data analysis (2015).

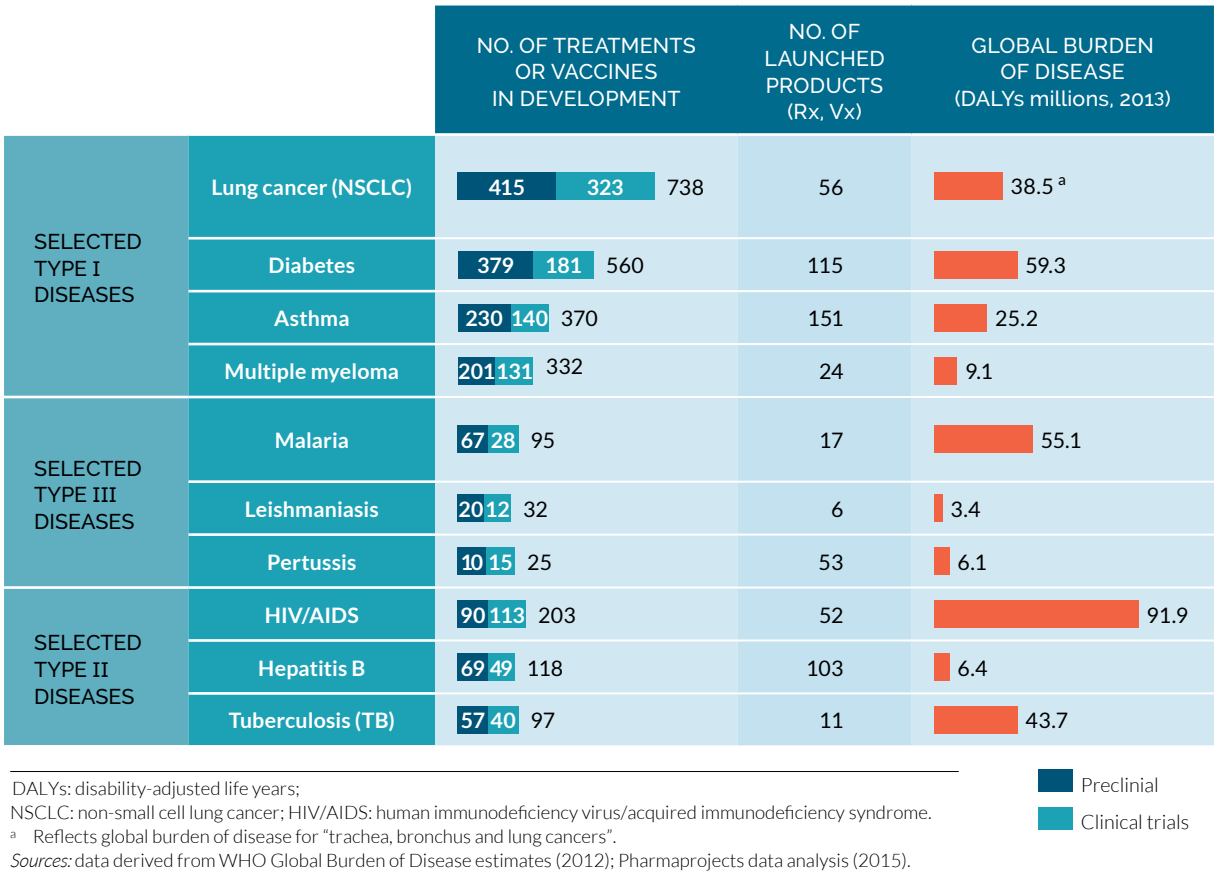
Key takeaways:

- HIV/AIDS and TB have mature markets with significant product procurers (i.e. Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR)).
- Hepatitis B has a large market due to inclusion in most immunization schedules globally.
- Dengue's very high prevalence (~400 million cases/year), mostly in middle-income countries (Brazil, Colombia, Mexico, Peru and South-East Asia) which can afford and are eager to introduce vaccines; this creates an attractive future market.
- Most other diseases have relatively smaller pipelines across treatments and vaccines.

Furthermore, the funding landscape indicates that Type III and II diseases are significantly under-funded relative to Type I diseases, despite the fact that many Type III and II diseases have significant disease burdens in LMICs. As illustrated in Fig 3.5, there are more assets under development in the pipeline for common Type I diseases, such as asthma, than those in the entire pipeline for all Type III diseases, even though the global disease burden for asthma is less than that for malaria, TB, or HIV/AIDS. Furthermore Type I "orphan" diseases,[15] such as multiple myeloma, have more assets under development than most Type III and II diseases *(15, 16)*.

15. An orphan disease is defined as a condition that affects fewer than 200,000 people nationwide. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143563.htm

FIG. 3.5 DEVELOPMENT PIPELINE FOR TREATMENTS AND VACCINES COMPARING TYPE III AND II DISEASES TO STED TYPE I DISEASES

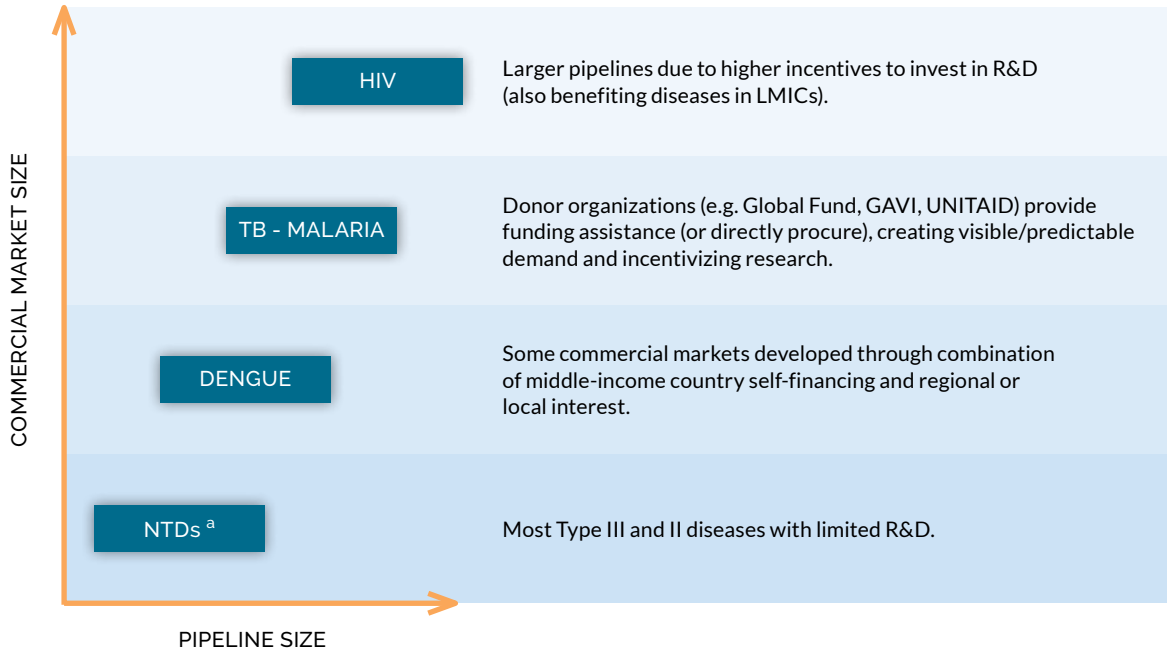


DALYs: disability-adjusted life years;
NSCLC: non-small cell lung cancer; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome.
[a] Reflects global burden of disease for "trachea, bronchus and lung cancers".
Sources: data derived from WHO Global Burden of Disease estimates (2012); Pharmaprojects data analysis (2015).

The level of product development activity appears to be primarily driven by whether or not some type of commercial market exists. Fig. 3.6 illustrates how the size of pipeline correlates with potential commercial market size. Developers have possibilities to recoup their R&D investments and potentially make a profit only when market-driven mechanisms exist. Diseases can broadly be grouped into four categories.

1. **Meaningful commercial markets exist in the developed world:** diseases with relatively larger pipelines because industry is incentivized to invest in R&D, thus also benefiting LMICs (e.g. HIV/AIDS and hepatitis C).
2. **Global public health (GPH) market mechanisms creating a commercial market:** donor organizations such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and Gavi, the Vaccine Alliance (GAVI), provide funding for (or directly procure) products for these diseases: creating visible demand once a needed product is developed (e.g. drug development against TB and malaria or malaria vaccines) and incentivizing innovative research (development of meningococcal A conjugate or pneumococcal conjugate vaccines).
3. **Global public health market mechanisms and middle-income country interest:** some commercial markets have been developed through a combination of middle-income country self-financing and interest (e.g. dengue or other vaccines common across global immunization schedules such as diphtheria and pertussis).
4. **No commercial market or market mechanisms exist:** most other Type III and II diseases with limited R&D investment have very few assets in the development pipeline, e.g. neglected tropical diseases (NTDs) such as schistosomiasis and hookworm disease.

FIG. 3.6 IMPACT OF MARKET ON PRODUCT PIPELINE



- Even diseases with larger pipelines, such as HIV/AIDS or malaria, **still have serious** and **specific unmet** needs.
- This underscores the **need to identify gaps** for all Type III and Type III diseases.
- A full review would be performed by the **WHO Global Observatory on Health R&D.**

Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria; GAVI: Gavi, the Vaccine Alliance; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; LMICs: low- and middle-income countries; NTDs: neglected tropical diseases; R&D: research and development; TB; tuberculosis.

[a] For example, schistosomiasis, hookworm, etc.

More importantly, even diseases with larger pipelines, such as HIV/AIDS or malaria, still have serious and specific unmet needs, underscoring the need to identify gaps for all Type III and II diseases. However, a full review is not within the scope of this report and will be best addressed by the WHO Prioritization Mechanism using the data collected by the WHO Global Observatory on Health R&D.

Interviews with a broad assortment of stakeholders highlight gaps throughout the R&D process, including basic research, and early development and phase III trials. Several reasons for these gaps are suggested below.

- Meaningful progress has been made on the highest burden diseases where various stakeholder efforts (e.g. PDPs, donors, industry) have "moved the needle", resulting in a reasonable development pipeline (e.g. malaria and TB). However, there has been mixed success in truly neglected diseases, which has resulted in minimal funding and relatively limited pipelines (e.g. ascariasis, lymphatic filariasis, trachoma and trichuriasis).
- A poor understanding of basic science and disease pathways partially underlies the lack of progress on several neglected diseases (e.g. Chagas disease).
- A lack of funding for early translational research (also referred to as "valley of death") is driven by the sizeable financial risk and relatively low chances of success in taking vaccine and therapeutic candidates from preclinical stage to clinical stage (through proof-of-mechanism).
- On the clinical development side, large-scale phase III studies have been difficult to fund and often require pharma co-development. However, pharmaceutical companies often lack the incentive to dedicate top talent to these neglected disease projects, which for them could be seen as of relatively low strategic priority.
- Stakeholders also identified several cross-cutting gaps that could be considered in the financial mechanism. These include antimicrobial resistance, emergency preparedness and drug repurposing. A financial mechanism may be able to capture synergies by combining R&D for Type III and II diseases with these themes.

The landscape analysis and stakeholder interviews clearly confirm a significant funding "chasm" and the need for additional financial mechanisms to address R&D gaps and needs. Any new mechanism's focus should be guided by priorities based on an analysis of current R&D activities, the global burden of disease and expert opinion. However, there is a wide range of options that this financial mechanism could focus on. Ultimately, the WHO Prioritization Mechanism will determine these focus areas. The rest of this report outlines the various options for creating and operating a financial mechanism that could address the global priorities determined by the WHO Prioritization Mechanism.

4

HOW THE PROPOSED R&D FINANCIAL MECHANISM FITS WITHIN A BROADER SYSTEM

At the Sixty-seventh WHA, Member States noted the assessment made by the Secretariat and the possibility of using an existing mechanism to host a pooled fund for voluntary contributions and agreed that Director-General should be requested to explore this option with TDR *(23)*.

Such an R&D financial mechanism could, if hosted by TDR, fit within the existing TDR governance structure. Moreover, the R&D financial mechanism would fit within a pre-defined broader system of priority definition managed by WHO, comprising the WHO Global Observatory on Health R&D *(6, 7, 10)* and a WHO Prioritization Mechanism *(24)*. An illustration of how the financial mechanism would fit within the broader system is detailed in Fig. 4.1. Once the WHO Prioritization Mechanism has defined the priorities, the TDR Scientific Working Group would determine the priorities for different interventions and operationalize them. The SWG may also recommend deploying incentive mechanisms depending on the needs of the funded projects. It is important to note that this global priority setting, as well as the focus on R&D, sets the R&D financial mechanism apart from other R&D financing initiatives that are more regionally focused and centred on capacity building, e.g. African Network for Drugs and Diagnostics Innovation (ANDI) and Association of South-East Asian Nations Network for Drugs, Diagnostics and Vaccines Innovation (ASEAN-NDI).

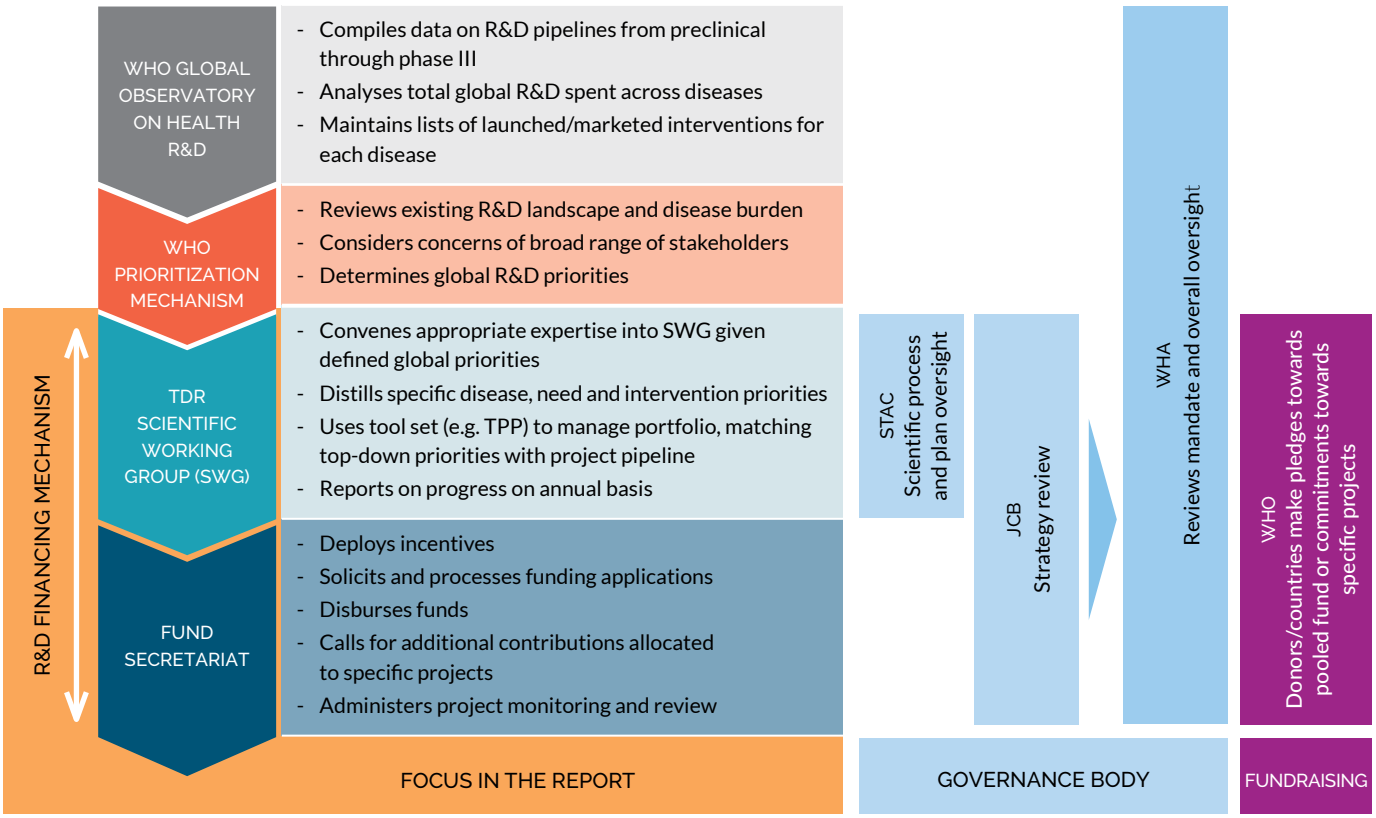
More specifically, the WHO Global Observatory on Health R&D would analyse R&D spending across diseases, compile the R&D pipeline and maintain lists of launched/marketed interventions for each disease *(6, 7, 10)*. The WHO Prioritization Mechanism would review these data and define global R&D priorities for the set of Type III, Type II and relevant Type I diseases *(24)*. At the time of writing this report,[16] the exact structure of the WHO Prioritization Mechanism had not been defined.[17]

It should be noted that this report focuses on the R&D financial mechanism itself (the orange area in Fig. 4.1), namely the strategic financing and down-stream operational considerations for success. The strategic value proposition and potential impact of the mechanism are explained in Section 5. Downstream operational considerations involve determining how the financial mechanism would be managed to transform the priorities set by the WHO Prioritization Mechanism in a portfolio of selected projects (Sections 6 and 7). Convened and managed by TDR, the SWG, aided by the specialized Secretariat, would be responsible for operationalizing the portfolio.

As stated above, both the financial mechanism and SWG would fit within the existing TDR governance structure (see right-hand side of Fig. 4.1 – additional details are given in Section 6.1) *(25)*. Most importantly, and as indicated by the WHA *(23)*, this means that the complete financial mechanism would be accountable to WHO Member States and governed by TDR's Joint Coordinating Board (JCB). It is assumed that WHO would be responsible for all of the financial mechanism's fundraising activities, either by drawing on Member State/donor pledges towards a pooled fund or by soliciting commitments to specific projects.

16. February 2016.
17. The set-up and operating procedure of the WHO Prioritization Mechanism was not within the scope of this study.

FIG. 4.1 SCHEMATIC OF ENVIRONMENT INCLUDING GOVERNANCE STRUCTURE



JCB: Joint Coordinating Board of TDR; R&D: research and development; STAC: Scientific and Technical Advisory Committee of TDR; TPP: target product profile; WHA: World Health Assembly.

5

OPTIONS FOR HEALTH PRODUCT R&D FINANCIAL MECHANISM

Several options exist for the size, focus, structure and strategy of the financial mechanism. These have been defined with input from key stakeholders and the P2I model used to determine the potential impact of each option, depending on fund size and overall strategy.

5.1 STAKEHOLDER PERSPECTIVES ON A FINANCIAL MECHANISM

Extensive stakeholder interviews were conducted to identify potential options for organizing the R&D financial mechanism. Particular care was taken to ensure that a broad range of perspectives were captured, including different clusters and units within WHO, organizations undertaking R&Ds, regulatory agencies, funding bodies, intergovernmental organizations, nongovernmental organizations (NGOs), health and other ministries (see Fig. 2.4 and Annex 2) for a breakdown of the stakeholders interviewed). Several of the key themes that emerged from these interviews are outlined below.

What the financial mechanism can offer

1. Setting global priorities across diseases, based on comprehensive landscape analyses, could have a significant impact by focusing existing donor investment and reducing redundant funding.
2. A mechanism that convenes donors providing them with a forum to discuss health product development priorities, review opportunities, and coordinate and collaborate in R&D would be valuable.
3. The establishment of the financial mechanism under the auspices of WHO would provide opportunities for setting priorities, and coordinating and tapping into new funding sources (such as governments of middle-income countries or private donors).
   - Priorities set by WHO could generate activity in R&D, especially if they emphasized the needs and stimulated enthusiasm among R&D organizations, e.g. academic researchers, R&D initiatives, PDPs or industries, in being part of the solution.
   - However, WHO may not be best suited to host a financial mechanism that includes managing an independent fund or partnering with private sectors.
   - On the other hand, TDR is viewed as a viable option given its successful track record in managing pooled funds, although TDR's current capacity to handle a significant fund size would need to be evaluated.
4. A standalone fund should incorporate a pooled fund ideally comprising "new" resources that have not been used to finance R&D in Type III and II diseases. However, flexibility may be needed to allow accepting of earmarked funds reserved for projects/diseases designated by other funders. The pooled fund would assure stability by providing a "base" level of funding throughout the multi-year timescale typically needed for R&D projects. The designated (or earmarked) funds could complement this by encouraging project-specific contributions from funders interested in certain areas; if such a flexible fund were to deploy a set of push and pull incentives, it might be quite effective in stimulating R&D in Type III and II diseases.

How the financial mechanism could operate

5. Based on lessons learned from various partnership and PDP-style models, the fund needs to be able to spread risk across a diversified portfolio, to leverage technically rigorous portfolio management practices and to engage in collaborative partnerships across the R&D value chain in order to spur R&D and product development in prioritized diseases.
6. To ensure relevant GPH stakeholders accept the financial mechanism's priorities and coordinating efforts, the governance model and decision-making process used by the SWG must be transparent and non-political. Furthermore, scientifically rigorous analyses must be conducted to lend credibility and legitimacy to the R&D chosen to be supported through this financial mechanism.
7. To promote the potential for health impact, applications should be screened to ensure that data are compliant with regulatory requirements, and should indicate their scientific and technical feasibility. Regulatory agencies must be engaged as early as possible and studies from preclinical studies to clinical trials should be designed and conducted in full compliance with regulatory requirements.

8. From a funding and planning prospective, critical "go" and "no-go" decision points should, as far as possible, be defined in advance and used to measure the achievement of milestones around key inflection points in the key stage-gate.

9. Clarification on the handling of intellectual property (IP) ownership should be made on a case-by-case basis. An open IP approach might be more relevant in cases where R&D projects are fully funded throughout the pipeline, but may be less relevant if the fund only finances a portion of the R&D costs.

10. All funding would be issued with the goal of developing a needed health product that would be acceptable, available, accessible and affordable to LMIC populations.

11. Depending on needs, special considerations should be given to funding large-scale long-term phase IV trials (post-marketing surveillance) in various populations to investigate the efficacy, safety and side effects of the approved product.

12. Instead of defining specific report formats, standardized reporting should be considered. Reporting frequency should be set according to specific needs, e.g. reporting and evaluation may be necessary every few months for early preclinical projects, while late-stage clinical trials may need to be evaluated once a year.

How to develop and set-up the financial mechanism on a tactical level

13. A high profile and widely respected political "champion" would be helpful to guide the financial mechanism through the international community and drive adoption of the idea (similar to Kofi Annan's role in setting up the Global Fund).

14. Currently, there is global interest and urgency to set up an R&D financial mechanism. This should be embraced rapidly so as not to lose the momentum generated by public emergencies such as Ebola in 2014/15 and Zika in 2016. Furthermore, efforts to address financing for emergency preparedness could be combined with this R&D financial mechanism for Type III and II diseases in a "two-speed approach".

These considerations served as the basis for designing financial mechanisms described in this report.

5.2 SET-UP AND DESIGN OF POTENTIAL FINANCIAL MECHANISM OPTIONS

The interviews revealed a broad spectrum of options for the financial mechanism, ranging from a specialized group that sets and communicates priorities, to a large global fund with its own secretariat. Seven options are explored in detail and are based on their feasibility and stakeholders' willingness to implement them (see Fig. 5.1 for summary). The first two options play an important coordination role by helping to channel funds to critical R&D gaps and do not assume specific funding allocated to manage R&D projects. The five remaining options illustrate funds of varying sizes and their projected capacities in accelerating health product development according to assigned priorities. The funds are described in terms of the annual disbursement of "steady-state" funding, with a wide range of potential fund sizes.[18] It should be noted that incremental increase over five to 10 years is expected to reach the steady-state fund size. The operating model and possible set-up are explored for each option. The estimated operating cost is calculated by assuming that: (a) the financial mechanism would be hosted by TDR or another Geneva-based UN organization; (b) the existing TDR mechanism would be used; and (c) the SWG would not be remunerated. The financial models are not disease-specific. It should be emphasized that these are models based on aggregated data and averages, and the outcomes are predictions.

1. "Priority Setter"

a. *Description:* defines global priorities across diseases at a detailed enough level to give stakeholders the clarity they need to choose initiatives and projects that clearly align with these priorities, and publicly communicates priorities and evaluation methodology.

b. *Operating model:* data from WHO Global Observatory on Health R&D and other sources will be examined through the WHO Prioritization Mechanism to determine prioritized set of interventions or projects; findings will be communicated to the GPH community.

c. *Set-up:* one staff member to facilitate WHO Prioritization Mechanism in performing detailed prioritization (estimated operating cost up to ~US$ 1 million annually); hosted by WHO.

A potential forum for active coordination is suggested in Annex 3.

2. "Priority Setter" with active coordination

a. *Description:* performs all functions of option 1; additionally, organizes global forum convening donors to review and discuss the "direction" of overall funding activities of each major donor and collectively set goals to closely align donor funding disbursement with priority areas.

b. *Operating model:* specialized advisory or expert group determines detailed priorities as in option 1 (if necessary); staff organizes forum while advisory group manages GPH leader outreach.

c. *Set-up:* three staff members to facilitate advisory/expert group in performing detailed prioritization and project evaluation (estimated operating cost up to ~US$ 5 million annually); could be hosted by WHO at headquarters.

A potential forum for active coordination is suggested in Annex 3.

3. "Small-pooled fund" – priority advocate with US$ 15 million annual fund

a. *Description:*

- performs all functions of option 1;
- funds one or a few targeted projects (e.g. several phase I drug trials in under-funded diseases);
- US$ 3 million is required at the launch to fund one simple project;
- on average, four simple projects per year will be funded at steady state, but funding of innovation-focused projects will not be possible;
- if a fund started operation in 2017, three simple reformulation/repurposing drugs may be launched by 2030;
- leverages co-investment from other funders.

b. *Operating model:*

- performs priority setting of option 1;
- evaluates projects against TPP criteria and identifies "high potential" projects;

18. Estimates are based on discussions with stakeholders. Note that fundraising strategies and the identification of sources were out of scope of this study and TDR's effort.

FIG. 5.1 OVERVIEW OF FUND OPTIONS AND MECHANISMS

	ANNUAL FUND SIZE US$ millions (m) [a]	STEADY STATE PROJECTS/YEAR	ESTIMATED STAFFING NEEDS (FULL-TIME EQUIVALENT)	IF DEVELOPMENT STARTS IN 2017, WHAT IS EXPECTED BY 2030?
1	Passive coordination Up to US$ 1 m	Define and communicate global priorities across diseases	1	
2	Prioritization Forum Up to US$ 5 m	Review funding directions with donors and evaluate if funding is aligned with global priorities	3	
3	~US$ 15 m (small)	Fund 3-4 projects (no innovation-focused projects)	3	3 repurposed drugs - simple
4	~US$ 50 m (PDP size)	Fund 15-20 projects (few innovation-focused projects)	9	1 new chemical entity (NCE) - simple
5	~US$ 100 m (medium)	Fund 25-40 projects (including ~5 innovation-focused projects)	14	1 repurposed drug - complex
6	~US$ 300 m (large)	Fund 80-100 projects (a novel intervention to approval)	26	1 simple biologic
7	>US$ 500 m (global)	Fund 140-160 projects (can fund many projects in priority areas)	40	1 NCE - complex

PDP: product development partnership.

[a] Costs shown represent annual amount of funds for disbursement to support R&D from preclinical to phase III. Costs related to management, infrastructure and fund hosting are not shown.

- determines appropriate incentive mechanism based on incentive mechanism framework;
- creates project selection criteria and employs rigorous portfolio management principles (e.g. project evaluation against decision points determined up front around key inflection points around key stage-gate and key performance indicators (KPIs), "go" / "no-go" funding decisions, etc.).

c. Set-up:

- three staff members to facilitate SWG/expert group in managing fund disbursement, priority setting and portfolio management (estimated additional operating cost up to~US$ 1.6 million including fund-hosting costs);
- could be hosted by TDR.

4. "PDP-sized fund" – priority advocate with US$ 50 million annual fund

a. Description:

- performs all functions of option 1 (and potentially option 2);
- funds multiple targeted funding gaps, primarily focuses on reformulation or repurposed compounds and simple NCEs;
- US$ 11 million is required at the launch to fund four reformulation or repurposed compounds or simple NCEs;
- 14 projects per year will be managed at steady state after 10 years of operation, but funding of innovation-focused projects will not be possible;
- if a fund started operation in 2017, more than 10 simple reformulation or repurposed drugs may be launched by 2030; if a mixed-model strategy is used, in addition to three simple reformulation or repurposed drugs, one simple NCE may be launched by 2030;
- potentially leverages co-investment from other funders through allocated funds.

b. Operating model: same as option 3.

c. Set-up:

- gradual increase to nine staff members required to facilitate SWG/expert group in managing fund disbursement, priority setting and portfolio management (estimated additional operating cost up to ~US$ 4.5 million including fund-hosting costs);
- could be hosted by TDR.

5. "Medium-pooled fund"– priority advocate with US$ 100 million annual fund

a. Description:

- performs all functions of option 1 (and potentially option 2);
- funds several targeted funding gaps (e.g. funding phase III trials to bring a single intervention through to approval);
- US$ 17 million is required at the launch to fund seven projects of mixed archetypes;
- an average of 28 projects with different archetypes will be managed at the steady state after 10 years of operation;
- if a fund becomes operational in 2017, more than 10 simple repurposed drugs or three reformulation or repurposed drugs, one simple NCE and one complex repurposed drug may be launched by 2030, but a launch of an innovation-focused product would be unlikely;
- it is possible to fund innovation-focused projects; potentially leverages co-investment from other funders through allocated funds;

b. Operating model: same as option 3;

c. Set-up:

- Gradual increase to 14 staff members required to facilitate SWG/ expert group in managing fund disbursement, priority setting and portfolio management (estimated additional operating cost up to US$ 7.6 million including fund-hosting costs);
- could initially be hosted by TDR, but the fund may ultimately have to be hosted elsewhere.

6. "Large-pooled fund": priority advocate with US$ 300 million annual fund

a. Description:

- performs all functions of option 1 (and potentially option 2);
- funds highest priority gaps with goal of bringing novel intervention to approval (e.g. vaccine approval);
- US$ 49 million is required at the launch to fund 17 projects of mixed archetypes;
- average of 96 projects with different archetypes will be managed at the steady state after 10 years of operation;
- if a fund becomes operational in 2017, three reformulation or repurposed drugs, one simple NCE, one complex repurposed drug and one simple biologic may be launched by 2030;
- potentially leverages co-investment from other funders through allocated funds.

b. Operating model: same as option 3.

c. Set-up:

- gradual increase to 26 staff members required to facilitate SWG/ expert group in managing fund disbursement, priority setting and portfolio management (estimated additional operating cost up to ~US$ 18.5 million including fund-hosting costs);
- probably be hosted outside TDR due to large size.

7. "Global R&D fund" – priority advocate with US$ 500 million annual fund

a. Description:

- performs all functions of option 1 (and potentially option 2);
- funds all projects in development for focused group of priority diseases (e.g. similar to the Global Fund);
- US$ 91 million is required at the launch to fund 29 projects of mixed archetypes;
- average of 163 projects with different archetypes will be managed at the steady state after 10 years of operation;
- if a fund becomes operational in 2017, three reformulation or repurposed drugs, one simple NCE, one complex repurposed drug, one simple biologic and one complex NCE (an innovation-focused product) may be launched by 2030;
- potentially leverages co-investment from other funders through allocated investments.

b. Operating model: same as option 3.

c. Set-up:

- gradual increase to 40 staff members required to facilitate SWG/ expert group in managing fund disbursement, priority setting and portfolio management (estimated additional operating cost up to ~US$ 30 million including fund-hosting costs);
- probably be hosted outside TDR due to large size.

The fund itself could be supported by annual contributions, by an up-front endowment, or by a combination of the two. Administrative costs would be drawn from a charge made on contributions.

It should also be noted that if industry developers were to provide in-kind contributions, especially in the context of partnerships with PDPs and other organizations, it would have the potential to reduce the funding needs for specific partnership projects. This could significantly increase the R&D impact of each fund size and result in a larger number of expected intervention launches and productions.

5.3 COMPARISON OF FINANCIAL MECHANISM OPTIONS

The P2I model evaluates each of the fund options (options 3–7 in Section 5.2 above) by estimating the expected impact of various investment portfolios. The analysis evaluates the full development costs from preclinical (or alternatively from lead optimization phase) through to phase III, accounting also for in-kind contributions from industry partners. Recognizing the numerous permutations of potential funding focus areas, a spectrum of financing focus strategies was constructed and explored for each of the fund sizes (see Fig. 5.2). In practice, portfolio scenarios should be modelled depending on the WHO Prioritization Mechanism disease priorities and the specific interventions required to address these priorities.

FIG. 5.2 SPECTRUM OF FINANCIAL MECHANISMS EXPLORED

REPURPOSED INTERVENTIONS ← → NOVEL INTERVENTIONS

	A "QUICK WINS"	B "MIXED MODEL"	C "INNOVATION-FOCUSED"
Investment focus	Finance only simple drug repurposing projects	Finance multiple projects across **several different archetypes**	Finance only **complex NCE** projects
Basis for strategy	Several **PDPs** focus on simple repurposing as a cost-effective and quick way to deliver products	Some **diversified funds** finance multiple interventions across several diseases	Some diseases will require completely **novel treatments** rather than repurposing

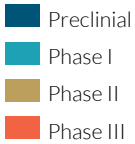
NCE: new chemical entity; PDPs: product development partnerships.

The "quick wins" strategy and "innovation-focused" strategy represent the two extremes of financing focus – the first pursues relatively low-cost and quick-to-deliver interventions and the latter pursues relatively expensive and high-risk novel/breakthrough interventions. An intermediate approach, namely a "mixed model" strategy, aims to strike a balance tailored to specific disease priorities and needed interventions.

If the financing strategy were to focus on developing as many products as possible, a "**quick wins**" mechanism focusing on drug reformulation or repurposing could be employed as a cost effective and relatively quick way to deliver interventions for neglected diseases. Fig. 5.3 shows the number of expected launches for each fund size under such a scenario. It should be noted that it is assumed that funding would start in 2017 and that a given set of new projects would be incorporated each year. If the fund were to focus only on drug repurposing and ifthere were ample preclinical projects available, smaller funds, even an annual disbursement of US$ 15 million, could potentially deliver three repurposed drugs by 2030. However, incorporating so many high quality and scientifically feasible reformulation or repurposing projects every year would be challenging even if funding were available.

FIG. 5.3 EVALUATION OF FUND SIZES IN "QUICK WINS" STRATEGY

ANNUAL FUND SIZE US$ millions (m)		NEW PROJECTS INITIATED PER YEAR [a]	STEADY-STATE PORTFOLIO PIPELINE [a]	EXPECTED LAUNCHES OF SIMPLE REPURPOSING DRUGS BY 2030
3	**Small-pooled fund (~US$ 15 m)**	1	3 1 4	2.8
4	**PDP-sized fund (~US$ 50 m)**	4	12 4 16	11.2
5	**Medium-pooled fund (~US$ 100 m)**	7 [b]	21 6 27	19.6
6	**Large-pooled fund (~US$ 300 m)**	22 [b]	66 20 86	61.6
7	**"Global" R&D fund (~US$ 500 m)**	36 [b]	108 33 141	100.8



PDP: product development partnership; R&D: research and development.

[a] These numbers represent the expected maximum, assuming there are no limitations in finding projects to fund.

[b] In practice, it is highly unlikely that there would be this many repurposing projects per year to be funded.

Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

If, on the other hand, the fund strategy were directed to "**focused innovation**", truly novel breakthrough intervention projects would be selected. As such, innovative projects are usually costly and require longer cycle times, and only the US$ 500 million annual fund would result in a potential launch of one or two complex NCEs by 2030. It should be noted that funding of early-stage projects starting in 2017 and 27 new projects are incorporated into the portfolio each year, managing approximately 150 projects at steady state (see Fig. 5.4; data obtained from P2I model). This pipeline size of 150 compounds would be reached by year 12.

The "quick wins" strategy focusing on drug repurposing is an efficient strategy that achieves R&D impact in a cost-effective way. However, as stated earlier, this strategy could probably not be employed in the long run (e.g. next several decades) as the fund would run out of viable existing candidates. Although it remains unclear when most of the viable candidates would be "exhausted", PDPs are increasingly shifting their portfolios from the "low-hanging fruit" of reformulation or repurposed drugs to new chemical entities. On the other hand, focusing exclusively on new, innovative products requires the fund to make large investments and assume significant risk (due to the low probability of candidate success). In reality, strategies must be tailored according to the specific disease priorities and interventions.

FIG. 5.4 EVALUATION OF FUND SIZES IN "INNOVATION-FOCUSED" STRATEGY

	ANNUAL FUND SIZE US$ millions (m)	NEW PROJECTS INITIATED PER YEAR [a]	STEADY-STATE PORTFOLIO PIPELINE [a]	EXPECTED NUMBER OF COMPLEX NCES LAUNCHED BY 2030
3	**Small-pooled fund (~US$ 15 m)**	0	0 0 0	0
4	**PDP-sized fund (~US$ 50 m)**	3	9 3 4 1 17	0.15
5	**Medium- pooled fund (~US$ 100 m)**	5	15 6 6 1 28	0.25
6	**Large-pooled fund (~US$ 300 m)**	16 [b]	48 18 20 3 89	0.80
7	**"Global" R&D fund (~US$ 500 m)**	27 [b]	81 30 34 5 150	1.35

NCEs: new chemical entities; PDP: product development partnership.
[a] Number of projects assumes no constraint on availability of actual preclinical projects to fund.
[b] In fact, the fund may not be able to identify the listed number of projects per year.
Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

The **"mixed model" scenario** considers a diversified fund that finances multiple interventions across several diseases. This hypothetical scenario assumes that four diseases were prioritized by the WHO Prioritization Mechanism, which were then reviewed to identify unmet R&D needs and translate them into desired intervention archetypes (see Fig. 5.5). The disease priorities and R&D gaps described are hypothetical and are not meant to suggest that these will be the financial mechanism's focus areas.

In order to model the potential of each option in this scenario, further assumptions were adopted: (a) the fund would invest in the development of these compounds from preclinical to phase III; (b) the financial mechanism would start with the same number of projects each year from 2017 through to 2030 (e.g. three projects per year); (c) the maximum annual spending would be approximately equal to the annual fund size; and (d) the maximum number of new projects started per year would be 200.

The current model is based on data that are currently available and works best when estimating the outputs from a mixed portfolio. It is not able to predict the outputs for specific disease areas. For example, the P2I model would not be appropriate for predicting the cost and timescale for the development of new vaccines for HIV and TB. As soon as enough sets of data become available, new parameters could be incorporated to improve the predictability of the model.

FIG. 5.5 MODELLING EXAMPLE SCENARIO FOR EVALUATING FUND OPTIONS

WHO PRIORITIZATION MECHANISM

Based on a detailed review of data from the Global Observatory on Health Research and Development (R&D) and other expert sources, the WHO Prioritization Mechanism identifies the **highest global priority diseases as:**

Disease 1 (e.g. MDR-TB) [a]
Disease 2 (e.g. schistosomiasis)
Disease 3 (e.g. trachoma)
Disease 4 (e.g. lower respiratory diseases – Andes virus)

SCIENTIFIC WORKING GROUP (SWG)

Based on these priorities, the SWG consults a variety of internal and external disease experts to **identify specific R&D gaps** for the four diseases:

DISEASE	EXAMPLE UNMET R&D NEED	EXAMPLE INTERVENTION ARCHETYPES
Disease 1 (e.g. MDR-TB) [a]	Combination therapy to combat antimicrobial resistance	A 1 drug repurposed - complex B 1 NCE - simple C 1 NCE - complex [b]
Disease 2 (e.g. schistosomiasis)	A vaccine	D 1 complex vaccine
Disease 3 (e.g. trachoma)	New treatment on the market (as soon as possible)	E 1 drug repurposed - simple
Disease 4 (e.g. lower respiratory diseases - Andes virus)	An antibody-based treatment	F 1 simple biologic

[a] MDR-TB: multidrug resistant tuberculosis.
[b] NCE: new chemical entity.

Annual funds of US$ 50 million and US$ 100 million may be ample to launch one NCE with a validated mechanism of action plus some repurposed drugs (see Fig. 5.6; data from P2I model). For a larger portfolio with more novel interventions, such as biologicals and simple NCEs in addition to repurposed drugs, a US$ 300 million fund would be needed. The annual fund of US$ 500 million is the only option that allows for truly innovative interventions, such as an NCE with a novel mechanism of action.

FIG. 5.6 EVALUATION OF FUND SIZES IN "MIXED MODEL" STRATEGY

ANNUAL FUND SIZE US$ millions (m)		NEW PROJECTS INITIATED PER YEAR [a]	STEADY-STATE PORTFOLIO PIPELINE	EXPECTED NUMBER OF COMPLEX NCES LAUNCHED BY 2030
3	Small-pooled fund (~US$ 15 m)	10 1 [b]	3 1 4	A B C D E 2.8 F
4	PDP-sized fund (~US$ 50 m)	1 3 4 [c]	9 4 7 2 22	A B 0.9 C D E 2.8 F
5	Medium-pooled fund (~US$ 100 m)	3 4 7 [d]	18 7 10 4 39	A 1.4 B 1.2 C D E 2.8 F
6	Large-pooled fund (~US$ 300 m)	3 14 17 [e]	50 17 23 6 96	A 1.4 B 1.2 C 0.4 D E 2.8 F 1.2
7	"Global" R&D fund (~US$ 500 m)	3 26 29 [f]	86 30 38 8 162	A 1.4 B 1.2 C 1.0 D E 2.8 F 1.2

A: Complex repurposing **B:** Simple NCE **C:** Complex NCE
D: Complex vaccine **E:** Simple repurposing **F:** Simple biologic

NCE: new chemical entity; R&D: research and development.

[a] Projects include all non-repurposing archetypes.
[b] Starting 1 simple repurposed project per year.
[c] Starting 3 simple NCEs and 1 simple repurposed project per year.
[d] Starting 2 complex repurposed, 4 simple NCEs and 1 simple repurposing project per year.
[e] Starting 2 complex repurposing, 4 simple NCEs, 8 complex NCEs, 1 simple repurposed and 2 simple biologics per year.
[f] Starting 2 complex repurposed, 4 simple NCEs, 20 complex NCEs, 1 simple repurposed and 2 simple biologics per year.

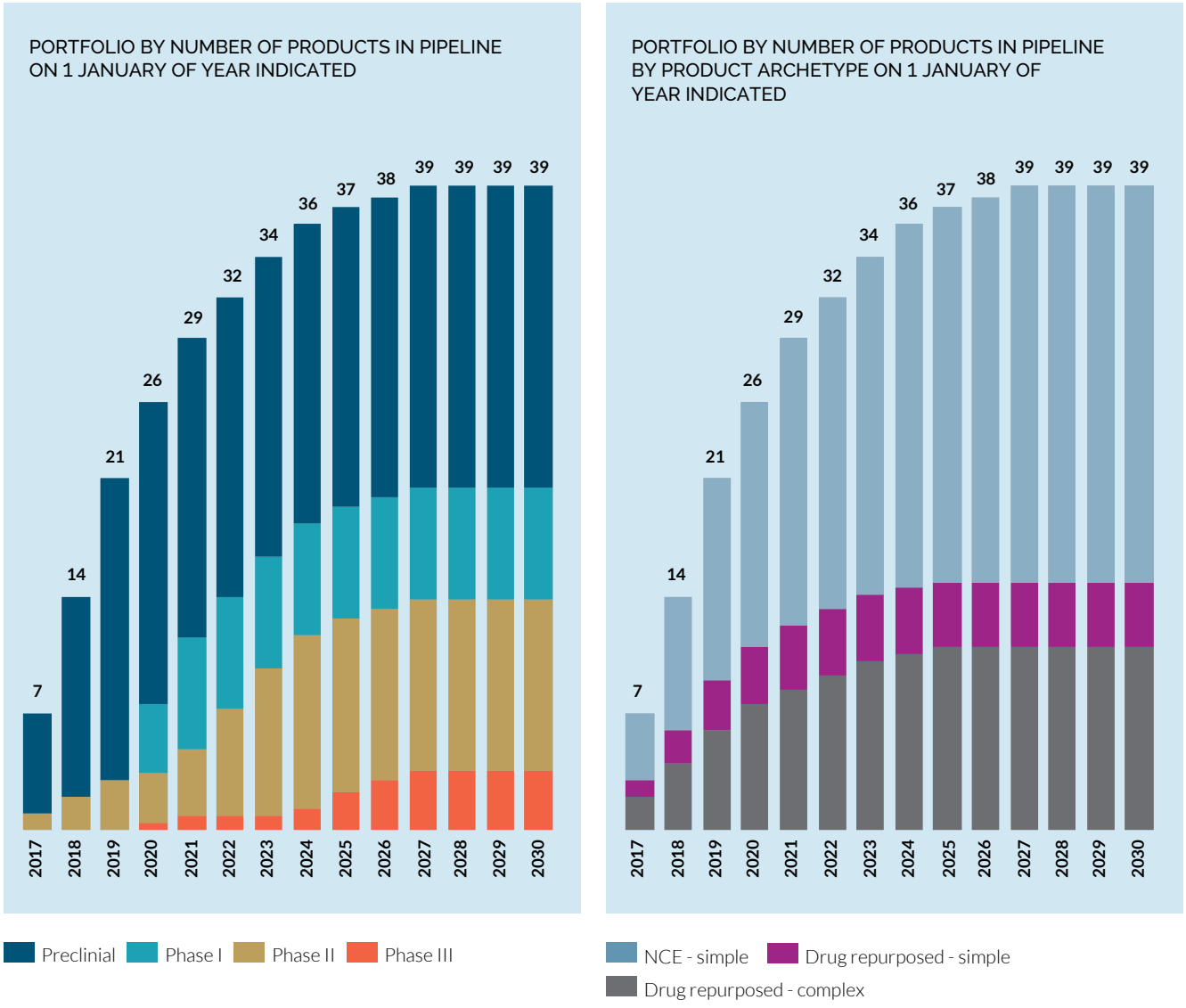
Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

Repurposing
Innovation-focused
Preclinial
Phase I
Phase II
Phase III

The P2I model estimates annual expenditures and the number of projects in the pipeline from 2017 through 2030. For example, the two figures below (Figs. 5.7, 5.8) provide a case project pipeline and cost portfolio for a US$ 100 million fund under the "mixed model" strategy to inform a potential fund financial/business plan. Fig. 5.7 shows how, in this case, the fund would support an average of 39 projects from year 11 onwards.

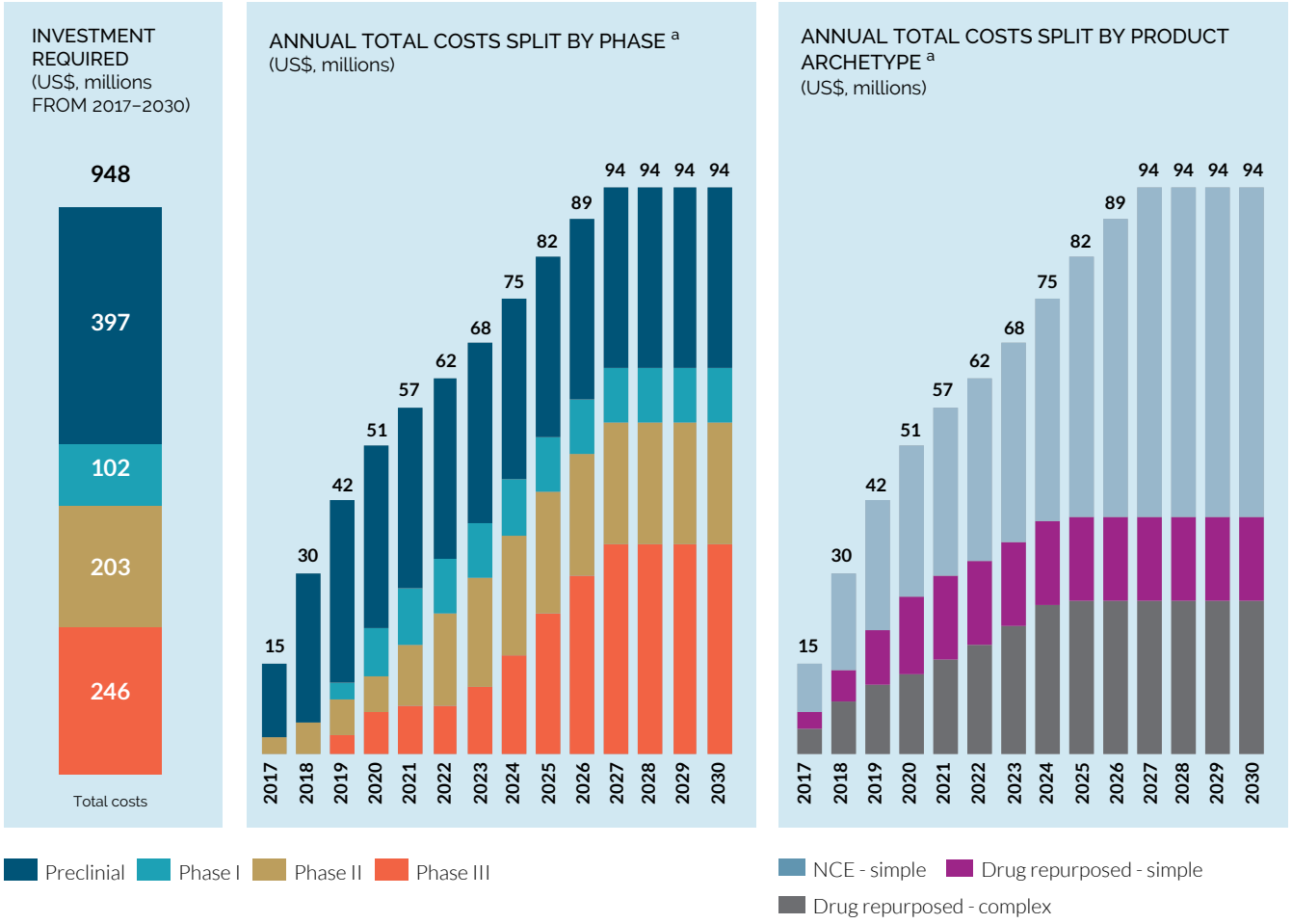
Also, the model predicts the incremental funding increase, from a US$ 15 million fund supporting seven selected projects in the first year to US$ 100 million supporting 39 portfolio projects over an 11-year period.

FIG. 5.7 POTENTIAL PIPELINE ASSOCIATED WITH MEDIUM-POOLED FUND (~US$ 100 MILLION ANNUALLY) IN "MIXED MODEL" STRATEGY



NCE: new chemical entity.
Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

FIG. 5.8 POTENTIAL COSTS ASSOCIATED WITH MEDIUM-POOLED FUND (~US$ 100 MILLION ANNUALLY) IN "MIXED MODEL" STRATEGY



NCE: new chemical entity.

[a] Costs represent the total development costs from preclinical to phase III including in-kind contributions from industry partners.

Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

Fig. 5.9 illustrates a summary of fund options and corresponding potential launches using different strategies. While the P2I model provides an objective method of comparing the potential impact of different fund sizes, there are several strategies a fund could employ to magnify the impact. If the fund were to identify co-investment partners which do not contribute to the pooled fund directly but wish to participate through "allocated" funds (e.g. some government agencies or private donors), the funding mechanism could be "stretched" to finance a larger number of projects.

Similarly, if the financial mechanism were only to fund specific development phases and obtain assurances that other funders would cover earlier/later phases, the financial mechanism could consider funding more expensive projects (e.g. phase III vaccine trials) or additional projects. In addition, there would be a potential to reduce the funding needs for specific partnership projects if industry developers were to provide in-kind contributions, in terms of capacity building or infrastructure development, especially in the context of partnerships with PDPs and other organizations. These leverage factors could significantly increase the R&D impact of each fund size and result in a larger number of launches.

Furthermore, it is important to note that the potential fund sizes in this report are irrespective of funding sources. While initial funding may be more likely to come from WHO Member States, it is likely that the funding supported by Member States may decrease over time if the R&D financial mechanism were able to accept money from private sources (including philanthropists and the pharmaceutical industry).

Stakeholder interviews provide further insight into the feasibility and potential impact of each of the seven financial mechanism options outlined above.

Priority setting would substantially increase impact and fill a major gap in the R&D landscape. However, without funder engagement, effective coordination is extremely challenging.

FIG. 5.9 SUMMARY OF FUNDS BY INVESTMENT STRATEGY

ANNUAL FUND SIZE US$ millions (m)		NEW PROJECTS INITIATED PER YEAR	STEADY-STATE PORTFOLIO PIPELINE [a]	EXPECTED NUMBER OF LAUNCHES BY 2030 [b]
3	Small-pooled fund (~US$ 15 m)			
	A	1	4	3
	B	1	4	3
	C	0	0	0
4	PDP-sized fund (~US$ 50 m)			
	A	4	12 16	11
	B	4	9 22	4
	C	3	9 17	0
5	Medium-pooled fund (~US$ 100 m)			
	A	7	21 27	20
	B	7	18 7 10 39	5
	C	5	15 6 6 28	0
6	Large-pooled fund (~US$ 300 m)			
	A	22	66 20 86	62
	B	17	50 17 23 96	7
	C	16	48 18 20 89	1
7	"Global" R&D fund (~US$ 500 m)			
	A	36	108 33 141	101
	B	29	86 30 38 8 163	7
	C	27	81 30 34 150	1

A: "Quick wins" strategy **B:** "Mixed model" strategy **C:** "Innovations-focused" strategy
PDP: product development partnership; R&D: research and development.
[a] Total number of projects shown in blue numbers; for individual phases, showing only numbers ≥ 8.
[b] Cumulative expected launches of any archetype.
Source: data derived from TDR's financial modelling tool Portfolio-to-Impact (P2I) (2016).

Preclinial
Phase I
Phase II
Phase III

- A fund is necessary to address the current gaps in product development. However, an annual fund size of US$ 15 million is too small to have any significant impact in both the short and long-term.
- Raising a US$ 500 million annual fund, drawn primarily from "new" funding sources, would be immensely difficult considering past performance, the current economic environment, and the limited availability of funds.
- A fund would, most likely, need to begin small and demonstrate quick short-term successes before growing at scale.

The model results and stakeholders' considerations show that a fund size of US$ 100 million or more per year would be necessary to reduce the gaps in R&D and produce the results in product development that are needed to have an impact on the targeted diseases.

6

OPERATIONAL CONSIDERATIONS FOR THE R&D FINANCIAL MECHANISM

In order to translate the above options into a functional financial mechanism, it is important to determine how it will operate and who will drive it. As described in Section 4, the operating model is developed using the current governing structures of TDR and WHO *(12)*. It should be noted that the Scientific Working Group (SWG), convened and managed by TDR, would be the main decision-making body in this operating model. The composition, structure and modus operandi of the SWG are defined below.

Stakeholder interviews suggest that the operating cycle should be guided by several principles:

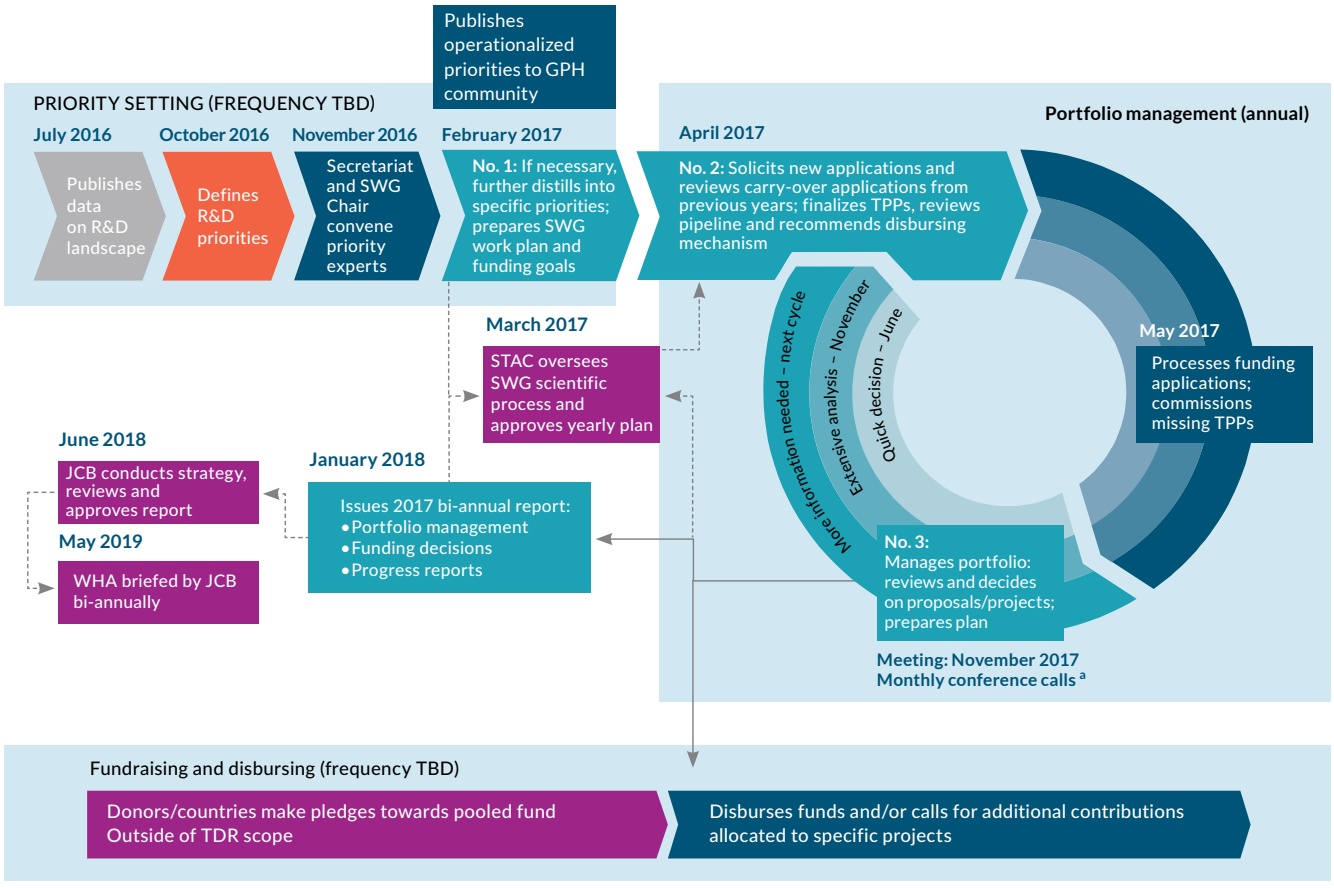
- A simple, evidence-based process should be used to quickly review projects and decide which to incentivize;
- Projects that have the potential to deliver impact should be prioritized rather than those that only build R&D capacity;
- The operating cycle should be fuelled by transparent, objective and non-political decision-making.

6.1 FINANCIAL MECHANISM'S OPERATING MODEL

The SWG would play a critical role in the operating model, being responsible for translating R&D priorities defined by WHO into a portfolio of incentivized projects. As outlined in Section 4, it is currently assumed that the financial mechanism and consequently the SWG would function within the existing structure of TDR (i.e. it would be convened and managed by TDR) *(12)*. However, it is the WHO Prioritization Mechanism that defines disease priorities based on data published by the WHO Global Observatory on Health R&D. The SWG would then be responsible for two main processes: further detailing priorities to an actionable level; and, managing the project portfolio and financing (including soliciting, selecting, monitoring and evaluating projects). This operating cycle and governance structure are exemplified in Fig. 6.1. This illustrates how the SWG would initiate its work under the governance framework of WHO and TDR, synchronized with existing meeting cycles of WHA and TDR's Scientific and Technical Advisory Committee (STAC) and JCB. Subsequently, the SWG would prepare for calls for proposals by analysing the existing pipeline and TPPs. The SWG may need to externally commission work to finalize TPPs and solicit applications (including, but not limited to, calls for proposals). The SWG would also prepare a recommendation on the most appropriate incentive/disbursement mechanism. Applications, as well as any externally commissioned work (e.g. creation of new TPPs), would be handled separately by the Secretariat.

This would trigger a "multi-speed" project review cycle, where projects could be continuously evaluated using the tools described later in Section 7. Some projects could be identified and incentivized quickly (e.g. straightforward projects or priority diseases with a very small pipeline). Depending on the level of complexity in identifying or soliciting applications (e.g. due to project technicalities or structure), the review cycle may be extended. Assisted by the Secretariat, the SWG would monitor and review funded projects to measure progress and evaluate their impact potential.

FIG. 6.1 POTENTIAL OPERATING AND GOVERNANCE CYCLE FOR THE FINANCIAL MECHANISM



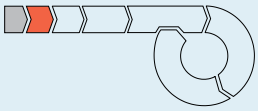
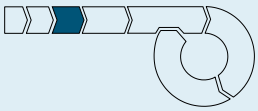
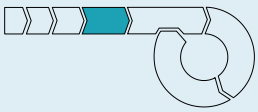
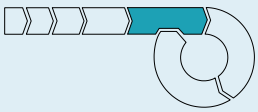
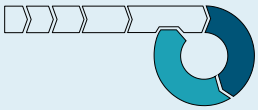
GPH: global public health; JCB: Joint Coordinating Board of TDR;
STAC: Scientific and Technical Advisory Committee of TDR;
TBD: to be determined; TPPs: target product profiles; WHA: World Health Assembly.

[a] Require unanimous decision.

A step-by-step example of how this operating cycle could work is shown in Fig. 6.2. As outlined in Section 4, the WHA would have oversight of the complete environment (WHO Global Observatory on Health R&D and the WHO Prioritization Mechanism).

The TDR-based functions of the SWG and the R&D financial mechanism would be governed by JCB, TDR's governing body. Additionally, TDR's STAC would have oversight of the SWG's scientific process and planning *(25)*.

FIG. 6.2 STEP-BY-STEP EXAMPLE OF HOW PRIORITIES GET TRANSLATED INTO A PROJECT PORTFOLIO

	ACTION	ILLUSTRATIVE EXAMPLE
 **Priority definition**	WHO Prioritization Mechanism defines (broad or specific) R&D priority	Broad example: onchocerciasis in sub-Saharan Africa
 **Convening of experts**	Secretariat and SWG Chair convene experts to address defined R&D priority area	Convenes onchocerciasis experts to SWG
 **Priority breakdown**	If necessary, SWG details specific priorities (i.e. specific product R&D need)	Target is non-ivermectin treatment for onchocerciasis
TPP finalization	SWG sources and validates TPPs that address granular priorities (from compendium or newly commissioned)	TPP for new non-ivermectin treatment is validated and published
 **Pipeline review**	SWG evaluates current pipeline against TPP to identify promising candidates	12 preclinical compounds fit TPP criteria
Determine incentive mechanism	SWG determines appropriate incentive mechanisms targeted for a given scenario	Given projects are in preclinical phase, direct project grants are recommended as most effective
 **Project assessment**	SWG reviews applications; Secretariat begins disbursement	Fund grants US$ 5 million over three years to two high-potential compounds that match TPP
Project monitoring	As part of portfolio management, SWG reviews project progress on regular basis	Every six months, applicant submits project status update

R&D: research and development; SWG: Scientific Working Group; TPP: target product profile.

6.2 SWG TO GUIDE AND MANAGE THE R&D FINANCIAL MECHANISM

Having a strong and effective SWG to guide and manage the R&D projects as well as financing would be critical to its success. It is important to first determine the competencies needed to fulfil the mechanism's remit. Second, the SWG should have the flexibility to manage a wide range of possible priorities. Finally, it would be important to adopt best practices in managing conflicts of interest (COI) and determining membership. This next section explores these three areas.

6.2.1 Landscape analysis and competencies

A number of organizations use technical advisory committees to guide portfolio management, advise on investments and perform other advisory and advocacy roles. As outlined in the method (Section 2), 24 different committees within 15 different organizations were analyzed to gather insights and distil best practices. The organizations were chosen in terms of similarities with the expected responsibilities to be performed by the SWG to manage the project portfolio and financing. Two hundred and fifty individual committee members' profiles were analysed by consulting web resources and annual reports. These were then classified in terms of affiliation (e.g. academic, private, not-for-profit, etc.) and expertise (e.g. infectious diseases, finance, regulatory, etc.). The composition of the most relevant committees is shown in the heat map in Fig. 6.3.

FIG. 6.3 HEAT MAP OF EXPERTISE IN VARIOUS TECHNICAL ADVISORY COMMITTEES

	FUNDING AGENCY/ PDP	COMMITTEE	REMIT	ACADEMIC EXPERT (%) [a]	R&D – INDUSTRY (%) [b]	BUSINESS, MANAGEMENT AND FINANCE (%) [c]	COMPLIANCE (LEGAL AND REGULATORY) (%)	NON-PROFIT/ INT. ORG./ DONOR COUNTRY (%) [d]	ENDEMIC COUNTRY HEALTH OFFICIAL (%) [e]	SWG SIZE
TECHNICAL PORTFOLIO MANAGEMENT ROLE	DND*i*	SAC	Selects projects while ensuring scientific quality	47	32	0	0	11	11	19
	FIND	SAC	Advises on technology and disease portfolio options	47	13	0	0	33	7	15
	GHIF	SAC	Advises on technical merits of investments	25	50	0	0	25	0	4
	GHIT Fund	Selection	Reviews and advises on investment proposals	25	63	13	0	0	0	8
	MMV	ESAC	Project selection and monitoring	48	45	0	6	0	0	31
		APMAC	Provides strategic advice on access and products	25	6	6	0	38	25	16
	Wellcome Trust	HICFP	Proposal review and funding decision	70	30	0	0	0	0	10
INVESTMENT ADVISORY ROLE	GHIF	Investment	Ensures investments meet financial return objectives	0	14	57	14	14	0	7
		Charitability oversight	Ensures investments' social impact	0	0	0	14	86	0	7
	3rd Rock Ventures	Partners	Manages venture capital initiatives and investments	0	33	67	0	0	0	9
GENERAL ADVISORY/ ADVOCACY ROLE	IAVI	SAC	Strategic advice on IAVI's programmes	58	21	5	0	16	0	19
	Komen	SAB	Strategic guidance and direction for R&D	100	0	0	0	0	0	8
	MMRC	Steering	Strategic direction and scientific oversight	90	0	0	0	10	0	10
	WHO	SAGE	Advising WHO on vaccines policy, R&D, delivery, etc.	53	0	0	0	20	27	15

1-15% 16-30% 30-60% 60-100%

APMAC: Access and Product Advisory Committee; DND*i*: Drugs for Neglected Diseases *initiative*; ESAC: Expert Scientific Advisory Committee; FIND: Foundation for Innovative New Diagnostics; GHIF: Global Health Investment Fund; GHIT: Global Health Innovative Technology Fund; HICFP: Health Innovation Challenge Fund Panel; IAVI: International AIDS Vaccine Initiative; Komen: Susan G. Komen for breast cancer; MMV: Medicines for Malaria Venture; MMRC: Multiple Myeloma Research Consortium; PDP: product development partnership; R&D: research and development; SAB: Scientific Advisory Board; SAC: Scientific Advisory Committee; SAGE: Strategic Advisory Group of Experts on Immunization; SWG: Scientific Working Group.

[a] Includes disease experts, immunology experts, academic public health experts, pharmacologists, etc.

[b] Includes R&D management, innovation sourcing.

[c] Includes general management, finance and business development.

[d] Includes WHO/UN personnel, non-profit orgs., e.g. Médecins Sans Frontières (MSF), PATH, Bill and Melinda Gates Foundation (BMGF) and donor governments, e.g. UK Department for International Development (DFID).

[e] Refers to ministry of health/public health officials of individual organizations' SWG members.

Source: data derived from organizations' websites and annual reports, and analyses (n=250).

The analysis revealed several key themes in terms of SWG competencies.

- Funds that evaluate projects (manage portfolios) rely strongly on R&D management expertise. This includes, but is not limited to, expertise covering early-stage feasibility; evaluation of formulation; manufacturing and controls; and evaluation of proposed clinical trials, in addition to academic disease experts (e.g. 30–50% is R&D management).
- Funds requiring investment guidance focus less on academic experts. These committees are also smaller and composed mostly of members with competencies in business, management and finance (e.g. 50–60% of their advisory boards).
- Initiatives with a specialized secretariat to manage a programme and financial portfolio have advisory committees predominantly composed of academic experts for setting research priorities (e.g. Susan G. Komen for breast cancer or Multiple Myeloma Research Consortium).

PDPs have larger SWGs, as they often need to guide the scientific development of large portfolios, e.g. DND*i*, MMV or International AIDS Vaccine Initiative (IAVI).

Further observations are listed below.

- Advisory committees with investors from public and private sector can increase accountability (e.g. the GHIF Advisory Committee has members from the Bill and Melinda Gates Foundation (BMGF) as well as the Swedish International Development Cooperation Agency).
- Both current and former employees of the pharmaceutical industry (e.g. many GHIT members are ex-industry working now with Wellcome Trust, the BMGF, or other non-profit organizations) often provide R&D management expertise.
- Endemic country health official representation is present in WHO-based committees (e.g. the Global Advisory Committee on Vaccine Safety (GACVS); the Pandemic Influenza Preparedness (PIP) Advisory Group; the Strategic Advisory Group of Experts (SAGE) on Immunization; TDR's JCB, STAC and SWGs; MMV; DND*i*; the Foundation for Innovative New Diagnostics (FIND)).
- Achieving equal gender and geographical representation may be challenging (the landscape analysis showed 26% female representation with 68% coming from Europe and North America).

Ultimately, an SWG will be most effective when its membership comprises specialists in diseases and/or public health who also have in-depth management expertise in product development, business development and finance.

These findings were confirmed in numerous stakeholder interviews. The ability to balance specific and broad expertise was highlighted as a key success factor. Importantly, regulatory compliance plays a critical role in selecting, as well as monitoring and evaluating R&D projects that are specific to product development. However, the size of an SWG may be more effective if it remains within the range of 10–15 members. Additionally, striving for prominent members as well as members with experience in accessing and deploying health products in LMIC settings would help to boost the organization's credibility and legitimacy.

Fig. 6.4 is based on an analysis of various organizations and interviewees' views. It shows the expertise and competencies needed for a SWG. The competencies were grouped into expertise domains and prioritized by how often each expertise would be needed. It should be noted that individual members may have the potential to fill multiple SWG competencies, while some expertise domains may require multiple SWG members.

In summary, together with a world-class knowledge of infectious diseases, SWG members should have experience in:

- leading product development;
- assessing risks;
- making challenging portfolio decisions, from feasibility evaluation of chemistry, manufacturing and controls (CMC) to clinical trials;
- evaluating regulatory compliance and providing regulatory guidance;
- working in health systems in low- and middle- income countries (LMICs);
- financing or developing businesses, including being able to assess projects' potential to deliver health impacts and their probability of success, and assess teams' capacities and experience;
- evaluating potential health impact and values from health economists' point of views.

This core SWG could be supplemented by expert groups, such as legal and intellectual property (IP) experts, and disease and product specialists from the individual priority disease areas set by the WHO Prioritization Mechanism.

FIG. 6.4 ANALYSIS OF COMPETENCIES REQUIRED IN SWG

	EXPERTISE DOMAINS	COMPETENCY [a]	NEED [b]	RATIONALE
INDUSTRY	**R&D**	• Managing Rx/Vx/Dx R&D portfolios including allocation of resources (prioritization) and stage-gate decisions • Assessing risk and return/impact • Guiding development and launch of compounds (including regulatory and access)	●	Interviews and landscape analysis confirm this is crucial
ACADEMIC EXPERT	**Public health**	• Field experience in implementation of novel health products in LMIC settings (i.e. coordination and design of large-scale Vx/MDA campaigns) • Public health research (e.g. implementation, epidemiology, etc.)	●	Interviews and landscape highlight access/ implementation issues
BUSINESS, MANAGEMENT & FINANCE	**Finance and business development**	• Portfolio management: evaluating potential of teams, initiatives and projects • Understanding of incentive mechanisms • Driving fund sustainability and accountability	●	Landscape shows importance of investor accountability
COMPLIANCE	**Regulatory**	• Conversant with LMIC and stringent regulations • Evaluation of collected and new data • Provision of guidance on study designs from preclinical to phase III trials	●	Interviews underscore a need for clear regulatory guidance
ACADEMIC EXPERT	**Infectious diseases (general)**	• Infectious disease clinician with clinical research and LMIC field experience • Leading basic or translational research laboratory in infectious diseases (multi-organism) [c]	●	Interviews stress ability to coordinate other experts; most Type II/III conditions are infectious diseases
	Specific disease and product	• Leading basic or translational research in specific disease (or disease group) • Expertise in specific product (Vx/Dx/Rx)	◕	Interviews confirm need for multiple disease experts
	Health economics	• Assessing health economic implications of particular R&D projects (financial and disease burden)	◕	Health economic evaluation is critical for project selection
	Maternal/neo-natal health	• Leading research in LMIC maternal/neonatal health • Maternal/neonatal clinician with clinical research and LMIC field experience	◑	Health economic evaluation is critical for project selection
COMPLIANCE	**Legal and IP**	• Assisting navigation of complex WHO legal structure • Understanding the IP implications of particular initiatives	◔	External (including WHO legal) counsel can be sourced ad hoc

● Always needed ◕ Often needed ◑ Occasionally needed ◔ Rarely needed ○ Not necessary

IP: intellectual property; LMIC: low- and middle-income country; MDA: mass drug administration; R&D: research and development; SWG: Scientific Working Group.

[a] Competencies might be represented by different people.

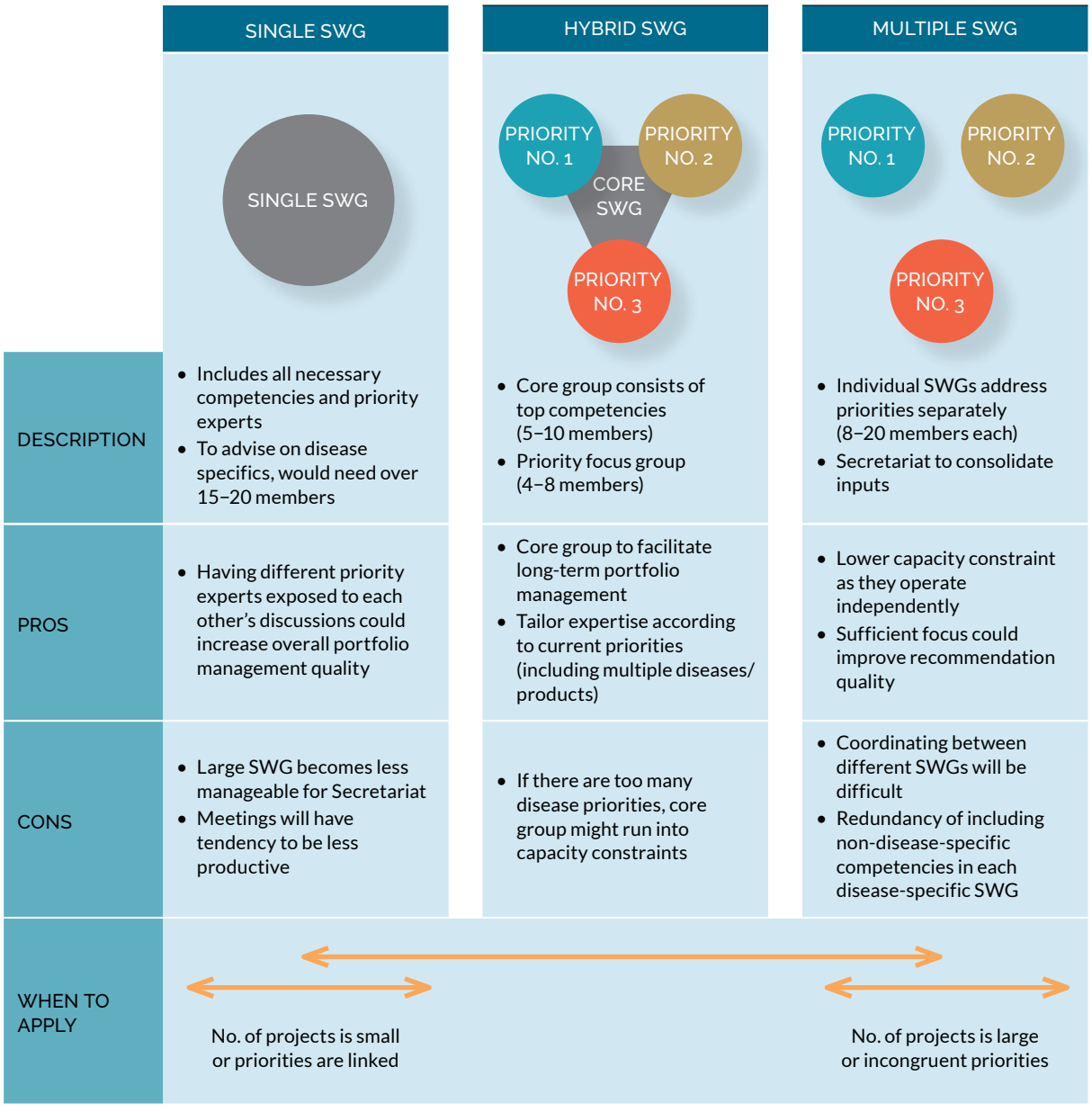
[b] Refers to how often that particular group of competencies will be required.

[c] Bacterial, viral and parasitic.

6.3 POSSIBLE SWG CONSTRUCTS

The priorities set by the WHO Prioritization Mechanism would determine how the SWG would combine these competencies. If a few detailed priorities were set, then a single SWG might be more effective in handling the portfolio, while multiple SWGs might be necessary if many disparate priorities were set at different levels of detail. Given the undetermined nature of priority setting, a hybrid model may be most appropriate, combining a permanent non-disease-specific core group with priority-specific sub-groups (Fig. 6.5). This structure was well received by various stakeholders.

FIG. 6.5 DIFFERENT SET-UPS FOR SWG INCLUDING THEIR RESPECTIVE ADVANTAGES AND DISADVANTAGES



SWG: Scientific Working Group.

The hybrid construct would enable broad portfolio management while drawing on deeper expertise specific to the defined priorities. The core group would include the critical non-disease-specific competencies, such as product development, public health, finance and business development, regulatory requirements, as well as general infectious disease expertise (such as multi-organism). The SWG Chair should be a member of this core group and also a member of STAC.

Before the first SWG meeting, the SWG Chair and the Secretariat would convene the experts of the priority-specific sub-groups. Additional non-disease-specific expertise (e.g. legal, specific product development experts, etc.) could be called in as required. It should be noted that such a mechanism has been used within WHO with the SAGE on Immunization which was established by the Director-General in 1999.[19] As WHO's principal advisory group, SAGE sets global policies and strategies on vaccines and immunization, ranging from vaccine safety, technologies and R&D to immunization schedules, delivery, and their linkages with other health interventions. SAGE is supported and/or works in concert with a number of technical advisory committees. For example, the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) provides advice and recommendations on immunization and vaccine-related implementation research, agenda setting, the prioritization of research as well as reviews of the relevance and applicability of quantitative methods, and of implementation progress and best practices. SAGE also receives vaccine safety information from WHO's Global Vaccine Safety Initiative (GVSI) as well as inputs from the United Nations Children's Fund (UNICEF) and Gavi, the Vaccine Alliance, on procurement of vaccines in low-income countries.

6.3.1 Best-practice operating procedure recommendations for SWG

Stakeholder interviews and landscape analysis have also provided guidance on the SWG's best practice operating procedures. The proposed model builds on the existing procedures for TDR's SWGs *(25)* by including core and priority focus groups with different competency needs.

As with the WHO's SAGE on Immunization or with existing TDR SWGs, core group members should serve two- to three-year terms, renewable once, with term lengths staggered to maintain continuity *(25, 26)*. Members of the priority focus groups should serve one-year terms, renewable indefinitely as long as the priorities remain the same. Overall, these measures would ensure that SWG membership would be consistently updated and would reflect the mandated priorities.

A diligent conflicts of interest (COI) policy would help ensure that guidance and decision-making would be objective and of high quality. This is particularly important because individuals with several competencies coming from companies in the private sector (e.g. product development or finance and business development) may also be potential funding applicants. For highly neglected diseases with a small number of active researchers, the COI risk may be higher, as SWG members might be direct collaborators in the funded research.

In order to determine best practices, a variety of organizations' policies were analysed by examining the way that they use experts' guidance for decision-making or setting policy recommendations. These included WHO regulatory bodies (e.g. European Medicines Agency (EMA); the U.S. Food and Drug Administration (FDA); pharmacopoeias (e.g. European and the United States); funding bodies (e.g. National Institutes of Health (NIH)); intergovernmental panels (e.g. Intergovernmental Panel on Climate Change (IPPC)). All those organizations use nuanced definitions of interest, including direct (e.g. research support, IP), indirect (e.g. family interests) and biases (e.g. professional or personal). Depending on the level of conflicts and its relationship to a given mandate, members can be excluded from a particular meeting or discussion. In cases where a member's contribution is crucial, policies allow for limited participation (e.g. non-voting rights related to a specific topic). Furthermore, it is crucial that members participate in an individual capacity rather than as representatives of an institution or government.

Overall, the current WHO policy *(27)* appears to be aligned with best practice. However, several stakeholders emphasized the need to diligently implement a COI policy due to the potential risk created by such a financial mechanism.

Overview of COI policies used by various organizations is shown in Annex 4.

19. WHO SAGE: http://www.who.int/immunization/policy/sage/en/ (accessed 8 February 2016).

7

TOOLKIT FOR SWG PORTFOLIO MANAGEMENT

The SWG could employ a number of tools to manage its project portfolio, including a compendium of Target Product Profiles (TPPs), an incentive mechanism framework, a portfolio management and prioritization framework, and a Key Performance Indicator (KPI) and milestone agreement framework (see Fig. 7.1).

7.1 COMPENDIUM OF TPPs

TPPs are a set of minimum and/or ideal characteristics for a potential health product, including diagnostics, vaccines or treatments. They can contain varying levels of detail and can be grouped as "broad" or "technical" (see Section 7.1.1). For example, detailed descriptions included in a medication package insert are derived from a technical TPP. As there are no agreed formats in existence around the world, TPP templates have been proposed in this report that could be used to assemble a TPP compendium (Section 7.1.2). Such a compendium would assist the SWG in its portfolio management.

7.1.1 TPP definition

Broad TPP characteristics

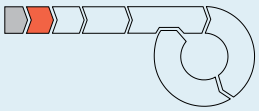
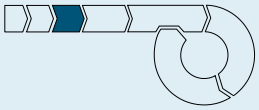
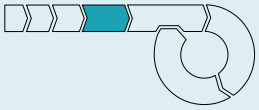
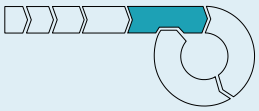
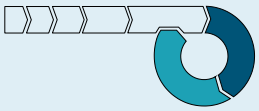
- Typically, a high-level intervention profile without universally agreed terminology, structure or level of detail. The profile does not necessarily refer to a specific product in the development pipeline. This broad TPP can be called an Ideal Product Profile, an Intervention Product Profile, or a Target Candidate Profile (among others).
- Primarily used by PDPs, academia and other public health stakeholders (e.g. donors).
- The main objective is to guide the direction of R&D efforts on a broad or global level.

Technical TPP characteristics

- A profile that provides detailed and granular information, typically following a well-defined structure suggested by the FDA *(28)*. This profile always refers to an existing, specific product at a particular time in development and requires frequent updates during the product development cycle.
- Primarily used by regulatory bodies (e.g. FDA) and the pharmaceutical industry.
- The main objective is to facilitate commercial product development by highlighting key inflection decision points, and tracking and guiding development processes as well as evaluating compliance with the regulatory process.

This report uses the "broad" definition when referring to TPPs, as this is more applicable to guiding global R&D efforts and comparing individual projects to a common set of criteria. However, the SWG may be requested to develop a technical TPP depending on the priorities set by the WHO Prioritization Mechanism and the level of detail.

FIG. 7.1 PORTFOLIO MANAGEMENT TOOLS FOR THE SWG

		ACTION	AVAILABLE TOOLS
	**Priority definition**	WHO Prioritization Mechanism defines (broad or specific) R&D priority	Data collected by WHO Global Observatory on Health R&D
	**Convening of experts**	Secretariat and SWG Chair convene experts to address defined R&D priority area	Key opinion leader list to quickly identify relevant experts
	**Priority breakdown**	If necessary, SWG details specific priorities (i.e. specific product R&D need)	Experts' experience and judgement
	**TPP finalization**	SWG sources and validates TPPs that address granular priorities (from compendium or newly commissioned)	Standardized TPP templates (See Figs. 7.2, 7.3, 7.4)
	Pipeline review	SWG evaluates current pipeline against TPP to identify promising candidates	Tools such as clinical trails registry (e.g. ICTRP) / pharmaprojects
	Determine incentive mechanism	SWG determines appropriate incentive mechanisms targeted for a given scenario	Incentive mechanism framework (See Annex 5, Figs. 7.5, 7.6)
	**Project assessment**	SWG reviews applications; Secretariat begins disbursement	Portfolio management and prioritization framework (See Figs. 7.7, 7.8)
	Project monitoring	As part of portfolio management, SWG reviews project progress on regular basis	Key performance indicators and milestone agreement framework (See Fig. 7.9)

ICTRP: international clinical trials registry platform; R&D: research and development; SWG: scienfitic working group; TPP: target product profile.

7.1.2 Suggested TPP templates for compendium

A number of stakeholders currently develop such broad TPPs and many organizations make their TPPs publicly available. These product profiles have a wide range of formats, which often differ by publishing organization.

As there is no universally agreed TPP format or template, a common TPP template was developed in this report for designing a compendium of TPPs. Such a compendium could assist the SWG to manage and evaluate its portfolio. More specifically, it could be a resource for quick landscape analysis or for reviewing projects, and be used to communicate specific intervention needs to spur additional R&D activity.

Therapeutic and vaccine products share the same overall TPP template structure, albeit with differences in specific attribute descriptions (Figs. 7.2, 7.3). On the other hand, diagnostic products have a separate template that addresses specific characteristics that are not relevant to vaccines or drugs (Fig. 7.4).

Using the literature and information shared by some PDPs, TPPs identified for Type III and II diseases could be converted into the common template structure and incorporated into a TPP database. Such a compendium would allow for comprehensive mapping and management of the product pipeline against R&D activity. It could form a major component of the information necessary to lead and facilitate a global dialogue on the priorities in health product R&D, and on how they could be addressed.

FIG. 7.2 THERAPEUTIC (Rx) PRODUCT TPP STRUCTURE

		EXAMPLE ATTRIBUTE DESCRIPTIONS
CONTEXT AND PRODUCT OVERVIEW	**Indication**	• Product indication
	Product	• Overall product description (e.g. single vs. combination drugs)
	Target populations	• Patient populations
	Target setting for deployment	• Target countries
PATIENT ACCESS	**Formulation**	• Drug formulation
	Route of administration	• Route of administration
	Dosing regimen	• Dosing schedule/pill burden
	Use setting	• Clinical use/convenience
	Price	• Cost per treatment/total cost per patient
PRODUCT PERFORMANCE	**Clinical characteristics**	• Clinical efficacy: day 7/day 28 • Rate of onset of action • Bioavailability • Relapse prevention
	Microbiological characteristics	• Transmission blocking • Proportional reduction in parasite load • Resistance • Specificity
	Safety	• Clinical safety and tolerability, safety monitoring requirement • Safety in special populations/contraindications (pregnancy, infants)
	Interactions	• Drug-drug interactions • Compatibility with potential partner drugs
	Shelf life, stability	• Storage requirements/shelf life, stability
OTHER CHARACTERISTICS	**Other characteristics**	• Other

TPP: target product profile.

FIG. 7.3 VACCINE (Vx) PRODUCT TPP STRUCTURE

		EXAMPLE ATTRIBUTE DESCRIPTIONS
CONTEXT AND PRODUCT OVERVIEW	**Indication**	• Product indication
	Product	• Product presentation/description (e.g. vial size, mono/multi dose)
	Target populations	• Target population/target age groups
	Target setting for deployment	• Target countries/geographical coverage
PATIENT ACCESS	**Formulation**	• Formulation
	Route of administration	• Delivery route/route of administration
	Dosing regimen	• Dosage schedule/regimen/adherence
	Use setting	• Use setting
	Price	• Yearly product cost per user/target price
PRODUCT PERFORMANCE	**Clinzcal characteristics**	• Expected efficacy • Duration • Reversibility • Immunogenicity
	Microbiological characteristics	• Vaccine serotypes, strain coverage
	Safety	• Safety, reactogenicity and contraindications • Warnings and precautions/pregnancy and lactation
	Interactions	• Interference and co-administration with other vaccines
	Shelf life, stability	• Shelf life • Storage and cold chain requirements
OTHER CHARACTERISTICS	**Other characteristics**	• Product registration and WHO prequalification • Post-marketing surveillance • Disposal, waste • Time to licensure, possible franchise • Packaging and labelling

TPP: target product profile.

FIG. 7.4 DIAGNOSTIC (Dx) PRODUCT TPP STRUCTURE

		EXAMPLE ATTRIBUTE DESCRIPTIONS
CONTEXT AND PRODUCT OVERVIEW	**Indication**	• Indication
	Use case	• Intended use (e.g. monitoring prevalence, post-elimination surveillance)
	Target populations	• Target populations
	Target setting for deployment	• Target countries/geographical coverage
	Product presentation	• Platform, analyte (diagnostic biomarker)
	Other information	• Clinical and/or surveillance need (value proposition) • Fit with clinical workflow/linkage to action (process map) • Availability of ideal diagnostic marker • Comparative reference method/reference test
PATIENT ACCESS	**Location of use**	• Infrastructure level requirements
	Target user	• Patient/health worker • Level of training needed to conduct analysis (none, consistent with tier 2 facility)
	Sample type and volume	• Blood, stool, urine, saliva, etc.
	Sample handling	• Sample preparation, possible sampling strategies • Sample transport stability
	Price	• Price for individual test • Capital cost of instrument
	Supply	• Channels to market • Supply, service and support
DESIGN AND OPERATIONAL CHARACTERISTICS	**Instrument handling**	• Instrumentation size and weight • Calibration need • Difficulty of techniques, number of steps • Ancillary supplies/additional 3rd party consumables • Waste management (hazardous materials/chemicals) • Incubation temperature
	Quality	• Quality control • Mean time between failures/false-recent rate (FRR)
	Performance	• Throughput • Analytical limit of detection (LOD) • Analytical specificity • Clinical sensitivity • Clinical specificity • Reproducibility and robustness • Time to result
	Shelf life, stability	• Desired stability, storage and cold chain requirements • Product shelf life
	Data analysis and results	• Nature of result (qualitative/quantitative) • Data export, data analysis
OTHER CHARACTERISTICS	**Other characteristics**	• Product registration path and WHO prequalification

TPP: target product profile.

7.2 FRAMEWORK OF INCENTIVE MECHANISMS

Extensive research has already been conducted by numerous organizations exploring incentive mechanisms for product development (e.g. efforts by WHO for antibiotic research *(29)* and R&D for neglected and tropical diseases *(30)*). Therefore, for this report, instead of conducting a comprehensive review of various mechanisms, a framework was developed to determine the effective incentive mechanisms depending on the given priorities. The SWG could use this framework to determine the appropriate incentive mechanisms for each priority, to make a call for proposals or to discuss further with relevant organizations in implementing the incentive mechanisms.

The SWG would use the framework to evaluate R&D priorities across three key dimensions: the level of market failure; the R&D gap; and the targeted R&D player. Fig. 7.5 details the evaluation criteria.

FIG. 7.5 INCENTIVE MECHANISM EVALUATION CRITERIA

	DESCRIPTION OF PRIORITY CHARACTERISTICS
LEVEL OF MARKET FAILURE	• **Significant market failure** – no commercial market/no financing mechanisms exist (e.g. NTDs) • **Some market failure** – some commercial markets may exist (e.g. dengue traveller market) • **Relatively small market failure** – commercial markets/financial incentives do exist (e.g. HIV/AIDS)
DEVELOPMENT GAP	• **Early development** (preclinical, phase I) • **Close to market** (phase III)
R&D PLAYER	• **Multinational** (e.g. large pharmaco) • **Small developer** (e.g. small biotech) • **Academic institution** (e.g. Johns Hopkins) • **R&D partnership** (e.g. PDP)

HIV: human immunodeficiency virus; NTDs: neglected tropical diseases; PDP: product development partnership; R&D: research and development.
Source: adapted by McKinsey from Mossialos et al. *(29)* and Pugatch, Chu & Torstensson *(30)*.

Based on these characteristics, each incentive mechanism was evaluated as "highly effective", "somewhat effective", or "not effective" (Fig. 7.6) in stimulating R&D. Several of the incentive mechanisms, such as direct grants, prizes or procurement guarantees, would require the financial mechanism to have a fund. Other incentives, such as vouchers or R&D tax credits, could be used by financial mechanisms without a fund by communicating the value proposition to regulators, governments or other relevant stakeholders (i.e. options 3–7 from Section 5.3).

Blueprints for determining the full list of highly effective incentive mechanisms for each scenario are listed in Annex 5.

FIG. 7.6 EFFECTIVENESS OF INCENTIVE MECHANISM

		LEVEL OF MARKET FAILURE			DEVELOPMENT PHASE		R&D PLAYER			
		RELATIVELY SMALL MARKET FAILURE	SOME MARKET FAILURE	SIGNIFICANT MARKET FAILURE	EARLY DEVELOP-MENT	CLOSE TO MARKET	LARGE PHARMA COMPANY	SMALL DEVELOPER (BIOTECH)	R&D PARTNERSHIP	ACADEMIA
PUSH	Direct grants	✓	✓	✓	✓	✓	--	✓	✓	✓
	Milestone payments	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Low-cost loan	✓	✓	--	--	✓	--	✓	✓	✓
	Equity/venture capital	✓	✓	--	✓	--	--	✓	--	--
	Matching/ co-investment	✓	✓	✓	✓	✓	✓	--	✓	✓
	R&D tax credits	✓	✓	✓	✓	✓	✓	--	--	--
	Open information sharing	✓	✓	✓	✓	--	✓	--	✓	✓
PULL	Prizes/grand challenge	✓	✓	--	✓	--	✓	--	✓	--
	Guarantees	--	✓	✓	--	✓	✓	✓	✓	--
	Exclusivity	✓	✓	--	✓	✓	✓	✓	--	--
	Patent buyout	✓	✓	✓	✓	--	✓	✓	--	--
	Vouchers	--	✓	✓	✓	✓	✓	✓	--	--
ENABLERS	Advocacy (excitement)	✓	✓	✓	✓	✓	✓	--	--	✓
	Public relations	--	✓	✓	✓	✓	✓	--	--	--
	Network assistance	✓	✓	✓	--	✓	✓	✓	--	✓

-- : not determined; PHARMA: pharmaceutical; R&D: research and development.

Source: adapted by McKinsey from Mossialos et al. *(29)* and Pugatch, Chu & Torstensson *(30)*.

Requires mechanism to have funds

Does not require mechanism to have funds

✓ Highly effective mechanism of incentivizing R&D

✓ Medium effective mechanism of incentivizing R&D

7.3 FRAMEWORK FOR USING TPPS IN PORTFOLIO MANAGEMENT

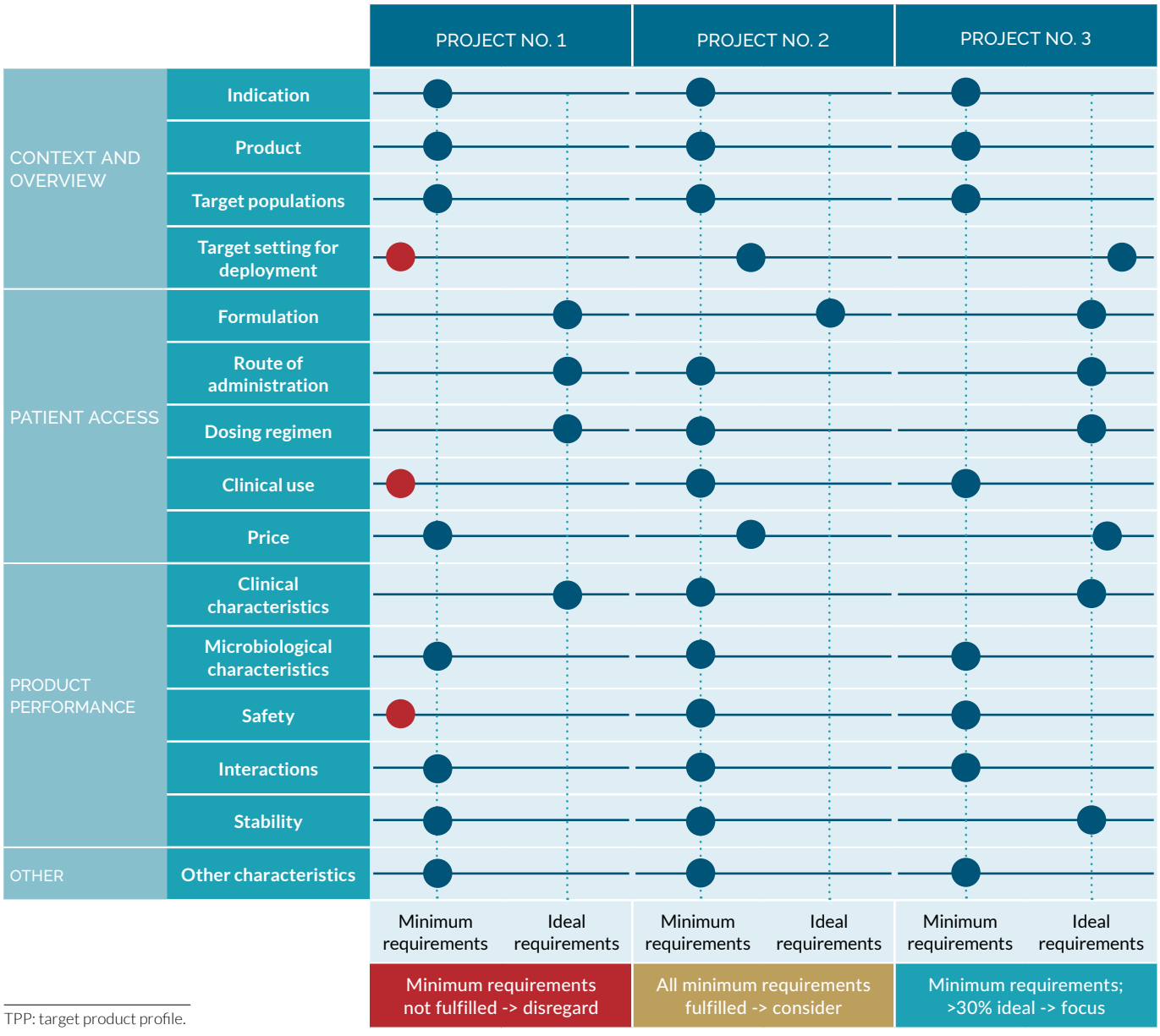
As described in Section 4, portfolio management would be one of the main tasks of the SWG. The SWG would complement the top-down priorities defined by the WHO Prioritization Mechanism with bottom-up portfolio management of individual projects that would be incentivized using a pull mechanism requiring funding. This involves translating priorities into a list of candidate projects. At this stage, the landscape analysis of the R&D pipeline would have already been completed and relevant TPPs finalized by the SWG.

TPPs would then be used as a filtering tool to identify projects that meet a minimum set of criteria. Projects that have a high proportion (e.g. above 30%) of characteristics at "ideal" levels or above could then be further prioritized. An example of this is shown in Fig. 7.7.

Projects would then be filtered and evaluated, and the SWG would consider the following four factors.

- **Impact:** For diseases of poverty, success in reducing the global burden of disease (e.g. estimates of DALYs averted [20] or other methods to measure burden) could be used to evaluate their potential to provide health impacts. Generally, funding applicants would be expected to submit health economic data as part of their application. Missing data could be estimated by using the P2I model.
- **Cost:** Refers to the product development cost for a specific phase or a project, highlighting projects that would enable faster/higher throughput. Funding applicants would submit cost estimates, which, for the purpose of this report, do not include costs associated with the development of infrastructure for the funded phase or to complete their projects.

FIG. 7.7 EXAMPLE OF HOW TPP CAN BE USED TO FILTER AND PRIORITIZE PROJECTS



TPP: target product profile.

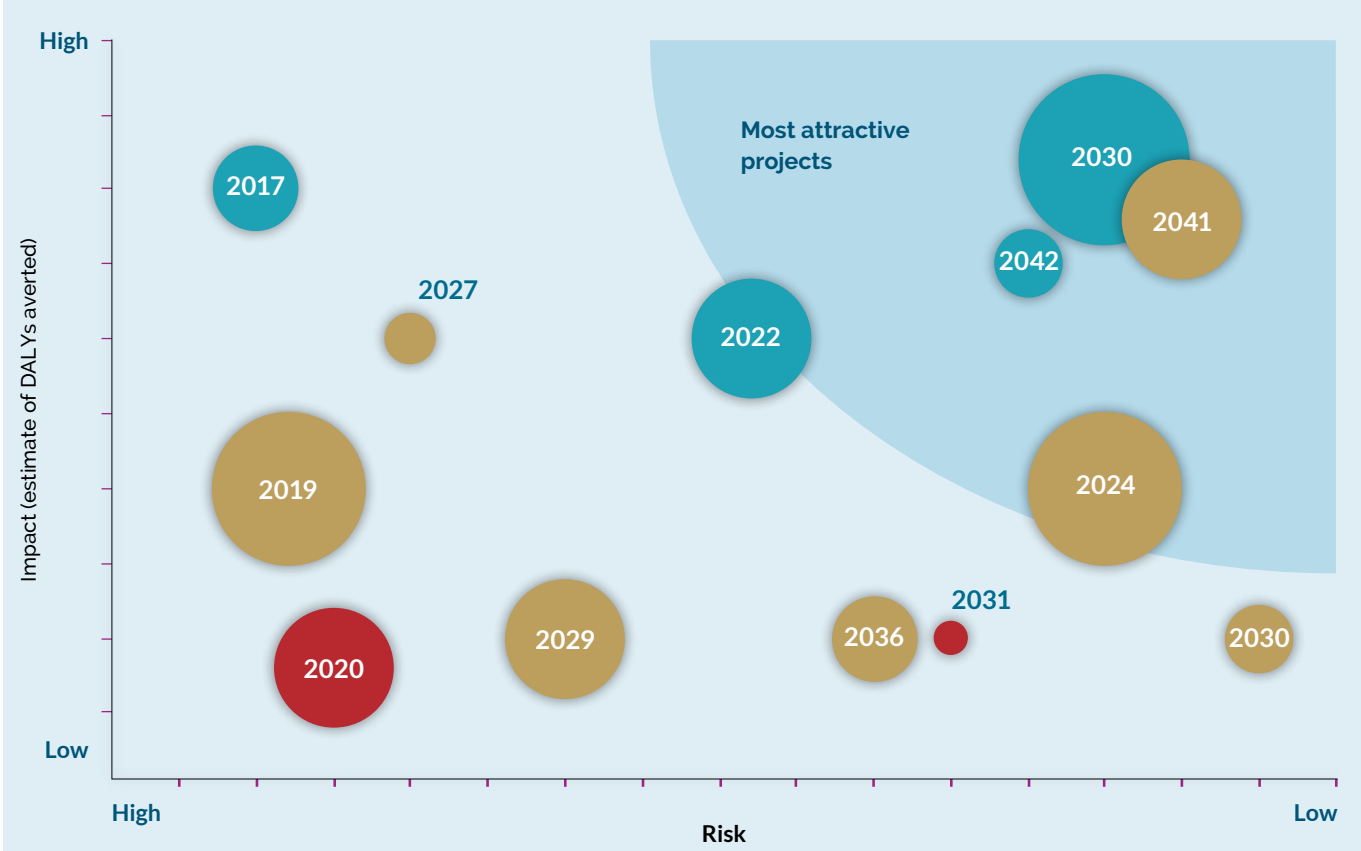
20. Diseases occurring in specific areas or regions may require different ways of expressing disease burden.

- **Risk:** The probability of a project's success could be measured by assessing the team's past experience, their capability, facilities and technologies, which would be necessary in executing the project, and the risks involved in achieving the projected impact within the expected timelines. The SWG could review and assess project risks by reviewing applications, and by conducting site visits and interviews.
- **Strategic fit:** Measures the level to which a project addresses strategic priorities and targets. The SWG members' judgement would be critical in this evaluation. Strategic fit specifically relates to end-product quality (i.e. TPP fulfilment/proportion of characteristic at "ideal" level, which would be provided by the applicant and assessed by the SWG) and time-to-launch (provided by the applicant or estimated using the P2I model). Accessibility and affordability (including de-linking the price from R&D cost, but focused more on production costs) would be factored into all TPP assessments.

These criteria could be combined to build a single framework for portfolio management. Individual projects within a given priority area could be mapped against these factors using tools such as the one illustrated in Fig. 7.8 (note that this portfolio prioritization framework should be used separately for each priority). The SWG would then be able to identify projects that best fit with the fund's requirements, risk and health impact goals.

Depending on the strategic focus, other frameworks may also be used to visualize portfolio options.

FIG. 7.8 FRAMEWORK FOR PORTFOLIO PRIORITIZATION CONSIDERING IMPACT, COST, RISK AND STRATEGIC FIT (TPP-FULFILMENT AND TIME-TO-LAUNCH)



DALYs: disability-adjusted life years; R&D: research and development; TPP: target product profile.

[a] Included only to show projects that must be improved before consideration.

After projects have been pre-selected for funding, the SWG would determine critical "go" and "no-go" decision-point milestones around key inflection points. At this stage, depending on the development stage of the funded project, the SWG would also determine the frequency of these decision-point milestones and agree on the reporting content.

Once projects have been selected for funding and confirmed by interviews with stakeholders and target-based milestone reviews, the decision points would be used to evaluate and monitor achievement. The SWG would also use these results to decide whether or not to continue or discontinue the funding at each critical point. In addition to the standard monitoring of project timelines and milestones, the four prioritization factors should be monitored to re-assess prioritization and determine whether or not to fund later stages of the project (as specified in the milestone agreement).

Fund recipients could monitor and report on the project using previously defined KPIs. In Fig. 7.9, a number of possible KPIs are shown, including suggestions on how they could be tracked. KPIs may need to be further elaborated depending on the project. Stakeholders emphasized the importance of setting milestone goals for specific projects and having clear milestone agreements that can be used to track them.

FIG. 7.9 EXAMPLE OF KPIs DETERMINED IN MILESTONE AGREEMENTS

	OBJECTIVE	METRIC	TARGET	TRACKING [a]		
			TIMELINE	HOW TO MEASURE	WHO	FREQUENCY [b]
TIMELINE AND MILESTONES	Ensure adherence to timelines/ milestones	• %-to-goal • %-to-next milestone	Milestone targets set by grantees	Measure progress against plan (e.g. patients enrolled)	Grantees	3 x per grant period
COST	Ensure effective use of financing	%-to-budget	Milestone targets set by grantees and funding amount	Measure cost against funding amount	Grantees and Secretariat	3 x per grant period
RISK	Re-evaluate risk to success	RPN-score	Milestone targets based on initial risk score and risk mgmt. plan	Reassess risk using questionnaire	SWG	2 x per grant period
IMPACT	Ensure project progress leads to public health impact	Effectiveness-adjusted expected DALYs saved	Milestone targets set by grantees	DALYs saved for measured effectiveness	Grantees and Secretariat	2 x per grant period
TPP-FULFILMENT	Ensure minimum TPP requirements are met; drive fulfilment of ideal requirements	• % at minimum or above • % at ideal or above	Milestone targets set by grantees and SWG	Measure TPP fulfilment potential	Grantees and SWG	2 x per grant period

- Replot on matrix and reassess prioritization and determine when to intervene (i.e. "no-go", guide, etc.)
- Further milestone agreements/KPIs should be set on a project-specific basis

KPIs: key performance indicators; DALYs: disability-adjusted life years; RPN: risk priority number; SWG: Scientific Working Group; TPP: target product profile.

[a] Outlines how KPI will be tracked, how it will be measured, who will be responsible for measuring and how often.

[b] May be set depending on specific project (i.e. phase III versus preclinical trial).

8

RECOMMENDATIONS AND CONCLUSIONS

A number of health experts, organizations and countries have called for financing needs to support R&D in diseases of poverty *(2, 3, 7, 9)*. Despite the repeated calls, the funding supported by traditional government funders, philanthropic and private funders remains insufficient to accelerate product development of diagnostics, vaccines and treatments for diseases of poverty compared to the public health need *(8, 23, 31)*.

As a response to the request by the WHA *(20)*, this report was developed to provide: (a) options for financial mechanisms together with their respective potential and limitations in health product development; (b) mechanisms needed to manage the fund and project portfolio; and (c) options for the development of other supportive tools, including the design of a compendium of TPPs, which would assist the SWG in efficiently managing the portfolio.

A special financial forecasting model, the P2I model, was developed to assist in estimating the minimum costs required for product development from preclinical studies to phase III trials. This model can also be used to provide approximate estimates of minimum R&D costs for the development of antibiotics or health products for emerging diseases.

Stakeholder opinions and landscape analyses in this report confirmed the clear need for a new R&D fund. The key recommendations for this financial mechanism are outlined below.

Even though various fund options with different funding levels are possible, a small fund may only have limited impact, whilst a fund of sufficient scale (e.g. gradually increasing up to US$ 100 million annually) could drive product development forward.

While the fund size could be scaled up over the first five to 10 years, a small fund in the long run could only focus on drug reformulation or repurposing – a very efficient approach, but one that may see diminishing returns after the "low-hanging fruit" are harvested. Fund sizes of at least US$ 100 million per year could drive R&D forward by supporting innovative product development. However, in order to significantly reduce the burden of diseases, additional supportive mechanisms (e.g. advance market commitment) may be required in parallel.

Regardless of the size and form of the future R&D financial mechanism, operational mechanisms described in this report would be useful for public health and R&D communities. These include approaches to setting up the SWG and best practices for portfolio management, and supplementary tools (e.g. the P2I model and TPP compendium), would be useful for public health and R&D communities.

The fund's portfolio of funded projects should be balanced between short-term goals and longer-term innovation-focused efforts.

Drug development, in general, is a long and costly process and its impact on public health may take even longer to be visible. In this context, stakeholders emphasized that it would be critical to gain momentum early on to generate excitement and trust among potential donors by aiming for some early successes. This could be achieved by focusing on drug reformulation/repurposing projects and/or on late-stage studies of some promising novel compounds, vaccines or diagnostics. However, it is unlikely that every priority disease could be addressed by such projects. Thus, to ensure long-term success, the funded portfolio should also contain some projects that are currently in earlier development stages given the long timelines.

A fund for R&D in diseases of poverty would need to have transparent, objective and non-political decision-making.

Some stakeholders raised concerns that a fund hosted by TDR may be constrained by bureaucratic processes and its decision-making may be subject to political influence. Therefore, clear, transparent and objective decision-making processes would be essential to ensure effective management of the fund and the project portfolio, and gain the trust of the community and potential donors. It would also be indispensable for SWG members to have appropriate expertise as well as experience in decision-making.

The fund would have to be able to access "new" and additional sources of funding.

Most stakeholders agreed that the impact of a new R&D fund mechanism would be limited if it simply pooled funds that were already being used for R&D in diseases of poverty. WHO's credibility in setting priorities and advocating for additional funding is critical in attracting new funders (e.g. middle-income country donors, private donors) to contribute to product development goals that combat diseases of poverty.

A new resource, a compendium of TPPs, would facilitate prioritization.

The creation of a new online resource bringing together in a comparable format the R&D priorities for Type III, II and R&D needs of Type I diseases would allow for the comprehensive mapping of the product pipeline against R&D activity. Hosted by the WHO Global Observatory on R&D, this compendium of product profiles would identify obvious gaps, and form a major component of the information necessary to lead a global dialogue on where the priorities lie in health product R&D, and how they could be addressed.

To conclude, this report emphasizes the need for a fund to support R&D in diseases of poverty, explores different options, and outlines possible operating and governance mechanisms. If such a fund were created under WHO's auspices and these recommendations were accepted, it would for the first time create a mechanism to identify and develop health products that would be affordable, accessible, acceptable and available to the countries that need them the most. All Member States would be able to participate in having a positive and lasting impact on the LMIC disease burden.

REFERENCES

1. Beyrer C, Villar JC, Suwanvanichkij V, Singh S, Baral SD, Mills EJ. Neglected diseases, civil conflicts, and the right to health. Lancet. 2007;370:619–27.

2. Hotez PJ, Pecoul B. "Manifesto" for advancing the control and elimination of neglected tropical diseases. PLOS Negl. Trop Dis. 2010;4:e718.

3. Pedrique B, Strub-Wourgaft N, Some C, Olliaro P, Trouiller P, Ford N et al. The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. Lancet GH. 2013;1:e371–9.

4. Background document provided by the WHO Secretariat, November 2012: defining diseases Type I, II and III. Geneva: World Health Organization; 2012 (http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf, accessed 26 January 2016).

5. Rottingen JA, Chamas C. A new deal for global health R&D? The recommendations of the Consultative Expert Working Group on Research and Development (CEWG). PLOS Med. 2012;9:e1001219.

6. Terry RF, Salm JF, Jr., Nannei C, Dye C. Creating a global observatory for health R&D. Science. 2014;345:1302–4.

7. Rottingen JA, Regmi S, Eide M, Young AJ, Viergever RF, Ardal C et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382:1286–307.

8. Moran M, Chapman N, Abela-Oversteegen L, Chowdhary V, Doubell A, Whittall C et al. Neglected disease research and development: the Ebola effect. Sydney: G-FINDER; 2015 (Policy Cures Series; http://policycures.org/downloads/Y8%20GFINDER%20full%20report%20web.pdf, accessed 28 January 2016).

9. Research and development to meet health needs in developing countries: strengthening global financing and coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva: World Health Organization; 2012.

10. Resolution WHA66.22. Follow up of the report of the Consultative Expert Working Group on Research and Development: financing and coordination. In: Sixty-sixth World Health Assembly, Geneva, 20–28 May 2013. Geneva: World Health Organization; 2013.

11. Consultancy to design a financial model for a Sustainable Health Product Research and Development Fund for Type III & II diseases and the specific R&D needs of developing countries in relation to Type I diseases: request for proposals (RFP). Geneva: WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2015.

12. Consultancy to prepare the TDR-based Scientific Working Group for the management of R&D portfolios and a Sustainable Health Product Research and Development Fund for Type III & II diseases and the specific R&D needs of developing countries in relation to Type I diseases: request for proposals (RFP). Geneva: WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2015.

13. Consultancy to design a compendium of target product profiles for Type III & II diseases and the specific R&D needs of developing countries in relation to Type I diseases: request for proposals (RFP). Geneva: WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2015.

14. Moran M, Guzman J, Chapman N, Abela-Oversteegen L, Whittall C, Howard R, et al. Neglected disease research and development: emerging trends. Sydney: G-FINDER; 2014 (Policy Cures; http://www.policycures.org/downloads/Y7%20GFINDER%20full%20report%20web%20.pdf; accessed 28 January 2016).

15. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386:743–800.

16. Citeline. Pharmaprojects database 2015: https://citeline.com/products/pharmaprojects/ (accessed 11 February 2016).

17. Horvath C. Comparison of preclinical development programs for small molecules (drugs/pharmaceuticals) and large molecules (biologics/biopharmaceuticals): studies, timing, materials, and costs. Ed: Cavagnaro JA. Hoboken, NJ: John Wiley & Sons, Inc.; 2010.

18. Liao XC. Early development of antibody therapeutics: key aspects of advancing an antibody drug from research to clinic. Trends in Bio/Pharm. Ind. 2009;18–23 http://www.tbiweb.org/tbi/file_dir/TBI2009/Early%20development.pdf (accessed 28 January 2016).

19. PAREXEL Biopharmaceutical R&D Statistical Sourcebook: Parexel; 2014.

20. Hughes et al. Early Drug Discovery and Development Guidelines: For Academic Researchers, Collaborators, and Start-up Companies to Assay Guidance Manual. 2012 May 01 [updated 2012 Oct 01]. http://www.ncbi.nlm.nih.gov/books/NBK92015/pdf/Bookshelf_NBK92015.pdf (accessed June 2015).

21. Paul SM. et al., How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010: 9, 203-214.

22. DiMasi JA et al., The price of innovation: new estimates of drug development costs. J. Health Economics 2003: 22, 151-185.

23. Decision of the 67th World Health Assembly, WHA67(15). In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. Geneva: World Health Organization; 2014.

24. Report of the Director-General A68/34. In: Sixty-eighth World Health Assembly, Geneva, 18–26 May 2015. Geneva: World Health Organization; 2015.

25. TDR's Scientific and Technical Advisory Committee and Scientific Working Groups: terms of reference. Geneva: WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2014.

26. Strategic Advisory Group of Experts (SAGE): terms of reference. Geneva: World Health Organization; 2013.

27. Declaration of interests for WHO experts: http://www.who.int/about/declaration-of-interest/en/ (accessed 28 January 2016).

28. Guidance for industry and review staff: target product profile – a strategic development process tool. Washington, DC: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2007.

29. Mossialos E, Morel CM, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. Copenhagen: World Health Organization; 2010.

30. Pugatch MP, Chu R, Torstensson D. Assembling the pharmaceutical R&D puzzle for needs in the developing world: an assessment of new and proposed de-linking initiatives aimed at encouraging R&D into neglected and tropical diseases and specific Type II diseases: Pugatch Consilium; 2012.

31. Balasegaram M, Brechot C, Farrar J, Heymann D, Ganguly N, Khor M, et al. A global biomedical R&D fund and mechanism for innovations of public health importance. PLOS Med. 2015;12:e1001831

FURTHER READING

Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. PLOS one. 2013;8:e57755.

Pearson M, Clarke J, Ward L, Grace C, Harris D, Cooper M. Evaluation of the International Finance Facility for Immunisation (IFFIm): executive summary. Geneva: Gavi, the Vaccine Alliance (GAVI); 2011 (http://www.gavi.org/results/evaluations/iffim-evaluation/, accessed 11 February 2016).

U.S. National Institutes of Health (NIH). AIDS info factsheet: https://aidsinfo.nih.gov/education-materials/fact-sheets (accessed 11 February 2016).

The gap report 2014. Geneva: UNAIDS; 2014 (http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf, accessed 11 February 2016).

Global update on HIV treatment 2013: results, impact and opportunities: WHO report in partnership with UNICEF and UNAIDS. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf?ua=1, accessed 11 February 2016).

BIO Ventures for Global Health (BVGH). Neglected tropical disease drug and diagnostic pipelines: http://www.bvgh.org/Current-Programs/Neglected-Disease-Product-Pipelines/NTD-Pipelines.aspx (accessed 11 February 2016).

World Health Organization (WHO) Product Development for Vaccines Advisory Committee (PDVAC): http://www.who.int/immunization/research/committees/pdvac/en/ (accessed 11 February 2016).

World Intellectual Property (WIPO). Research: http://www.wipo.int/research/en/ (accessed 11 February 2016).

International AIDS Vaccine Initiative (IAVI): http://www.iavi.org/ (accessed 11 February 2016).

Global Health Investment Fund (GHIF): http://www.ghif.com/ (accessed 11 February 2016).

Juvenile Diabetes Research Foundation (JDRF): http://jdrf.org/ (accessed 11 February 2016).

Multiple Myeloma Research Foundation (MMRF): http://www.themmrf.org/ (accessed 11 February 2016).

ANNEX 1a
LIST OF TYPE III DISEASES

GBD NO.	GBD CAUSE NAME	LOW INCOME	LOWER MIDDLE INCOME	UPPER MIDDLE INCOME	LOW + MIDDLE INCOME	HIGH INCOME	DALYs RATIO LOW + MIDDLE INCOME/HIGH INCOME PER 100 000 OF POPULATION
23	Chagas disease	0.00	3.85	14.32	7.94	0.00	1869.12
31	Trachoma	68.76	18.06	17.91	24.80	0.02	1358.34
22	Trypanosomiasis	158.93	22.79	0.17	31.12	0.04	867.12
26	Lymphatic filariasis	282.28	169.92	0.84	110.61	0.19	569.48
14	Diphtheria	8.04	4.89	0.16	3.23	0.01	390.20
56	Vitamin A deficiency	57.68	8.76	0.52	11.71	0.03	338.60
15	Measles	389.48	518.38	7.46	276.22	1.03	266.90
16	Tetanus	235.88	145.59	10.50	98.27	0.37	264.13
20	Malaria	2537.27	674.78	8.13	631.60	3.41	185.06
27	Onchocerciasis	11.31	13.32	0.06	7.21	0.05	152.11
25	Leishmaniasis	42.79	69.63	2.99	36.70	0.30	122.67
28	Leprosy	4.75	5.98	0.95	3.60	0.03	118.17
43	Maternal haemorrhage	242.03	107.99	9.00	82.43	0.72	114.74
5	Syphilis	161.49	64.90	7.93	52.80	0.68	78.02
45	Hypertensive disorders of pregnancy	77.92	50.71	6.67	34.98	0.58	60.13
30	Japanese Encephalitis	12.90	19.52	5.91	12.64	0.22	58.61
33	Ascariasis	67.80	46.97	11.86	34.32	0.62	54.96
47	Abortion	325.01	193.03	26.50	137.47	3.32	41.46
55	Iodine deficiency	159.20	66.99	35.17	65.37	1.65	39.60
24	Schistosomiasis	115.67	31.32	6.25	31.62	0.81	38.85
12	Pertussis	361.00	301.87	13.73	183.01	4.89	37.39

DALYs: disability-adjusted life years; GBD: global burden of disease.
Source: Background document provided by the WHO Secretariat, November 2012: defining diseases Type I, II and III. Geneva: World Health Organization; 2012 http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf

ANNEX 1b
LIST OF TYPE II DISEASES

GBD NO.	GBD CAUSE NAME	LOW INCOME	LOWER MIDDLE INCOME	UPPER MIDDLE INCOME	LOW + MIDDLE INCOME	HIGH INCOME	DALYs RATIO LOW + MIDDLE INCOME/HIGH INCOME PER 100 000 OF POPULATION
46	Obstructed labour	92.03	83.55	12.21	53.29	1.54	34.65
34	Trichuriasis	33.69	22.45	10.56	18.73	0.56	33.36
3	Tuberculosis	1263.97	771.42	306.48	632.98	20.03	31.60
10	Diarrhoeal diseases	3893.35	1609.69	313.16	1345.90	45.66	29.48
54	Protein-energy malnutrition	882.15	386.36	89.14	322.17	13.32	24.19
29	Dengue	22.33	17.78	4.05	12.35	0.61	20.34
17	Meningitis	574.63	259.51	52.00	210.52	11.42	18.43
35	Hookworm disease	38.80	19.64	14.84	20.10	1.10	18.20
9	HIV/AIDS	3759.08	745.15	578.03	1076.48	63.00	17.09
51	Birth asphyxia and birth trauma	1605.14	967.32	314.41	765.68	49.65	15.42
39	Lower respiratory infections	5185.63	2072.82	352.81	1734.05	128.12	13.53
50	Low birth weight	1399.47	1120.39	328.56	809.42	76.35	10.60
44	Maternal sepsis	256.75	152.00	44.58	118.80	14.22	8.35
100	Cataracts	411.32	354.22	261.82	321.23	45.34	7.09
105	Rheumatic heart disease	90.76	129.23	60.82	93.96	13.29	7.07
40	Upper respiratory infections	87.26	26.64	20.71	32.18	5.57	5.78
18	Hepatitis B	67.65	42.24	22.37	36.91	8.01	4.61
57	Iron-deficiency anaemia	443.40	356.03	173.57	287.47	65.95	4.36
116	Peptic ulcer disease	102.67	114.76	57.85	88.09	21.97	4.01

DALYs: disability-adjusted life years; GBD: global burden of disease; HIV/AIDS: acquired immunodeficiency syndrome/human immunodeficiency virus.
Source: Background document provided by the WHO Secretariat, November 2012: defining diseases Type I, II and III. Geneva: World Health Organization; 2012 http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf

ANNEX 1c
LIST OF TYPE I DISEASES

GBD NO.	GBD CAUSE NAME	LOW INCOME	LOWER MIDDLE INCOME	UPPER MIDDLE INCOME	LOW + MIDDLE INCOME	HIGH INCOME	DALYs RATIO LOW + MIDDLE INCOME/HIGH INCOME PER 100 000 OF POPULATION
41	Otitis media	38.79	28.63	18.86	25.70	10.08	2.55
85	Epilepsy	203.67	147.39	102.40	135.15	55.34	2.44
121	Nephritis and nephrosis	205.14	188.05	109.43	155.75	65.04	2.39
99	Glaucoma	97.61	79.76	75.19	80.15	39.56	2.03
118	Appendicitis	9.55	7.26	6.13	7.07	3.60	1.96
84	Schizophrenia	268.96	294.75	269.56	280.20	161.76	1.73
70	Cervix uteri cancer	80.45	74.12	44.62	61.99	36.97	1.68
101	Refractive errors	321.35	456.20	510.14	461.82	279.31	1.65
62	Oesophagus cancer	61.76	42.71	119.40	79.02	49.97	1.58
106	Hypertensive heart disease	167.82	114.87	138.10	132.21	85.85	1.54
108	Cerebrovascular disease	617.87	595.36	977.12	766.39	514.96	1.49
83	Bipolar affective disorder	247.43	238.47	232.62	237.10	159.58	1.49
122	Benign prostatic hypertrophy	34.49	42.93	46.81	43.50	30.87	1.41
113	Asthma	356.88	283.57	221.16	265.95	191.53	1.39
93	Panic disorder	117.09	118.61	108.36	113.90	82.60	1.38
129	Low back pain	39.86	39.54	38.66	39.20	28.57	1.37
112	Chronic obstructive pulmonary disease	271.72	465.98	580.95	490.48	366.26	1.34
92	Obsessive-compulsive disorder	100.36	79.26	79.87	82.36	63.97	1.29
65	Liver cancer	87.24	42.16	178.97	108.42	84.48	1.28
109	Inflammatory heart disease	126.55	100.31	92.88	100.57	78.97	1.27

DALYs: disability-adjusted life years; GBD: global burden of disease.
Source: Background document provided by the WHO Secretariat, November 2012: defining diseases Type I, II and III. Geneva: World Health Organization; 2012 http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf

List of Type I diseases (continued)

GBD NO.	GBD CAUSE NAME	LOW INCOME	LOWER MIDDLE INCOME	UPPER MIDDLE INCOME	LOW + MIDDLE INCOME	HIGH INCOME	DALYs RATIO LOW + MIDDLE INCOME/HIGH INCOME PER 100 000 OF POPULATION
61	Mouth and oropharynx cancers	64.60	81.48	40.38	61.12	48.13	1.27
128	Gout	32.56	55.16	62.51	55.36	45.35	1.22
117	Cirrhosis of the liver	157.93	253.99	201.68	218.06	182.92	1.19
107	Ischaemic heart disease	791.16	1249.88	818.29	998.33	849.43	1.18
63	Stomach cancer	61.93	47.37	204.26	118.37	107.90	1.10
76	Leukaemia	48.27	75.38	89.65	78.02	71.38	1.09
91	Post-traumatic stress disorder	50.67	55.35	54.26	54.24	52.61	1.03
19	Hepatitis C	24.72	17.31	9.50	14.87	14.79	1.01
82	Unipolar depressive disorders	858.90	1124.18	964.19	1018.14	1023.11	1.00
102	Hearing loss, adult onset	362.68	486.80	384.59	425.15	429.11	0.99
103	Macular degeneration and other sense disorders	116.43	157.58	136.63	142.83	153.98	0.93
79	Diabetes mellitus	250.23	283.46	318.90	294.59	366.65	0.80
86	Alcohol use disorders	111.63	234.67	547.27	355.71	442.97	0.80
95	Migraine	100.51	120.55	116.74	116.18	144.72	0.80
127	Osteoarthritis	183.96	200.04	278.78	232.53	293.95	0.79
126	Rheumatoid arthritis	49.99	63.47	92.30	74.35	100.10	0.74
94	Insomnia (primary)	49.10	55.79	49.63	52.18	77.93	0.67
75	Lymphomas and multiple myeloma	77.93	71.02	47.69	61.68	92.13	0.67
89	Multiple sclerosis	17.20	21.27	24.16	22.00	32.86	0.67
90	Drug use disorders	100.65	125.93	117.46	118.81	188.03	0.63
72	Ovary cancer	17.86	25.56	21.84	22.89	49.07	0.47
69	Breast cancer	59.24	84.21	96.32	86.18	190.51	0.45
77	Other malignant neoplasms	111.02	110.29	125.63	117.14	269.23	0.44
74	Bladder cancer	12.24	18.77	19.19	18.08	45.70	0.40
67	Trachea, bronchus and lung cancers	67.23	79.99	230.74	144.62	381.30	0.38
71	Corpus uteri cancer	3.62	6.80	11.67	8.52	27.21	0.31
64	Colon and rectum cancers	28.18	51.42	92.56	66.41	219.64	0.30
87	Alzheimer and other dementias	70.77	94.81	164.15	122.10	437.84	0.28
73	Prostate cancer	18.87	19.03	21.68	20.17	72.60	0.28
66	Pancreatic cancer	12.08	15.65	35.57	23.93	88.95	0.27
88	Parkinson disease	20.97	14.06	21.52	18.27	69.48	0.26
68	Melanoma and other skin cancers	7.11	4.90	8.18	6.64	33.28	0.20

DALYs: disability-adjusted life years; GBD: global burden of disease.
Source: Background document provided by the WHO Secretariat, November 2012: defining diseases Type I, II and III. Geneva: World Health Organization; 2012 http://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf

ANNEX 2
LIST OF STAKEHOLDERS

Blue background denotes stakeholders interviewed or consulted; white denotes stakeholders contacted but not interviewed.

Some organizations have multiple functions in the categories below but, to avoid redundancy, one category was selected depending on the expertise of the individuals contacted.

FUNDERS
Administrative Department of Science, Technology and Innovation (Colciencias), Government of Columbia, Columbia
African Development Bank, Nigeria
Asian Development Bank, Philippines
Bill and Melinda Gates Foundation, USA
Carter Center, USA
Department for International Development (DFID), United Kingdom
Directorate-General for International Cooperation (DGIS), Netherlands Ministry of Foreign Affairs, Netherlands
DLR Project Management Agency, International Cooperation in Health Research, Germany
Dutch Ministry of Foreign Affairs (DGIS), Netherlands
European Commission – Horizon 2020, Belgium
Federal Ministry of Education and Research, Germany
Gavi, the Vaccine Alliance, Switzerland
German Federal Ministry for Economic Cooperation and Development (BMZ), Germany
Global Health Innovative Technology Fund (GHIT), Japan
Global Health Investment Fund (GHIF), USA
INCLEN Trust, India
Indian Council of Medical Research (ICMR), India
Innovative Medicines Initiative (IMI), Netherlands
Irish AID, Department of Foreign Affairs and Trade, Ireland
KfW Development Bank, Germany
Medical Research Council, South Africa
Medical Research Council, United Kingdom
Multiple Myeloma Research Foundation, USA
National Institutes of Health, USA
New Development Bank BRICS (Brazil, Russia, India, China and South Africa), People's Republic of China
Novo Foundation, USA
Paul Allen Foundation, USA

funders cont.

Science and Technological Development Fund (STDF), Egypt
Tanzania Commission for Science and Technology (COSTECH), United Republic of Tanzania
The Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
United States Agency for International Development (USAID), USA
Versant Ventures, USA
Wellcome Trust, United Kingdom
World Bank, USA
Wyss Foundation, Switzerland

MINISTRIES
Federal Department of Foreign Affairs, Switzerland
Her Majesty's Treasury, Commercial Secretary to the Treasury, Economic and Finance Ministry, United Kingdom
Ministry of Finance, Nigeria (former)
Ministry of Health, Nigeria (former)
Ministry of Health, Kenya
Ministry of Health, Malaysia
Ministry of Health, Zambia
National Pharmaceutical Procurement Unit, Ministry of Health, Sierra Leone

NOT-FOR-PROFIT NGOs
African Federation of Public Health Associates (AFPHA), Ethiopia
BIO Ventures for Global Health (BVGH), USA
Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH, Germany
European & Developing Countries Clinical Trials Partnership (EDCTP), Uganda
European & Developing Countries Clinical Trials Partnership (EDCTP), United Republic of Tanzania (former)
European Federation of Pharmaceutical Industries and Associations (EFPIA), Belgium
International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Switzerland
Médecins Sans Frontières, Switzerland
Médecins Sans Frontières, France
Milken Institute (FasterCures), USA
Osafric Water and Energy Conservation, Kenya
Pharmaceutical Research and Manufacturers of America (PhRMA), USA
Policy Cures, Australia

ORGANIZATIONS CONDUCTING R&D
Abbott Diagnostics, Switzerland
Abbott Diagnostics, USA
AbbVie, USA
Academy of Scientific Research and Technology (ASRT), Egypt
AERAS, USA
Alere Inc., USA
Bavarian Nordic (BVN), Germany
Bharat Biotech, India
Biosciences Eastern and Central Africa-International Livestock Research Institute (BecA-ILRI), Kenya
Bristol-Myers Squibb, USA

organizations conducting R&D cont.

Cairo University, Egypt
Department of Defence/Defence Advanced Research Projects Agency (DOD/DARPA), USA
Drugs for Neglected Diseases *initiative* (DND*i*), Switzerland
Foundation for Innovative New Diagnostics (FIND), Switzerland
GlaxoSmithKline (GSK), Singapore
GlaxoSmithKline (GSK), United Kingdom
H3 Drug Discovery Partnership, South Africa
Harvard Kennedy School, USA
Harvard School of Public Health, USA
Health Science Center, Peking University, People's Republic of China
Hilleman Laboratories, India
Hoffmann-La Roche AG, Switzerland
Ifakara Health Institute, United Republic of Tanzania
Immunobiological Technology Institute, Bio-Manguinhos, Oswaldo Cruz Foundation, Brazil
Institut National de la Santé et de la Recherche Médicale (INSERM), France
Instituto Nacional de Salud Pública, Mexico
International AIDS Vaccine Initiative (IAVI), USA
Interuniversity Microelectronics Centre (IMEC), Belgium
Janssen Diagnostics, Belgium
Janssen Diagnostics, Netherlands
Janssen, Belgium
Janssen, USA
Johns Hopkins University, USA
Johnson & Johnson, USA
Kenya Medical Research Institute (KEMRI), Kenya
London School of Hygiene & Tropical Medicine, United Kingdom
Massachusetts Institute of Technology, USA
Medicines for Malaria Venture (MMV), Switzerland
Merck & Co. Inc., USA
National Health and Medical Research Council (NHMRC), Australia
National Institute for Pharmaceutical Research and Development (NIPRD), Nigeria
Nigerian Institute of Medical Research, Nigeria
Noguchi Memorial Institute for Medical Research (NMIMR), Cameroon
Norwegian Institute of Public Health, Norway
Novartis Foundation, Switzerland
Novartis Institute for BioMedical Research, USA
Novartis, Singapore
Novartis, Switzerland
Novartis, Switzerland (former)
Novartis, USA
Novavax Inc., USA
Oswaldo Cruz Foundation (Fiocruz), Brazil
PATH, USA
Roche Diagnostics, Switzerland
Sanofi Pasteur, France
Sanofi S.A., France

organizations conducting R&D cont.

Serum Institute of India, India
Swiss Tropical and Public Health Institute, Switzerland
Takeda Pharmaceutical Company, USA
TB Alliance, USA
Tropical Diseases Research Centre, Zambia
XOMA Ltd., USA
Zhejiang University, People's Republic of China

REGULATORY AGENCIES
Brazilian Health Surveillance Agency (ANVISA), Brazil
Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED), Cuba
China Food and Drug Administration (CFDA), People's Republic of China
European Medicines Agency (EMA), United Kingdom
Food and Drug Administration (FDA), Thailand
Food and Drug Administration (FDA), USA
Korea Food and Drug Administration (KFDA), Republic of Korea
Medicines Control Council, South Africa
National Administration of Drugs, Food, and Medical Technology (ANMAT), Argentina
National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria
Paul Ehrlich Institut, Federal Institute for Vaccines and Biomedicines (PEI), Germany
Pharmaceutical and Medical Device Agency (PMDA), Japan
Saudi Food and Drug Authority (SFDA), Saudi Arabia
Swissmedic, Switzerland
Tanzania Food and Drug Administration (TFDA), United Republic of Tanzania

INTERGOVERNMENTAL ORGANIZATIONS
UNITAID, Switzerland
United Nations Children's Fund (UNICEF), USA
United Nations Development Programme (UNDP), USA
World Health Organization: headquarters, Switzerland
Family, Women's and Children's Health (FWC)
Health Systems and Innovation (HIS)
HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases (HTM)
Noncommunicable Diseases and Mental Health (NMH)
Special programme for Research and Training in Tropical Diseases (TDR), Switzerland
World Health Organization: regional offices
WHO Regional Office for Africa (AFRO), Congo
WHO Regional Office for Europe (EURO), Denmark
WHO Regional Office for the Americas (AMRO)/Pan-American Health Organization (PAHO), USA
WHO Regional Office for the Eastern Mediterranean (EMRO), Egypt
WHO South-East Asia Regional Office (SEARO), India
WHO Western Pacific Regional Office (WPRO), Philippines

ANNEX 3
POTENTIAL FORUM FOR ACTIVE COORDINATION

PURPOSE	Provide an opportunity for major funders to convene a R&D Funding Summit and identify/pursue opportunities for improved coordination and collaboration in R&D for priority diseases
ATTENDEES	• All major funding organizations to be represented, ideally by representatives of CEOs/executive directors (cf. HIROs forum) • Example organizations (not exhaustive): BMGF, NIH, US DOD (DARPA), Wellcome Trust, USAID, European Commission, Inserm, DFID, MMV, PATH, pharmaceutical industry, governments, etc.
LOGISTICS	• Forum to be hosted by financing mechanism and its host organization (e.g. TDR, World Bank) • TDR Joint Coordinating Board (JCB) Chair and senior WHO representatives (e.g. ADG-level) to facilitate forum with TDR and financing mechanism leadership
KEY AGENDA ITEMS / TOPICS FOR DISCUSSION	• Discuss global R&D priorities determined by TDR JCB and SWG • Review "direction" of current R&D spend at an aggregate funder level (i.e. funders provide summary of R&D spend by disease to financing mechanism, which aggregates and analyses against priorities) • Assess and discuss "high potential" projects, as determined by the funders, and collaboration/ financing opportunities • Review challenges / concerns and consider means of addressing and counteracting • Discuss R&D, regulatory, government fiscal policy, political, and other trends and the impact they may have on financing mechanism/ability to deliver new interventions

ADG: Assistant Director-General; CEO: Chief Executive Officer; DFID: UK Dept. for International Development; HIROs: Heads of International Research Organizations; INSERM: French Institute of Health and Medical Research; MMV: Medicines for Malaria Venture; NIH: National Institutes of Health; PATH: Program for Appropriate Technology in Health; R&D: research and development; SWG: Scientific Working Group; USAID: US Agency for International Development; US DOD (DARPA): US Department of Defence (Defence Advanced Research Projects Agency).

ANNEX 4
OVERVIEW OF CONFLICTS OF INTEREST (COI) POLICIES

ORGANIZATION	DESCRIPTION OF CONFLICTS OF INTEREST	DESCRIPTION OF POLICIES FOR DEFINING, EXCLUDING CONFLICTS; PARTIAL EXCLUSIONS	PAST ISSUES WITH CONFLICTS? HOW HANDLED?	HOW ACTIVE INDUSTRY INVOLVEMENT IS HANDLED
WHO	A COI is defined as "any interest declared by an expert that may affect or reasonably be perceived to: (1) affect the expert's objectivity and independence in providing advice to WHO, and/or (2) create an unfair competitive advantage for the expert or persons or institution with whom the expert has financial or business interest (such as adult children or siblings, close professional colleagues, administrative unit or department)." Covers direct (e.g. financial, business, intellectual property (IP) and indirect (e.g. family, professional) interests, bias, unfair or competitive advantages, or a link with tobacco industry.	Conflict does not automatically lead to disqualification, but the process is designed to identify and avoid potentially compromising situations. Four steps of assessment: 1. initial review: relevancy and significance of the interest 2. factors to consider and evaluate items declared 3. the balancing test 4. possible options: determine possible conditions, including conditional participation, partial exclusion options. WHO Declaration of interests forms and guidance documents. COI policy for SAGE members. COI policy for TDR JCB members.	Questions were raised on the role of contributions from consumer packaged goods companies and nutrition policy. COI policy was strengthened in 2011.	Industry and other interest group representatives are not required to complete a COI form as they are invited to exchange information or present views as an industry spokesperson, but not to make an assessment or to give advice as an independent expert.

Overview of conflicts of interest (COI) policies cont.

International Agency for Research on Cancer (IARC)	Follows WHO regulations. A 2004 publication in an academic journal, in response to questions about COI, outlined the policy: any COI relating to employment with commercial entities must be declared (including WHO's definitions of direct and indirect conflicts).	Scientific Conduct Team (which signs COI forms) reviews any allegations of conflicts/misconduct. In 2004, a new category of participant, "Invited Specialist", was created to allow participation of experts who have real or perceived conflicts. Such specialists are blocked from certain activities (drafting policy text, evaluations), and must agree to participate in their individual capacity rather than representing any institution. Declaration of interest for IARC/WHO experts	Past allegations of bias due to conflicts led to creation of "Invited Specialist" category. Publication of policies in an academic journal.	Activities restricted based on conflicts.
European Medicines Agency (EMA)	The Scientific Advice Working Party (SWAP) members, including alternates and short-term experts, must not have financial or other interests in the pharmaceutical industry (direct and indirect conflicts).	Financial statements and any indirect conflicts must be declared annually; the latter are made public. Specific conflicts must be declared prior to meeting. Levels of conflict are defined, and activities for members are restricted based on the level of conflict (by assessing the nature of the declared interest, the timeframe during which such interest occurred, as well as the type of activity). COI policy for scientific experts, agency staff and Management Board members Policy on handling of declarations of interest of scientific committee members and experts.	N/A	Active employment in the industry is not generally compatible, except in case of expert witnesses. A tiered system of categorizing conflicts and associated level of participation is used.
U.S. Food and Drug Administra-tion (FDA)	COI include financial and other matters (personal relationships, interests, etc.).	COI is vetted by at least four (and as many as six) levels, including external reviewers. Waivers and exemptions may be provided when a conflict is determined if the disqualifying financial interest is not so substantial that it is likely to affect the integrity of the services to the government. Policies and procedures for handling of COI with Advisory Committee members, consultants and experts. Guidance for the public, FDA Advisory Committee members, and FDA staff on procedures for determining conflicts of interest and eligibility for participation in FDA Advisory Committees.	N/A	Industry participation is not specifically outlined, but waiver can be provided if a conflict is outweighed by value of service to the FDA.

N/A: not applicable

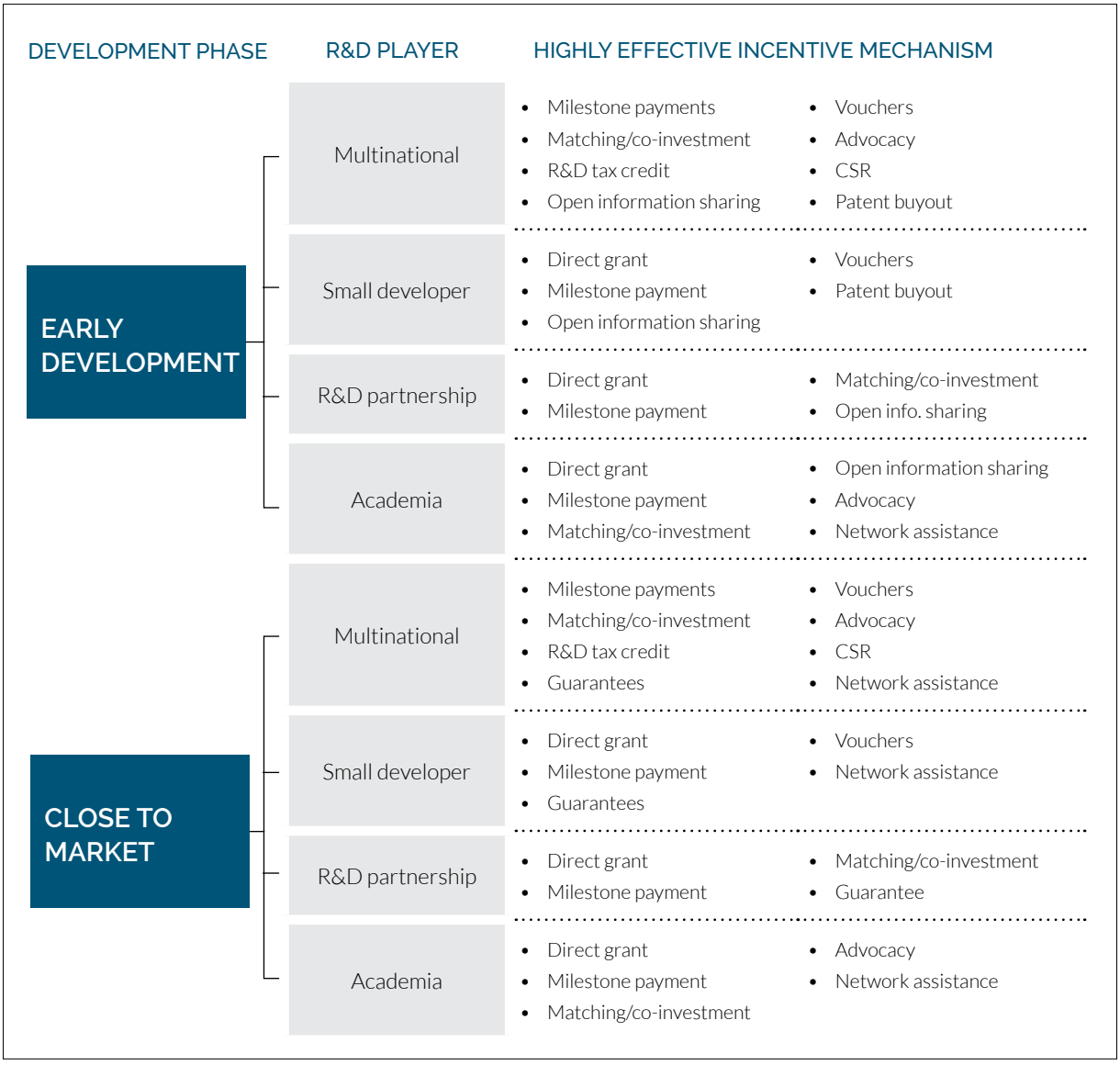
Overview of conflicts of interest (COI) policies cont.

EU Pharmacopoeia	COI to be declared includes financial, bias and other.	Interests in specific agenda items must be declared and recorded. Chair (in consultation with Secretariat) resolves outcomes. Code of practice for the work of the European pharmacopoeia.	Process in place for Chair to handle specific declared conflicts as they arise.	Participants can still have industry interests, but need to comply with Code of Practice and declare specific interests in meetings.
US Pharmacopoeia (USP)	COIs are primarily defined as financial and professional. Bias is not addressed.	Forms that define conflicts must be signed annually; new conflicts reported to USP leadership. No mention of exclusions, but actions taken to mitigate each conflict. 2015–2020 USP Bylaws. USP FAQ: USP Council of Experts and Expert Committees COI (question 10).	N/A	Industry is still able to provide donations, but policies in place to ensure transparency and prevent donations from providing any advantage over competitors.
National Institutes of Health (NIH), USA	Policy covers "significant financial interest" conflicts (those exceeding US$ 5000 in the previous 12 months) that could affect the design, conduct or reporting of research. This includes IP rights, travel benefits but excludes ownership in companies and royalty salaries. Applies to contractors, investigators, researchers who receive NIH funding.	Reports to NIH must be made annually. No exemptions made in advance, but retrospective reviews start a process of mitigation for any conflicts found. Financial COI.	N/A	Industry participation is not specifically addressed.
Intergovern-mental Panel on Climate Change (IPPC)	COI includes professional, financial and other – but not bias. Members are carefully selected so that bias can be balanced over the course of discussion.	Expert Advisory Group on Conflicts of Interest advises on issues for potential members. If issue cannot be resolved, individual is ineligible. Exceptions can be made where individual offers a unique perspective and conflicts can be managed; conflicts will be disclosed. COI Policy. Methods of work of the COI Committee.	N/A	Process in having industry representation is not specifically outlined.

N/A: not applicable

ANNEX 5a

INCENTIVE DECISION TREE FOR DEVELOPMENT OF HEALTH PRODUCTS WITH "SIGNIFICANT MARKET FAILURE"



Source: Mossialos et al. *(29)*; Pugatch, Chu & Torstensson *(30)*.

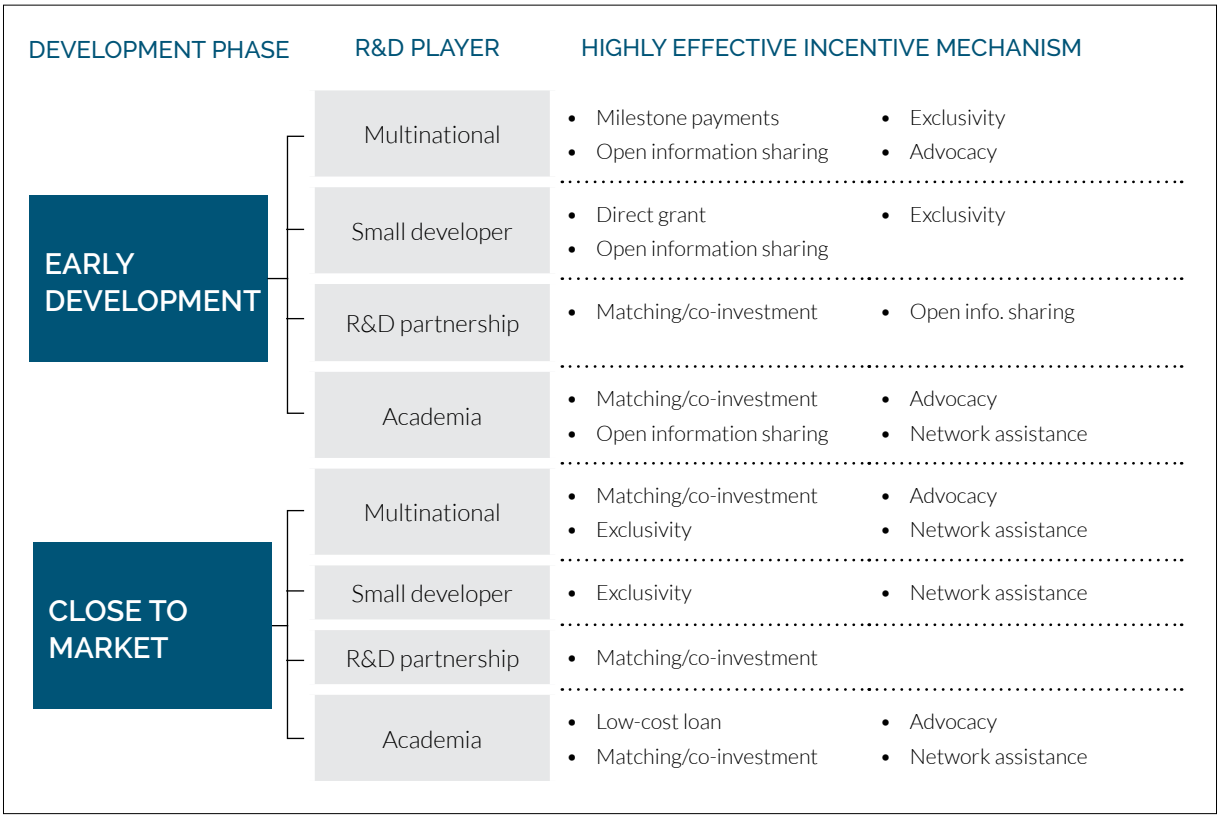
ANNEX 5b

INCENTIVE DECISION TREE FOR DEVELOPMENT OF HEALTH PRODUCTS WITH "SOME MARKET FAILURE"

Source: Mossialos et al. *(29)*; Pugatch, Chu & Torstensson *(30)*.

ANNEX 5c

INCENTIVE DECISION TREE FOR DEVELOPMENT OF HEALTH PRODUCTS WITH "RELATIVELY SMALL MARKET FAILURE"



Source: Mossialos et al. *(29)*; Pugatch, Chu & Torstensson *(30)*.

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

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The Special Programme for Research and Training in Tropical Diseases (TDR) is an independent global programme of scientific collaboration established in 1975. It has a twin mission to improve existing and develop new approaches for preventing, diagnosing, treating, and controlling neglected infectious diseases, and to strengthen the capacity of developing endemic countries to undertake this research and implement the new and improved approaches. TDR is sponsored by the following organizations:

unicef
UNDP
World Bank
World Health Organization