

# Strengthening Mechanisms to Prioritize, Coordinate, Finance, and Execute R&D to Meet Health Needs in Developing Countries

**Peter Hotez, Rachel Cohen, Carol Mimura, Tadataka Yamada, Stephen L. Hoffman, and Deepali M. Patel\***

January 15, 2013

*\*Participants in activities of the IOM Global Health Interest Group*

---

*The views expressed in this discussion paper are those of the authors and not necessarily of the authors' organizations or of the Institute of Medicine. The paper is intended to help inform and stimulate discussion. It has not been subjected to the review procedures of the Institute of Medicine and is not a report of the Institute of Medicine or of the National Research Council.*

---

**INSTITUTE OF MEDICINE**  
OF THE NATIONAL ACADEMIES

**Advising the nation • Improving health**

# Strengthening Mechanisms to Prioritize, Coordinate, Finance, and Execute R&D to Meet Health Needs in Developing Countries

Peter Hotez, National School of Tropical Medicine at Baylor College of Medicine, James A. Baker III Institute for Public Policy at Rice University, and Sabin Vaccine Institute; Rachel Cohen, Drugs for Neglected Diseases *initiative*; Carol Mimura, University of California, Berkeley; Tadataka Yamada, Takeda Pharmaceuticals; Stephen L. Hoffman, Sanaria Inc.; Deepali M. Patel, Institute of Medicine<sup>1</sup>

## EXECUTIVE SUMMARY

In response to issues raised in the report of the World Health Organization (WHO)-affiliated Consultative Expert Working Group (CEWG) on research and development (R&D) financing and coordination and the desire of the U.S. government to obtain a wide range of nongovernmental perspectives on the funding and coordination of the global health research enterprise, several members of the IOM Global Health Interest Group and other experts combined efforts to produce an IOM discussion paper to capture their views on approaches to research priority-setting, the leading gaps in global health R&D, R&D planning and costing, the private-sector role in global health R&D, the creation of effective global health research networks, the building of R&D capacity in developing countries, innovations in financing the global health R&D enterprise, and principles of global health R&D management.

Overall, we agreed with many fundamental elements of the CEWG report, including its concerns about market failures for many diseases of global health importance and its assessment of the hurdles for advancing global health innovation, especially those required for product development, product licensure, and global patient access. There was agreement on the importance of establishing a well-functioning Global Health R&D Observatory as a first step toward improving global health R&D priority setting and coordination. The co-authors also recognized the complexities around some of the specific CEWG report recommendations, such as those for a binding international treaty or other legal instrument, a common pool of R&D funds, and the call for specific financial targets rather than identified global health R&D deliverables.

We wish to emphasize agreement with the need for a “framework” to expand the role of governments in supporting and enabling global health R&D that could incorporate the following elements: 1) financing, 2) priority setting and coordination, 3) other nonfinancial R&D gaps, and 4) key principles and global norms.

Our analysis of R&D financing summarized in this paper employed new information just issued from the 2012 Global Funding for Innovation in Neglected Diseases (G-FINDER) report and the Global Burden of Disease 2010 study to confirm that there remains a severe gap in R&D funding for many global health conditions, especially malaria, diarrheal diseases, bacterial pneumonia and meningitis, and almost all of the neglected tropical diseases (NTDs).

---

<sup>1</sup> Participants in activities of the IOM Global Health Interest Group.

Our observation is that *public* spending for global health R&D—particularly for neglected diseases—relies almost exclusively on the U.S. and U.K. governments and a few other European governments. Therefore, it is urgent that other high-GDP nations, such as Japan, contribute, and that some of the larger emerging market economies, such as China, Japan, India, Brazil, Indonesia, Mexico, and South Korea, also invest more. We recognize the existence of a two-pronged problem in which most traditional donor governments do not consider R&D a component of overseas development assistance, while most R&D support from traditional donors is used to support scientists from their own nations. This indicates that the new U.S. Department of State Office of Global Health Diplomacy must play a key role in exerting diplomatic pressure to encourage emerging economies and other countries to increase their support for global health R&D.

At the same time, U.S. government (USG) support for neglected disease R&D—especially for new late-stage product development—is limited by a number of factors, including a flat-lined National Institutes of Health (NIH) budget and low investment by the U.S. Agency for International Development (USAID) in late-stage product development, especially when it comes to NTDs. In order to expand USG support for product development, we believe that consideration should be given to the possibility of committing annually to late-stage product development for priority global health technologies up to 1 to 2 percent of the financial support currently committed for global health overseas development assistance (most of which, up until recently, was committed through the auspices of the President’s Global Health Initiative), depending on specific needs and gaps identified through a collaborative international process. Potentially, these funds could be pooled with R&D support from other donor countries, either in one centralized fund or through various pooled funds.

Globally, the co-authors recognized that public financing for global health R&D requires a broad range of actors from both the public and private sectors. Thus, accelerating innovation may require a “blurring” of the traditional boundaries and firewalls that exist among industry, universities, and governments. Ultimately, it may become necessary to use public funds to support private and not-for-profit entities, including multinational companies, biotechs, and product development partnerships; such public funding for R&D carried out in the public interest will need to come with strong conditions that will guarantee affordability and access for patients. Increasingly, it will become necessary to support public–private partnerships (PPPs). A promising example is a forthcoming PPP initiative between five major Japanese pharmaceutical companies, the Japanese government, and the Bill & Melinda Gates Foundation.

As mentioned above, we concur that establishing a Global Health R&D Observatory represents an important first step for prioritizing global health R&D needs and gaps. A well-managed and transparent observatory will be essential, especially if funding pools become established. At present there is no politically legitimate system for R&D priority setting at the global level, so an observatory would be a key starting point. While by itself an observatory will not address all of the challenges posed in the CEWG report, WHO member states should allocate resources to ensure that a Global Health R&D Observatory can function. At a minimum, the observatory should perform two critical functions: one that is primarily technical (monitoring) and one that is more “political,” namely, priority setting and coordination. In regard to priority setting, the structure, governance, and accountability mechanisms are critical and need to be carefully designed.

There are several key areas for which governments need to provide nonfinancial mechanisms of assistance, especially in the areas of human resource needs, regulatory science,

and capacity building for research laboratories. The USG needs to identify specific mechanisms by which it can promote regionalization of regulatory processes for developing countries, adoption of streamlined and harmonized requirements, work sharing for dossier assessment, inspections, product testing, and an agreed-upon framework for post-assessment decision making.

Finally, there are no clear rules to govern how international R&D collaborations in the public interest are carried out and how benefits can be shared. In the view of the co-authors, a new normative framework that adheres to several key principles is needed. In addition, delivery of global health technologies by the international research community requires awareness of R&D needs and opportunities, improved coordination, greater and more open cooperation, and shared values/principles. In the area of intellectual property (IP) management, guidelines are needed to facilitate more open and collaborative research and broader access and affordability of health products.

## INTRODUCTION AND BACKGROUND

Over the last two decades there has been a growing recognition that the current system for stimulating research and development (R&D) has failed to deliver needed health technologies, particularly for diseases that disproportionately or exclusively affect poor people. This crisis in R&D is most acutely felt with neglected diseases, which include HIV/AIDS, tuberculosis (TB), malaria, and the neglected tropical diseases (NTDs). These are primarily infectious and parasitic diseases for which there is an enormous need but little to no lucrative market.

Although this report will focus primarily on neglected disease R&D, the challenge of discovering and delivering effective, affordable, and suitable health technologies is not limited to this subset of diseases; other examples include neglected causes and manifestations of non-communicable diseases (NCDs), rare diseases, diseases for which a high level of scientific risk is required or a high level of scientific uncertainty exists, and even the need for antibiotics to address the growing threat of antimicrobial resistance (Røttingen et al., 2012).

### BOX 1

#### Definitions

**Neglected tropical diseases (NTDs):** Group 17 chronic parasitic and related infections initially defined by Molyneux et al. (2005); Hotez et al. (2006, 2007); and modified by WHO (2010) (an example of WHO Type III diseases).

**Neglected diseases:** The NTDs in addition to HIV/AIDS, tuberculosis, malaria, and other neglected infections (Moran et al., 2012) (an example of WHO Type II diseases).

**Non-communicable diseases:** Major non-infectious conditions such as cancer, cardiovascular disease, and diabetes (an example of WHO Type I diseases).

In the first part of the 20th century, colonial and shipping interests still drove drug discovery and development for many neglected diseases, leading to important therapeutic breakthroughs (Trouiller et al., 2002). However, despite the burden of these diseases in the developing world—and major advances in molecular biology, pathophysiology, and genomics—

by the early 21st century, R&D for infectious diseases of the developing world had reached a near-standstill (Pecoul et al., 1999; MSF, 2001; Trouiller et al., 2002; Chirac and Torreele, 2006). In addition, not only is there increasing recognition of the impact of lifestyle changes in low- and middle-income countries (LMICs) as a risk factor for NCDs, but there are also important yet neglected causes of cancer, cardiovascular disease, and diabetes, which require new products and new delivery systems (Hotez and Daar, 2008; Moolani et al., 2012).

Numerous reports and publications, over the last 10 years in particular, have acknowledged the gap in R&D for neglected diseases. In response, an international policy process has been under way since the World Health Organization (WHO) established an independent Commission on Intellectual Property Rights, Innovation and Public Health, which produced a report presented at the 2006 World Health Assembly (WHO, 2006).

An Intergovernmental Working Group was established to follow up on the recommendations of the CIPIH report and ongoing discussions at subsequent World Health Assemblies. Several resolutions were eventually adopted, as was a Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, which endorsed by consensus in 2008 a “strategy designed to promote new thinking in innovation and access to medicines, which would encourage needs-driven research rather than purely market-driven research to target diseases which disproportionately affect people in developing countries” (WHO, 2008).

A WHO Expert Working Group (EWG) was then tasked with examining existing financing and coordination mechanisms for R&D and reviewing the more than 90 proposals it received for new R&D financing mechanisms from member states and other stakeholders. A second Consultative Expert Working Group (CEWG) on R&D Financing and Coordination was established in 2010 to deepen the EWG’s analysis and take forward key recommendations.

In April 2012, the CEWG released its final report and made several major recommendations for consideration at the 65th World Health Assembly in May 2012 (WHO, 2012a).

## **SUMMARY OF THE CEWG RECOMMENDATIONS**

The CEWG identified the following major hurdles for advancing global health R&D, particularly as it pertains to neglected diseases (WHO, 2012a):

- There is inadequate funding for all stages of global health R&D, but especially for late-stage product development and for a full range of needed global health technologies, including drugs, diagnostics, and vaccines.
- Given that existing incentive mechanisms have not effectively induced private-sector investment in global health R&D (especially for diseases for which there is little or no market), greater public investments are needed, including expanded contributions from emerging market economies (EMEs) and from traditional donors for the gap areas identified above.
- New approaches to R&D collaboration are needed to leverage support from the private sector (e.g., pharmaceutical and biotechnology companies), major foundations, and other R&D organizations. This collaboration requires more “open” approaches to R&D, including knowledge sharing and management of intellectual property (IP).
- Progress in global health R&D is uneven, efforts are fragmented, and there is no global mechanism to assess R&D needs and gaps, set R&D priorities, monitor R&D resource flows, or coordinate activities.

- Current incentives, including the IP system, do not adequately stimulate R&D when it comes to health needs of people in LMICs and do not sufficiently ensure access to the fruits of innovation.

The CEWG assessed 109 proposals from a variety of experts and evaluated them based on their public health impact; efficiency and cost-effectiveness; technical and financial feasibility; the role of IP and how it can promote innovation and enhance access; delinkage of product pricing and the financing of R&D; global access and the potential for lower prices and promoting demand; governance and accountability; and, finally, capacity building

In the view of the co-authors, the CEWG report's recommendations also include the following elements:

- Further exploration of approaches most likely to incentivize research, including open approaches to R&D, pooled funding mechanisms, direct grants to companies, prizes, and patent pools.
- Establishment of a Global Health R&D Observatory, under the auspices of WHO, as a coordinating body to collect and analyze data related to the R&D pipeline, financial flows for R&D, and documentation of lessons learned, etc. Advisory mechanisms would be established to feed into and oversee this body.
- Specific and binding financial commitments from countries (e.g., commitment of 0.01 percent of gross domestic product [GDP] to global health R&D), and a suggestion that 20 to 50 percent of such funding be administered through a pooled funding mechanism.
- Specific steps to strengthen R&D capacity in developing countries, including steps to enhance technology transfer to developing countries, infrastructure, and human resource capacity.
- Establishment of a global framework (convention) for R&D that could serve as an umbrella for implementation of the priority-setting and coordination mechanisms, incentives, financing mechanisms, and capacity-strengthening activities outlined in the report.

### **Overview Assessment**

The authors of this discussion paper are in *broad agreement* with many aspects of the CEWG report's assessment of the global health R&D space, particularly its comments on market failure for selected diseases. There was also agreement with CEWG about many of the major hurdles for advancing innovations for global health, including those required for product development, product licensure, and global patient access. We understand that the U.S. government (USG) is also in broad agreement with many aspects of the CEWG report.

We wish to emphasize agreement with the need for a “framework” to expand the role of governments in supporting and enabling global health R&D that could incorporate the following elements: 1) financing, 2) priority setting and coordination, 3) other, nonfinancial R&D gaps, and 4) key principles and global norms. Further, it seems that transnational R&D collaboration is already happening and will need to continue because diseases transcend international boundaries. However, there are no clear “rules” for how to conduct global health R&D in the public interest, which requires international cooperation among governments, product development partnerships (PDPs), developing-country manufacturers, and the private sector, among others.

Based on information provided by representatives from the USG (the Department of Health and Human Service [HHS] and the National Institutes of Health [NIH]), we also recognize that the USG might *disagree* with some elements of the CEWG report. Some, but not all, of the co-authors of this discussion paper agreed with HHS and NIH in their assessment. Specifically,

- It might not be appropriate or feasible to set a percentage of GDP as a financing goal. Financing programs work best when they begin with a rigorous, *result-based framework that sets clear expectations, rather than simply starting with a financial goal*. Moreover, it is not at all clear that 0.01 percent of GDP would provide appropriate funding after 10 years or decades into the future, particularly since the mix of low-, middle- and high-income countries is already evolving dynamically, with many lower- and middle-income countries moving into higher categories. LMIC research needs and incentives are likely to change significantly in the next generation. Finally, financing goals around health R&D needs for LMICs should be time-limited, reviewed periodically, and made on a voluntary basis.
- It is doubtful that the USG is prepared to initiate negotiations for a binding international instrument on R&D. Treaty negotiation is both lengthy and expensive, and formal negotiations would consume policy makers and draw the resources of national governments and WHO away from steps that could be taken immediately. Moreover, enforcement mechanisms are difficult and might not avert a “free-rider” problem—most of the signatory states are currently not even close to approaching a soft norm.
- Most of the estimated \$1.4 billion in neglected disease R&D funds is managed through the National Institute of Allergy and Infectious Diseases (NIAID) at NIH. It seems unlikely that 20 to 50 percent of these funds could be ceded to an international funding pool or multilateral organization (as proposed in the CEWG report)—although a proportion of funds designated for specific diseases, such as NTDs, from the U.S. Agency for International Development (USAID) and other sources potentially could be committed for this purpose.
- Overall, it is unlikely that the USG would be able to maintain its current level of investment if the funds and responsibility for their use were not connected to the organization or budget accountable for the request and results specified.

We emphasize that there was not consensus among the co-authors of this document about the statements above.

## **ASSESSMENT OF CURRENT STATUS OF R&D FINANCING FOR NEGLECTED DISEASES**

Funding for R&D to address diseases that primarily or exclusively affect LMICs has lagged behind financial support and expenditures for R&D targeting diseases that affect wealthy markets, including NCDs such as cancer, cardiovascular disease, and diabetes, as well as nonmedical (“lifestyle”) conditions for which there is no pressing public health need but significant R&D activity, such as baldness, erectile dysfunction, and cellulite reduction, etc.

According to a report issued by the Global Forum for Health Research, in 2008 the public and private R&D investments in France, Germany, Japan, the United Kingdom, and the United States exceeded \$40 billion, of which almost \$30 billion was invested by major multinational

pharmaceutical companies headquartered in those nations (Feletto and Matlin, 2009). In contrast, according to Policy Cures' 2012 G-FINDER report, only \$3 billion was spent on neglected disease R&D globally, including support for HIV/AIDS, TB, and malaria (Moran et al., 2012). Of that \$3 billion, approximately \$2 billion came from public (government) funds, with more than two-thirds coming from the U.S. government.

Although a component of NCD R&D would also benefit LMICs, it was not possible to identify specific numbers for NCD R&D for developing countries (perhaps this is an area for further research by others). Therefore, as an illustrative example of gaps in R&D support for diseases in LMICs, we will focus here on neglected disease R&D expenditures.

In 2000, the Global Forum for Health Research report found that only 10 percent of the world's health research was devoted to conditions that represented 90 percent of the global disease burden—often referred to as the “10-90 gap” (GFHR, 2000). As highlighted below, while the gap may no longer be as extreme as 10-90, it remains substantial.

With respect to NTDs, a group of 13 to 17 chronic parasitic and related infectious diseases, such as hookworm, Chagas disease, and leishmaniasis, which almost exclusively affect the “bottom billion” who live in extreme poverty (Hotez et al., 2007), the disparity in R&D expenditures is even more extreme. Much of the gap can be explained by the profound dearth of NTD investments from multinational pharmaceutical companies, as well as an overall absence of government support.

Another way to examine financial support for neglected diseases versus NCDs is to link R&D expenditures to disease burdens (as measured in disability-adjusted life years [DALYs]). The DALYs for almost 300 different diseases and injuries were published in a multi-authored study led by the Institute of Health Metrics and Evaluation (IHME) of the University of Washington (Murray et al., 2012).

As shown in Table 1, differences in financial support on the basis of DALYs roughly reflect a modern-day 10-90 gap. However, even among the NTDs, there is considerable variability in research support. For example, on a per-DALY basis, the R&D expenditures for dengue are quite high. This observation may reflect the recent large-scale investments made by several multinational pharmaceutical companies, including Merck & Co., GlaxoSmithKline, Sanofi-Pasteur, and some developing-country manufacturers, in order to develop and test a dengue vaccine. Dengue, unlike many other NTDs, affects wealthy countries like Singapore and the United States and wealthy coastal areas of Brazil, the Caribbean, and Southeast Asia, so there is a traditional commercial market for the condition. Similarly, leprosy investments appear high when linked to DALYs, but this figure does not consider global efforts at leprosy elimination. In other words, leprosy investments are tied to the “end game” for disease reduction and elimination.

Among the most underfunded neglected diseases in terms of R&D are malaria, bacterial pneumonias and meningitis, the helminth infections, rheumatic fever, and diarrheal diseases for which there is an extreme paucity of investment, i.e., under \$10 per DALY. The support listed for kinetoplastid infections is also low, but does not consider the likelihood that the DALYs published by the IHME probably grossly underestimate their true disease burden, especially for Chagas disease. Moreover, the disease burden assessment does not consider the extreme socioeconomic impact of NTDs, which actually cause poverty. Therefore, new drugs, diagnostics, and therapeutics represent critically important antipoverty measures (Hotez et al., 2009).

**TABLE 1** Research Funding for the Neglected Diseases and Comparison with Disease Burdens

<b>Disease</b>	<b>R&amp;D Funding 2011 Nominal<sup>a</sup></b>	<b>DALYs<sup>b</sup></b>	<b>Approximate Dollars/DALY</b>
NCDs (cancer, cardiovascular disease, and diabetes)	\$43.2 billion (U.S., UK, France, Germany, Japan)	605 million	\$71
Neglected diseases (NTDs + HIV/AIDS, TB, malaria)	\$3.3 billion (globally)	240 million	\$14
Neglected tropical diseases (not including dengue)	\$256 million	25 million	\$10
<b>Specific Neglected Diseases</b>	<b>R&amp;D Expenditures</b>	<b>DALYs</b>	<b>Dollars/DALY</b>
HIV/AIDS	\$1.117 billion	81.5 million	\$14
Tuberculosis	\$584 million	49.4 million	\$12
Malaria	\$596 million	82.7 million	\$7
Dengue	\$249 million	0.8 million	\$311
Diarrheal diseases	\$169 million	89.5 million	\$2
Kinetoplastids (Chagas disease, leishmaniasis, sleeping sickness)	\$142 million	4.4 million	\$32
Bacterial pneumonia & meningitis	\$107 million	48.9 million	\$2
Helminths (worms & flukes)	\$90 million	14.3 million	\$6
Salmonella infections	\$48 million	12.2 million	\$4
Leprosy	\$8 million	6,000	\$1,333
Buruli ulcer	\$6 million	Not determined	Not determined
Trachoma	\$10 million	0.3 million	\$33
Rheumatic heart disease	\$1 million	10.1 million	<\$1

<sup>a</sup>Data for neglected diseases including HIV/AIDS, tuberculosis, and malaria from Table 2 in “Total R&D funding by disease 2007-2011,” in G-FINDER 2012. 2010 Nominal (US\$) figures are in current (2010) U.S. dollars. Data for non-communicable diseases from Table A8 in Feletto and Matlin (2009).

<sup>b</sup>DALY data from Murray et al. (2012).

NOTES: DALY = disability-adjusted life year; NCD = non-communicable disease; NTD = neglected tropical disease; R&D = research and development; TB = tuberculosis.

Finally, in December 2012, a new assessment of the state of R&D for neglected diseases from 2000 to 2011 showed that of the 756 new drugs approved between 2000 and 2011, 29 (3.8 percent) were indicated for neglected diseases, even though the global burden of neglected diseases is estimated at 10.5 percent. Of these, only four were new chemical entities, three of which were for malaria, with none for TB or NTDs (MSF/DNDi, 2012).

### **Assessment of International Government Support for Neglected Disease R&D**

According to the G-FINDER report, the USG provides approximately 70 percent of the world’s \$2 billion in public funding for neglected disease R&D (mostly from NIH). Together, the USG and the Bill & Melinda Gates Foundation provide about one-half of the global support

for neglected disease R&D. In addition, the multinational pharmaceutical companies provide approximately \$500 million, while the UK government provides almost \$100 million.

Outside the United States and United Kingdom, the remainder of the world's governments combined currently provides less than one-third (less than \$1 billion) of all neglected disease R&D funding. As shown in Table 2, among the European contributors, the governments of the United Kingdom, France, Germany, the Netherlands, and to some extent Spain have done the most to support neglected disease R&D. Australia has also recently become an important contributor. Although not shown in Table 2 because of their low GDPs, the governments of Sweden and Norway have also become important contributors to neglected disease R&D.

**TABLE 2** Comparisons of GDPs with Public Funding for Neglected Disease R&D

Country	2011 GDP <sup>a</sup>	2011 GDP Rank	Percentage of Global GDP (\$70 Trillion) <sup>a</sup>	Support for Neglected Disease R&D <sup>b</sup>	Percentage of Global Public Neglected Disease R&D Support (\$1.95 billion) <sup>b</sup>	Rank in % of Global Public Neglected Disease R&D Support
United States	\$15.0 trillion	1	21%	\$1.35 billion	69.2%	1
China	\$7.2 trillion	2	10%	<\$10 million	<0.5%	Not ranked
Japan	\$5.9 trillion	3	9%	<\$10 million	<0.5%	Not ranked
Germany	\$3.6 trillion	4	5%	\$32 million	1.6%	5
France	\$2.8 trillion	5	4%	\$60 million	3.1%	3
United Kingdom	\$2.4 trillion	6	3%	\$133 million	8.2%	2
Brazil	\$2.4 trillion	7	3%	\$11 million	0.6%	10
Italy	\$2.2 trillion	8	3%	<\$10 million	<0.5%	Not ranked
India	\$1.9 trillion	9	3%	\$34 million	1.7%	4
Canada	\$1.7 trillion	10	2%	\$10 million	0.5%	9
Russia	\$1.8 trillion	11	2%	<\$10 million	<0.5%	Not ranked
Spain	\$1.5 trillion	12	2%	\$11 million	0.6%	8
Australia	\$1.5 trillion	13	2%	\$31 million	\$1.6	6
Mexico	\$1.1 trillion	14	1%	<\$10 million	<0.5%	Not ranked
South Korea	\$1.1 trillion	15	1%	<\$10 million	<0.5%	Not ranked

Netherlands	\$0.8 trillion	16	1%	\$24 million	1.2%	7
<i>Indonesia</i>	<i>\$0.8 trillion</i>	<i>17</i>	<i>1%</i>	<i>&lt;\$10 million</i>	<i>&lt;0.5%</i>	<i>Not ranked</i>

<sup>a</sup>[http://en.wikipedia.org/wiki/List\\_of\\_countries\\_by\\_GDP\\_\(nominal\)](http://en.wikipedia.org/wiki/List_of_countries_by_GDP_(nominal)).

<sup>b</sup>Table 21, “Top 12 public funders 2010,” G-FINDER 2011.

NOTE: GDP = gross domestic product; R&D = research and development. Italics indicate underperforming countries with respect to their contribution to global health R&D.

We believe there is an opportunity to considerably expand government funding from the other European governments, in addition to some of the very important EMEs, including the BRICS economies (Brazil, Russia, India, China, and South Africa), as well as Japan, several Middle Eastern countries (Hotez, 2010), the MIST economies (Mexico, Indonesia, South Korea, and Taiwan), and other middle-income nations in Latin America and Asia, which could also make major contributions to research.

The USG, through its Department of State and its office of Global Health Diplomacy, can play an important international role in promoting science diplomacy for global health R&D, along with HHS as appropriate. We believe the Department of State should embark on high-level discussions to exert diplomatic pressure on nations that have “underachieved” in their commitments to global health R&D, with emphasis on the emerging economies and the large-GDP nations of China, Japan, Brazil, India, Mexico, South Korea, and Indonesia. These nations need to support global health R&D and become international players on this front.

Although the United States and the United Kingdom are the major global health R&D investors, their funding is predominantly for basic research by academic investigators, and could be expanded for R&D to support late-stage product development for new drugs, diagnostics, vaccines, and other health technologies. There is very little funding, relatively speaking, for late-stage neglected disease product development (with the possible exception of HIV/AIDS drugs and vaccines), including funds for phase 2 and phase 3 clinical trials that could lead to actual product licensure and delivery.

The USG has provided impressive global leadership for support of global health R&D, especially for neglected diseases. However, there remains an urgency to find mechanisms to support late-stage product development, including clinical trials. Hotez (2011) suggested that the USG commit 1 to 2 percent of the President’s Global Health Initiative to such product development R&D, which would place an estimated \$100-\$200 million into the system annually and would be transformative in providing new support for products and clinical trials. Rather than dictating this amount, for reasons outlined above, we suggest that the USG consider this possibility, depending on the specific needs of the global health R&D community.

In summary, three of the most pressing issues facing neglected disease R&D are

1. There is an urgent need to expand the investment portfolio (additional funders and increased amounts per donor) for the neglected diseases for which the market has failed to deliver innovation and/or access.
2. Global support for neglected disease R&D relies heavily on the U.S. and U.K. governments and other European governments. There is urgency for other high-GDP nations to contribute, including some of the larger EMEs.
3. There is urgency to support late-stage product development, especially for phase 2 and 3 clinical trials.

Some important questions to consider include the following:

- How can the global community best expand global financial support for global health R&D, especially for late-stage product development/clinical trials and possibly operational research/implementation sciences?
- How should global health R&D needs and gaps be identified and priorities be set for funding?
- What might be suitable mechanisms and governance structures for embracing the heightened support for neglected disease R&D, if existing mechanisms are not adequate?
- What are some of the salient, nonfinancial elements of global health support that require expansion and emphasis?
- What are the key principles and norms, especially around IP, that need to be established and agreed upon in order to ensure global health R&D in the public interest?

### **POTENTIAL FINANCING MECHANISMS**

As highlighted above, currently, the USG is the only government that meets or exceeds the 0.01 percent GDP target as proposed by the CEWG report. However, there are opportunities for both expanding the players currently engaged in supporting global health R&D and increasing the amount of funding provided by existing players.

Among the traditional donors that are members of the Organisation for Economic Co-operation and Development (OECD), neglected disease R&D has not been a high-priority except for Australia, France, Germany, the Netherlands, Spain, the United Kingdom, the United States, and the Nordic countries. Among the significant hurdles we identified was a two-pronged problem: most traditional donor governments do not consider R&D a component of overseas development assistance, and most R&D support from these donor countries is typically used to support their own scientists.

As pointed out above, there is urgency for the BRICS and MIST countries to contribute more to global health R&D, especially China (which has the world's second largest GDP and is currently investing billions of dollars in Africa) and Japan (which has the world's third largest economy). The oil- and energy-rich nations of the Persian Gulf are also considered underperformers, as well as a few of the large disease-endemic nations, including Indonesia and Nigeria.

There are significant issues regarding how the funds should be raised, who should contribute to global R&D funding and how much. It is also important to ensure that resource allocation happens according to agreed-upon priorities and gaps.

We considered several different mechanisms now under way to help finance global health R&D:

- In regard to “pull mechanisms,” such as government purchase agreements, we recognize that the much-touted advanced market commitment for the pneumococcal vaccine was not designed to be an incentive for innovation but to scale up production of an existing product, and that, thus far, it could not be said to be effective for neglected disease

product development. Similarly, priority review vouchers (PRVs), while relevant in some circumstances, have not yet stimulated neglected disease product development. The first award of a PRV was for a medicine that already existed and had been available in the developing world for years (an artemisinin-based combination therapy for malaria), and the second was awarded for the new TB drug bedaquiline (although it is not clear how much the PRV functioned as an actual incentive for the development of this product). Reducing transaction costs and awarding prizes are considered useful supplementary mechanisms, but further exploration and piloting of such initiatives is needed before they can be properly evaluated.

- In regard to “push mechanisms,” we applaud efforts by some of the European governments and related agencies, including the UK Department for International Development, the Dutch Ministry of Foreign Affairs, and the German Ministry of Research and Education, as well as support from the Swedish, Norwegian, and Spanish governments for PDPs and other organizations for specific neglected disease products. The Special Programme for Research and Training in Tropical Diseases of the WHO (WHO-TDR) is also providing some product development support, but we understand that these activities may soon end under the new WHO-TDR leadership. A new mechanism that could have relevance in Europe is a financial transaction tax (FTT), also known as a “Robin Hood Tax,” which is essentially a fee paid whenever shares of stock, bonds, or futures are traded, or in conjunction with other financial instruments, that could raise substantial amounts of funds.<sup>2</sup> Recently, 11 European countries have agreed to coordinate the implementation of an FTT, including Austria, Belgium, Estonia, France, Germany, Greece, Italy, Portugal, Slovakia, Slovenia, and Spain.<sup>3</sup> The French FTT came into force this year, with commitments by French President Francois Hollande to commit at least 10 percent of the revenues to the French Development Agency (Lomas, 2012). At a public conference in New York in December 2012, France announced that a portion of its FTT would be allocated to global health R&D. The United States historically has been very reluctant to set up an FTT; although several bills have been proposed in Congress, none has advanced and none has been directed toward global health R&D.
- The USG is now supporting more than 600 research projects in sub-Saharan Africa, mostly through NIAID and NIH’s Fogarty International Center, but this support is largely for upstream (basic research) or epidemiological investigations, as well as training. In regard to USG support for product development, currently, through specific congressional appropriations, USAID is providing some support for late-stage product development for HIV/AIDS, TB, and malaria but has no similar program for supporting late-stage development for NTDs, for example. However, to lobby or advocate for congressional funds on a yearly basis is considered a highly cumbersome mechanism and is not likely sustainable in the current fiscal climate. According to some accounting, USG federal agencies, primarily NIH, may be partially or fully supporting more than half of the estimated 365 products in the pipeline of global health products, and possibly more than half of the 45 products introduced between 2000 and 2010. Some of these products may be supported through small business innovative research (SBIR) grants. The SBIR mechanism should be further encouraged to support neglected disease R&D and that it should be extended to some nonprofit organizations, possibly including PDPs. Overall,

---

<sup>2</sup> See <http://www.robinhoodtax.org>.

<sup>3</sup> See <http://www.france24.com>.

there is a need for a more detailed inventory of neglected disease products currently supported by the NIH and other USG agencies.

Some of the government activities highlighted above represent a good start, but they are certainly not sufficient to initiate or sustain a meaningful pipeline of global health products, especially for the “high-ticket” expenses associated with phase 2 and 3 clinical trials.

The following could constitute a set of guiding principles for supporting global health R&D:

1. Any public financing for neglected disease products should include support for academic scientists but at the same time should support the lead organizations whose primary mission is to develop and test products (e.g., drugs, diagnostics, vaccines, and vector control agents), including PDPs, biotechnology and pharmaceutical companies, and developing-country manufacturers. With public financing, though, must come strong conditions to ensure affordability and access for end-users.
2. Flexibility in financing is paramount in fostering partnerships among these different types of organizations, as well as for establishing PPPs among the organizations listed above and sovereign governments.
3. PPPs might also include co-financing among governments and commercial investors, including venture capital funds.
4. Thus accelerating innovation may require a “blurring” of the traditional boundaries and firewalls that exist among industry, universities, and governments. We recognize the challenges of implementing public financing for the private sector. The SBIR type of mechanism is an attractive example, particularly if it could be employed to encourage neglected disease investments that might not lead to profits and expanded to selected nonprofit organizations, including PDPs. Again, public funding for private companies and other entities must be tied to strong conditions that will ensure affordability and access for patients.
5. Targets should be set around specific R&D and product needs (including those established through a Global Health R&D Observatory or similar national or regional mechanisms), rather than specific financial targets.
6. FTTs are a promising mechanism to raise funds for global health R&D.

In addition, and in regard to pooling funds from different governments, challenges would be faced by national science-funding agencies that might be required to relinquish autonomy in order to establish and maintain a common fund. Representatives of HHS have indicated concern about whether the department would be able to maintain its current level of investment if the funds and responsibility for their use were not connected to the organization or budget accountable for the request and results specified. Of particular concern is the declining NIH research support in light of NIH’s flat-lined or even declining budget over the last decade.

However, short of a common fund, the USG has engaged previously in PPPs with the Bill & Melinda Gates Foundation and the Wellcome Trust, for example, in order to support specific projects. Similarly, the USG supports certain public partnerships with governments to sustain projects in developing countries. For instance, a joint Sino-U.S. partnership for sub-Saharan Africa has been proposed (Hotez, 2012). Another example is a previously successful U.S.-Japanese fund for supporting science. An interesting new development is the Global Health

Innovation Partnership being developed in Japan by a three-way partnership among five leading Japanese pharmaceutical companies, the Japanese government, and the Bill & Melinda Gates Foundation to support the various drug/vaccine development efforts being undertaken by PDPs. A key element of establishing PPPs is to ensure that they are sufficiently large to support product development, consistent, sustainable, and not “one-off” arrangements. PPPs could vary in size, interest area, geography, and scope of coverage, up to and including some sort of centralized global funding mechanism for R&D in global health.

Funding pools should be clearly articulated in purpose and governance to make it easy for donors to contribute with confidence that their money will be well spent. For this to occur, a higher level of global governance may be required, and various institutional arrangements are possible.

### **SETTING ESSENTIAL HEALTH R&D PRIORITIES: MONITORING, PRIORITY SETTING, AND COORDINATION**

On November 26-28, 2012, WHO member states, including the United States, met to develop concrete steps for implementing some of the recommendations of the CEWG report around which there was consensus. Among other things, member states agreed to establish a Global Health R&D Observatory under the auspices of WHO. In particular, member states *provisionally* agreed to

establish a Global Health R&D Observatory within WHO’s Secretariat to monitor and analyse relevant information on health R&D, building on national and regional observatories (or equivalent functions) and existing data collection mechanisms with a view to contributing to the identification of gaps and opportunities for health R&D and defining priorities in consultation with Member States, as well as, in collaboration with other relevant stakeholders, as appropriate, in order to support coordinated actions (WHO 2012b).

We believe this is an important and necessary first step, and that an observatory could promote more innovative and coordinated approaches to generating evidence-based information on various aspects of essential health R&D, upon which to base critical needs assessments and priority-setting decisions. This is particularly relevant as various funding pools get established, so that funding mechanisms can all consider a global agenda in making their priority decisions and maximize the impact of their investments without fear of redundancy.

At present, there is no politically legitimate system for R&D priority setting at the global level; an observatory could be a very effective starting point for developing such a system. Moreover, there is no clear precedent for how to move from purely national (or institution-specific) priority setting to more global decision making regarding biomedical R&D, particularly taking into account the ultimate metric of global public health benefit, rather than market return. A credible and legitimate process for priority setting thus needs to be established.

Alone, a Global Health R&D Observatory will not be sufficient to address the magnitude of the challenges outlined in the CEWG report and elsewhere, and, at a minimum, WHO member states will need to allocate sufficient resources to ensure that an observatory could function properly (something not guaranteed in the draft resolution quoted above). Furthermore, the more detailed consideration of critical tradeoffs that will have to be made in each of the funding pools

in choosing which projects will move forward and which to terminate will require a level of sophistication not covered in this document. But much can be done in the short term to strengthen monitoring and coordination of R&D through an observatory.

We believe that an observatory should perform at least two critical functions: one that is primarily technical (monitoring) and one that is more “political” (priority setting and coordination).

*Monitoring* activities could include

- **Mapping key health information data** for an agreed-upon group of diseases (could include burden of disease/DALYs, morbidity/mortality data, prevalence, incidence, etc.). Care would need to be taken to ensure that this mapping is closely linked to other tracking activities, as well as a gap analysis exercise (see below), because diseases may appear to be high-priority in terms of annual mortality rates, for example, but existing tools may be sufficient, making it low- or medium-priority in terms of R&D needs. Similarly, a lower-burden disease may appear to be low-priority according to certain criteria, but if existing tools are insufficient, it could be considered high-priority following an assessment of technology needs and gaps.
- **Tracking the “pipeline”** for agreed-upon diseases or groups of diseases. Although there is no globally agreed-upon methodology for analyzing pipeline activities, several private initiatives already exist for monitoring the pipelines of certain diseases. Examples include the Treatment Action Group/HIV i-Base annual “Pipeline Report” for HIV/AIDS, TB, and hepatitis C, available publicly online,<sup>4</sup> and BioVentures for Global Health’s annual “Global Health Primer” for 25 “neglected diseases.”<sup>5</sup> In addition, various PDPs have their own methods for tracking pipeline activities per disease (mostly available on individual PDP websites), and the Bill & Melinda Gates Foundation has an internal process for monitoring pipeline activities in various diseases, though these are not publicly available. In addition, the private pharmaceutical and biotechnology companies have their own methods. Finally, WHO-TDR, which has been a major player in neglected disease R&D for 25 years, also has a system for tracking pipelines, which could be useful, although it is unclear whether TDR will continue to play this role in the future. These initiatives could potentially be brought together, or at least follow a similar methodology, so that comparisons can be made and a “master” pipeline tracking function can be developed. But the challenge must not be underestimated: Maintaining an up-to-date tracking mechanism for global health R&D pipelines has challenges and requires considerable investments of time and energy to keep current.
- **Monitoring R&D resource flows** from the public, private, and philanthropic sectors. This is a crucial function, which until 2007 was not carried out by any actor. Since 2007, the G-FINDER report has been released annually by Policy Cures, with support from the Bill & Melinda Gates Foundation, and includes an analysis of funding trends year to year per sector, disease, and R&D stage. The report covers a specific list of neglected diseases and could form the basis of a monitoring tool that includes a broader range of agreed-

---

<sup>4</sup> See <http://www.treatmentactiongroup.org/pipeline-report/2012>.

<sup>5</sup> This project is funded by the Bill & Melinda Gates Foundation and is soon to be transferred to the Emory University Institute for Drug Development; it remains publicly available online for now at <http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer.aspx>.

upon diseases. Whether G-FINDER activities alone are sufficient to monitor current R&D flows or whether additional mechanisms are required deserves further discussion.

- **Mapping of R&D actors** from the public, private, academic, and nonprofit sectors. This function does not yet exist but could include a dynamic process for mapping key R&D players by sector, disease, R&D stage, and/or technology platform in order to lay the groundwork for improved coordination.
- **Analysis and evaluation** to begin the crucial exercise of identifying gaps and opportunities.

*Priority-setting and coordination* activities could include

- **Identifying needs and gaps** based on clearly defined and independently evaluated analyses of the evidence generated through the “monitoring” arm of the Global Health R&D Observatory.
- **Determining priorities** through a clear and comprehensive review of evidence per disease, area of technology, stage of the R&D process, etc. It will also be important to identify through this process “low-hanging fruit” or “high-impact” opportunities. It will be critical to take a portfolio view when setting priorities as to proportional distribution of funding within a limited budget envelope.
- **Issuing target product profile (TPPs)** or similar tools to lay out ideal (and acceptable) specifications needed for a new health technology in order to best respond to the needs of patients. TPPs could be developed with leading experts from endemic countries, researchers, clinicians, disease control program managers, patient associations, WHO, and others.<sup>6</sup>
- **Highlighting complementarities of different actors** to avoid duplication and enhance efficiency. This is particularly important given the complexity of existing R&D collaborations and the need to both increase knowledge sharing and decrease the cost of R&D.

It is important to recognize explicitly that the process of priority setting implies decision making, and this is a fundamentally political project. Hence, **structure, governance, and accountability mechanisms** are critical and need to be carefully designed. There will not likely be one body responsible for governing some sort of central global funding pool that will also serve the function of monitoring, priority setting, and coordinating R&D activities. Nevertheless, we feel that some guidance as to what good governance might consider would be useful to the Global Health R&D Observatory as well as other (e.g., financing) mechanisms that might evolve in the future.

We considered several key questions in relation to priority setting and coordination, including

- How should R&D priorities be set?
- Who should be at the table?

---

<sup>6</sup> In the case of treatments, for example, TPPs can include the target indication, population, clinical efficacy requirements, safety and tolerability profile, stability needs, route of administration, and target price. TPPs should be reviewed and, if necessary, updated annually in order to keep pace with the latest available scientific and clinical evidence.

- How can the political element of priority setting be managed in a fair, equitable, and transparent way?
- How, specifically, should decisions get made?
- What should the evidence be and what methodologies should be used (burden of disease, DALYs, etc.)?
- What should the scope be (diseases, technologies, types of research, etc.)?

While it is not possible to answer all of these questions at this stage, a report from a Multi-Stakeholder Technical Meeting on Implementation Options Recommended by the WHO CEWG, convened by the Thai Ministry of Public Health and the Harvard Global Health Institute and held in Bellagio, Italy, in October 2012 (Røttingen et al., 2012), highlighted several principles that would be important to consider when designing various new mechanisms, such as a Global Health R&D Observatory, including

- multi-stakeholder engagement from all sectors with appropriate conflict-of-interest policies;
- open access to information through specific transparency policies; and
- clear oversight and accountability mechanisms.

Hoffman and Røttingen (2012) further lay out options for decision making, including (a) a unanimous or consensus model for decision making (e.g., many United Nations [UN] agencies); (b) majority or supermajority voting for decision making (e.g., UN General Assembly); (c) modified voting (e.g., weighted or priority voting such as at the World Bank or International Monetary Fund); or (d) delegation of decision making to a smaller body (e.g., WHO Executive Board).

Without taking a specific position on which mechanisms will be best, what is clear to the co-authors is that a forum will need to exist in a neutral venue where evidence can be presented, priorities can be proposed, and decisions can be made in a transparent manner with clear input from both the relevant stakeholders and the “independent” experts.

But in the end, it will not be enough to monitor, set priorities, and coordinate R&D. If these functions are not explicitly linked to sustainable financing—either through direct budget authority or a closely coupled system/feedback loop with a single or various pooled funding mechanisms, and leading to allocation of national or regional resources according to identified needs and gaps—there might be more information and better knowledge about the essential health R&D landscape, but it will not fundamentally accelerate needs-driven R&D for the benefit of patients.

### **OTHER NONFINANCIAL R&D GAPS<sup>7</sup>**

There are many barriers to effective development of new health interventions for the developing world that extend beyond the purely financial, and also extend beyond priority setting, coordination, and monitoring, as discussed above. They cover a spectrum of the pharmaceutical value chain, including discovery research, pre-licensure development, licensure, and post-licensure stewardship. Issues that arise are typically clustered around pre-clinical

---

<sup>7</sup> Additional input in this section was provided by Vincent Ahonkhai of the Bill and Melinda Gates Foundation.

activities, the conduct of clinical trials, and companion regulatory systems that should be applied over a product's life cycle.

### **Human Resource Needs**

First among the barriers is the lack of trained personnel to undertake clinical trials and science personnel to provide support for them. There are examples of successful clinical trial sites that have been set up in Africa, for example, but they have required special resources from the United States and Europe. The HIV Vaccine Trials Network set up by NIH and other HIV vaccine trials sites set up by the International AIDS Vaccines Initiative are two examples, but they have provided evidence for just how difficult it is to maintain such sites. Smaller examples also exist, including Drugs for Neglected Diseases *initiative*-supported clinical research platforms for leishmaniasis in East Africa, Chagas disease in Latin America, and human African trypanosomiasis in Central Africa. But whether large or small in scale, it takes considerable effort and expense to train people to run clinical trials. Everything works well when the sites are busy; the problem is that the work comes in spurts, with very busy times interspersed with stretches when there are no trials to be assigned to these sites. During the latter times, the sites become a large financial burden in that the people must be paid even if no work is being done. If people are laid off during the fallow periods, considerable time may be required to retrain others when work starts up again. Some contract research organizations have enough business to keep such operations up and running on a continual basis, but it has proven hard even for them in remote locations.

Given the difficulties in maintaining clinical trial sites in operational order, it is not surprising that developing-country governments have been largely passive observers in the effort. Outside of a handful of key countries (e.g., Brazil, India, South Africa), there is little government support for the training of science personnel, let alone for the development of specific clinical trial capacity. However, recently, there has been a surge in training by European and U.S. regulatory authorities, pharmaceutical industry associations, individual pharmaceutical firms, development agencies, academic institutions, not-for-profit R&D organizations, professional societies, and donor groups. To maximize efficiency and impact, these training efforts have endeavored to be accessible, affordable, and at the largest scale possible. In this regard, increased use of Web-based training has been helpful. Internet-based systems have been applied successfully for multiple purposes, such as self-identification of clinical trialists, trial sites, and ethics committee members, as well as for training and accreditation.

### **Regulatory Barriers**

According to a study carried out by the WHO Regional Office for Africa in 2004 and recently corroborated in 2010, 90 percent of National Regulatory Authorities (NRAs) lack not only the capacity to carry out medicines registration, but also other key regulatory functions, including ensuring that clinical trials are conducted according to ethical and Good Clinical Practice (GCP) standards. Challenges these NRAs face include lack of technical expertise to review clinical protocols, low capacity to monitor and audit clinical trials, and nonexistent or suboptimal Ethics Review Committees, all culminating in an inability to contribute to clinical data for the very disease conditions which burden their countries.

In the area of product registration and licensure, there is another set of unique challenges. Technical capacity to review and approve new chemical entities or vaccines is not available in most developing countries. Accordingly, NRAs in these countries limit their assessments to products that have been reviewed and have received marketing authorization from fully functional “stringent” regulatory authorities (SRAs) in the industrialized world, such as the European Medicines Agency and the U.S. Food & Drug Administration (FDA). WHO Prequalification, a process that assures the quality of products procured through UN or international aid funding, is also considered an important quality-assessment pathway. This circuitous approval pathway from SRAs and/or WHO to developing-country NRAs results in long delays in product registration. The requirement for navigating this convoluted process on a country-by-country basis, on top of a marginal commercial case to begin with, results in low manufacturer interest for introducing novel products in resource-constrained settings.

In order to address this range of constraints in regulatory processes, innovative approaches to improve efficiency and technical functionality are being developed through public–private partnerships. Examples include the Association of Southeast Asian Nations (10 countries), the Gulf Cooperation Council (6 countries), the Pan American Network for Drug Regulatory Harmonization, and the African Medicines Regulatory Harmonization (starting with an East African Community of 6 countries). The overarching principles for these initiatives are

- regionalization of regulatory processes, as opposed to country-based approaches;
- adoption of streamlined and harmonized requirements, including dossier content and format;
- work sharing, including dossier assessment, inspections, and product testing to improve efficiency in resource utilization; and
- an agreed-upon framework for post-assessment decision making.

Such platforms and resulting networks aim to benefit manufacturers and product developers and ultimately improve public health through faster access to essential medicines, vaccines, and medical devices and diagnostics.

### **Inadequate Research Laboratories**

Clinical trials provide critical data that support the licensure of medicines and vaccines. Recent addition of new drugs, vaccines, and diagnostics for neglected infectious diseases into the global health product pipeline makes it likely that clinical trials will have to be conducted in disease-endemic settings, e.g., LMICs. However, as noted above, the infrastructure for clinical trials is almost nonexistent. In many countries, there are virtually no government-sponsored research laboratories and even hospital laboratories are substantially under-resourced. It is a stunning contrast to see a crowded teaching hospital laboratory with just a few instruments and a chronic shortage of reagents but with many able students situated just down the corridor from a spacious, extremely well-equipped, air-conditioned laboratory with no students that has been set up to support the U.S. President’s Emergency Plan for AIDS Relief sites. The tests undertaken in under-resourced clinical laboratories are far removed from any regulatory standards that may be in place to govern them, and the possibility that GCP laboratories could be set up by public funding authorities is remote. To address these problems, WHO is pushing to establish regional

centers of excellence for laboratory facilities, and has initiated the establishment of quality-testing regional laboratories and bioequivalence centers.

### **Strengthening Regulatory Capacity and Establishing “Essential” Standards**

Another serious barrier to R&D in developing countries is understanding the risks and benefits associated with clinical trials. An illustrative example is the termination of an AIDS prevention trial in one country when a trial to test the efficacy of microbicides in other countries reported negative results. This points to at least two problems: first, the need to ensure true and meaningful involvement of local actors in clinical trials to strengthen capacity and engender a sense of local ownership over clinical trials; and second, the need to have a more open dialogue about “essential” regulatory standards that are adapted to the epidemiological reality of the countries hosting trials and approving medicines and other health technologies for their citizens.

Clearly, innovative regulatory pathways are needed both to expedite access to essential health technologies in developing countries—while ensuring that new treatments are safe, effective, and of high quality—and to reduce costs linked to regulatory approvals while strengthening local regulatory capacity. In addressing developing countries’ health needs, the argument that Western regulatory authorities are the only certified sources for evaluating the quality, safety, and efficacy of medicines should be challenged, particularly when it comes to the risks and benefits of health products for diseases predominant in developing countries for which therapeutic options are often severely limited. It is therefore urgent to strengthen capacities of under-resourced regulatory bodies in endemic countries through enhanced formal collaboration with the regulatory bodies of well-resourced and experienced endemic countries or of SRAs, in partnership with WHO. In addition, it is fundamental to stimulate, support, and promote regional initiatives that aim to accelerate scientific risk-benefit-adjusted reviews and rationalize mutual recognition of regulatory policies within regional zones where disease prevalence is similar.

### **Key Questions**

In today’s global health environment of limited financial and nonfinancial resources, it is desirable to develop working principles for R&D that can promote efficiency in resource utilization, expediency in process, and, ultimately, access to innovative tools designed for impact in the world’s poorest regions. Key questions around such principles for any initiatives include

- How can it be built to the largest scale?
- What existing systems are available to build upon?
- How can stakeholder commitment be attained?
- How can initiatives be sustained?

### **KEY PRINCIPLES AND GLOBAL NORMS**

The international research community lacks a clear set of “rules” to guide how R&D collaborations in the public interest are carried out and ensure that the benefits of such R&D can be shared globally. A normative framework is needed that will not only ensure the delivery of

needed innovations in the form of new health technologies but will also facilitate access to these technologies, notably in LMICs.

Several organizations and recent reports have outlined key guiding principles for the development of a normative policy framework for global health R&D, echoing many of the CEWG report recommendations. We agree that many of these guiding principles are crucial, for example:

- Global health R&D should be **needs-driven** and its outputs should be considered **public goods**.
- **Affordability** should be ensured, notably through **delinkage** of the costs of R&D from the prices of end products.
- **Norms** that encourage both **innovation** and **access** should be fostered through open licensing and equitable management of IP, for example.
- R&D collaborations should be strengthened through more open approaches and greater **knowledge sharing**.

### **Research, and Research Outputs, as Public Goods**

The dire needs of patients in LMICs are not being fulfilled by the current innovation paradigm. Funding for research and how and where it is conducted—not to mention for which purposes and by whom—affect the *translation* of research results into tangible benefits for patients.

Efficacious global health R&D programs design projects from the start with the needs of patients in mind, including in-country infrastructure needs and readiness (or lack thereof) for deployment. Efficacious programs also ensure that projects are managed appropriately from the start, not only by managing logistics, but also by managing the philosophy—the “rules of the game”—that governs the participants. It is counterintuitive to some, but keeping a project “open” and “clean,” free of encumbrances to deployment, requires more management than is necessary for projects that are not “open.”

The concept of global health R&D as a public good for the benefit of LMICs is one such “rule of the game”. Public good research should be accessible to all; its use is not incrementally parceled out to protect its value (i.e., its value is not eroded by repeated use), and it creates open knowledge for public use and engenders reuse, improvement, and diffusion.

Barriers to knowledge access lead to scarcity and inaccessibility, which increases prices; reducing those barriers causes prices to fall. Thus, knowledge diffusion reduces costs by spreading the knowledge base. Moreover, putting real-time access to knowledge in the laboratories of multiple participants allows simultaneous “tinkering” and feedback among collaborators that speeds the pace of innovation, a process that takes discovery to the next steps.

Another rule governing public health R&D is that the actors themselves create public goods and become stewards of the assets in the public interest. Multiple actors operating under a public goods research paradigm—from international research teams to research institutions to research funding agencies—must be “keepers of the vision” so that the goal at the end of the project can be realized. Appropriate public good outcome measures for R&D include collaboration, network optimization, relevance, uptake, delivery, use, freedom to operate, and competitive pricing.

## Assurances of Affordability and Access Through Delinkage

The CEWG report defined the concept of “delinkage” in the following way: “Delinking, which can happen in a number of different ways, is a means of divorcing the funding of R&D from product pricing. Once a patent has expired, delinking occurs naturally because generic competition should bring the price down to levels determined by market conditions and the cost of production rather than by R&D costs” (WHO, 2012). Of course, patients cannot wait for a patent to expire to get access to a life-saving medicine they might need.

The lack of traditional market economics to drive commercial investment in R&D for certain diseases has been explained in previous sections. This crisis of market failure and the resulting prolonged dearth of health technologies for NTDs, neglected diseases, and certain NCDs in LMICs is largely due to a highly skewed risk-to-reward ratio under the traditional IP rights regime. In short, when the cost of R&D is high and there is insufficient potential for profit to justify the necessary investment, then there is no incentive to invest. De-risking R&D programs and delinking the cost of R&D from the price of products are important ways to address this market failure, and both concepts have been achieved through a variety of partnerships and creative financing (for example, see Box 2 on artesunate and amodiaquine).

Thus, international R&D projects that aim to promote widespread accessibility and affordability of health technologies and health care in LMICs must consider the fundamental challenge of providing access to those who cannot pay. Each project must consider the need for sufficient commercial incentives, the need to promote the public good, and the need to have a true health impact. Private, for-profit entities, for example, must balance the goal of making a profit, including the role of market forces (such as price elasticity, which is determined by supply and demand), with societal needs that are not market-driven. When it comes to R&D for the public interest, it is critical to analyze and consider incentives to encourage “at-cost” or “cost-plus” sustainable pricing strategies, including ways to achieve the “break-even” point in a “no-profit, no loss” humanitarian corporate research program.<sup>8</sup>

The sources of funding for R&D affect incentives, IP management strategies, delinkage, and how research outcomes are used. Industry sponsors of academic research typically commercialize the resulting inventions. Foundational funding of basic research is often invested “on top” of years of prior research that is funded by others. This mixed funding can result in rights and benefits being obligated to more than one entity, an outcome that may or may not affect commercial investment decisions.

### BOX 2

#### The Example of Artesunate and Amodiaquine (ASAQ) to Treat Uncomplicated Malaria

In 2007, the Drugs for Neglected Diseases *initiative* (DNDi) launched its first treatment, developed in partnership with Sanofi: a fixed-dose combination (FDC) of artesunate and amodiaquine (ASAQ) to treat uncomplicated malaria. ASAQ is one of four artemisinin-based combination therapies recommended by the World Health Organization since 2001 to address the emergence of drug resistance. DNDi coordinated the development of ASAQ through collaboration with various public and private partners while keeping the ownership of the related intellectual property (IP). DNDi then licensed its IP to Sanofi for the industrial production, registration, and distribution of the FDC in African and other developing

<sup>8</sup> No-profit–no-loss models may or may not be transacted through a corporation’s unit of corporate responsibility. Making a convincing value proposition to a corporate board may be aided by creating and disseminating case studies of previous successful strategies.

countries. Under the DNDi/Sanofi agreement, Sanofi has committed to supply the FDC to the public sector in endemic countries at a no-profit–no-loss maximum price of \$1 (50 cents for children). In the private sector, Sanofi is free to sell the FDC at market price and is paying a small royalty back to DNDi, which is reinvested in additional studies. DNDi and Sanofi agreed not to file any patent on the new FDC, which can therefore be freely produced and distributed by any other pharmaceutical company in the world. Today, ASAQ is registered in 30 sub-Saharan countries as well as in India, Bangladesh, and Colombia. To date, more than 190 million treatments have been distributed in more than 20 countries. In addition, DNDi is currently facilitating technology transfer to ensure production of ASAQ in Africa by a Tanzanian manufacturer, Zenufa.

## Open Licensing and Equitable Management of IP Rights

The CEWG report highlights clearly that current incentives, including the traditional IP system, do not adequately stimulate R&D when it comes to health needs of people in LMICs. The definition of “delinkage” in the CEWG report cites patent rights as an impediment to introduction of generic drugs into the market at lower prices; this is one key element of the discussion about IP.

Traditionally, IP rights have been used to provide incentives to invest in risky and expensive R&D programs and to enable monopoly pricing of pharmaceutical products. The biotechnology and pharmaceutical industries rely heavily on IP portfolios to protect their investments and to justify prolonged expenditures in view of regulatory risk and market uncertainty.

IP rights can also be used in nontraditional ways, for example, to maximize positive social impact of research results and encourage follow-on research without direct monetary returns to the owner (although they are not always mutually exclusive). IP rights are intangible; they can bring additional intangible benefits such as affiliation, reputation, and good will, and other valuable outcomes such as collaboration, diversification of research funding sources, and access to networks and tools. Importantly, IP rights can be used to create industry standards, including more-open standards.

IP owners should consider the consequences of patenting and licensing IP rights in countries that are best served through competition by generic drug manufacturers, and the breadth and timing of rights protection and licensure. They should also enable humanitarian uses by third parties if a licensee does not provide access of licensed products to target populations (e.g., by using “claw-back” provisions such as mandatory sublicensing or humanitarian reservation of rights clauses in contracts, or, alternatively, a promise not to assert the rights against third-party use for humanitarian purposes) (Mimura, 2006; Mimura, 2010; Stevens and Effort, 2008).<sup>9</sup>

If public good research results are to be protected with proprietary rights such as patents, patent owners should not impair nonprofit use of their inventions for research and education, including robust rights to publish findings and share data. They should also preserve rights to transfer tangible materials and research tools to others who wish to verify results, create improvements, and advance the field.<sup>10</sup> Know-how is often as important as patent rights in terms of being able to practice an invention, so if know-how is licensed, it should be licensed on a nonexclusive basis.

<sup>9</sup> See also selected contract clauses at <http://ipira.berkeley.edu/socially-responsible-licensing-ip-management>.

<sup>10</sup> By themselves or through repositories such as through ACCT, the Global Bioresource Center, and Addgene.

PDPs and other nonprofit R&D initiatives have to sign legal agreements and negotiate licensing terms with IP owners in order to access their assets and secure the necessary “freedom to operate,” but they have an obligation, given their mission, to do so in a manner that will ensure access and affordability. Most PDPs and other initiatives do not make the terms of these agreements available in the public domain, and greater transparency is desirable. But some broad principles for licensing terms can and should be something that many parties agree to. For example, DNDi has had in place since its inception an IP policy that ensures that treatments developed by DNDi are affordable and that access is equitable. When it negotiates with partners that hold relevant IP, the policy requires that such IP will not be used “in a manner that impedes equitable and affordable access to the products of the research, or that impedes additional or follow-on research by DNDi, its partners and other researchers”<sup>11</sup>. After several years of experience, DNDi has been able to negotiate favorable licensing terms with many companies and has come to define “gold standard” terms, including

- perpetual, royalty-free, nonexclusive, sub-licensable licenses in the specific disease areas determined in the contract;
- worldwide research and manufacturing rights;
- commitment to make the final product available at cost plus a minimal but sustainable margin, in all endemic countries, regardless of income level; and
- nonexclusivity enabling technology transfer and local production.

IP rights are only one factor among many that ultimately affect price, but a very important one. Drug discovery, development, and translation are extraordinarily expensive endeavors and costs can be lowered or shared through various measures throughout the R&D process. These include, for example, widespread dissemination and use of research results, data<sup>12</sup>, know-how,<sup>13</sup> and research tools such as tangible biological materials,<sup>14</sup> open licensing,<sup>15</sup> data repositories,<sup>16</sup> patent pools,<sup>17</sup> information-sharing and partnering initiatives,<sup>18</sup> open innovation “campuses” that co-locate collaborators and provide shared resources,<sup>19</sup> crowd-sourced financing,<sup>20</sup> and reduced duplication of effort through open-access innovation and crowd-sourced drug discovery.<sup>21</sup>

---

<sup>11</sup> See: [http://www.dndi.org/images/stories/pdf\\_aboutDNDi/ip%20policy.pdf](http://www.dndi.org/images/stories/pdf_aboutDNDi/ip%20policy.pdf)

<sup>12</sup> Including clinical trial data such as under a portable informed consent document. See: <http://www.nature.com/news/open-data-project-aims-to-ease-the-way-for-genomic-research-1.10507>

<sup>13</sup> Through teaching and publication, including through open-access journals.

<sup>14</sup> For example, through standardized and simplified material transfer “bailment” agreements.

<sup>15</sup> Such as software open source licenses and the suite of Creative Commons flexible copyright licenses. See <http://creativecommons.org/licenses>.

<sup>16</sup> Such as the NCBI Gene Expression Omnibus and the Worldwide Protein Databank.

<sup>17</sup> Such as the Medicines Patent Pool for HIV and the Pool for Open Innovation against Neglected Tropical Diseases.

<sup>18</sup> Such as WIPO Re:Search.

<sup>19</sup> Such as the GlaxoSmithKline Tres Cantos Medicines Development Campus in Spain.

<sup>20</sup> See, for example, <http://www.petridish.org>.

<sup>21</sup> The Internet was largely developed through open knowledge sharing, open standards, and tools developed by users who contributed on the heels of others through iterative phases of development without fee-bearing transactions. In biology, for examples of PPPs that are working under open frameworks to discover new drug targets and achieve clinical proof-of-mechanisms (i.e., bring projects through Phase II clinical trials), see Sage Bionetworks

## Open Innovation and Collaboration to Accelerate R&D and Enhance R&D Efficiencies

In recent years, new collaboration models have arisen to address the R&D crisis where the market has failed. All employ tailored IP management strategies and business models that achieve a different type of risk-to-reward balance by advancing projects through critical stages in the discovery, development, or delivery of global health technologies (see Box 3 on creative capitalism).

### Box 3 Creative Capitalism

IP management strategies with global health aims rely on IP rights that range from strong to weak to nonexistent. Those that are strong can sometimes rely on traditional market dynamics to balance risk and reward under a bifurcated business model.

The semisynthetic artemisinin partnership among the Institute for One World Health (iOWH), Amyris Biotechnology, and University of California (UC), Berkeley, received startup capital under a “creative capitalism” approach from the Bill & Melinda Gates Foundation (Kiviat and Gates, 2008). The Bill & Melinda Gates Foundation was motivated to fund a project that ultimately produced low-cost malaria drugs for LMICs. Startup (for-profit) companies are not in a position to pursue a charitable, humanitarian project due to high “burn rates” (high and sustained R&D capital needs), the need to secure a series of financing from private capital sources, and, ultimately, to become profitable. Startup companies can thus ill afford to invest in a global public health goal that does not fit the profit motives of investors. Amyris was successful, however, because its business strategy consisted of a short-term, nonprofit, *public good* project and a long-term, for-profit, *commercial* project (Mimura et al., 2011).

Under an IP license from UC Berkeley, Amyris was not allowed to make a profit on the malaria project but committed to “at-cost” pricing targets on the malaria drug. The public good project “reduced to practice” a platform technology that is capable of producing many commercially valuable products (based on a common chemical building block), including biofuels. The biofuels application attracted significant venture capital funding and enabled the company to achieve an impressive initial public offering. In this example of “bootstrap philanthropy,” Amyris parlayed philanthropic funding for development of a malaria application into commercial applications under a traditional IP rights model. In short, Amyris engineered, through “synthetic biology,” a malaria drug with its “nonprofit hat” on, then commercially viable products with its “for-profit hat” on.

Berkeley’s IP license to the iOWH was limited to the malaria field only, contained “at-cost” pricing restrictions, and was also limited in terms of “licensed territory” to 88 LMICs.

Moreover, Sanofi, the pharmaceutical sublicensee of both licenses, “inherited” the same terms with respect to drug pricing, thus fulfilling the original motive of the Bill & Melinda Gates Foundation to fund the project. Sanofi also then received a grant from the Gates Foundation to refine the manufacturing process, thereby expanding its own non-dilutive financing, as well.

“Open innovation” principles can and should be applied to international collaborative R&D.<sup>22</sup> When the urgency of finding and delivering solutions to those in need is driven by public good values, research participants are motivated to share data, results, reports, and materials and to engage in robust exchanges of personnel and know-how. They are furthermore

---

(<http://sagebase.org/WP/com>) and Arch2POCM (<http://sagecongress.org/WP/wp-content/uploads/2012/04/Sci-Transl-Med-June-2011-7.32.25-AM.pdf>).

<sup>22</sup>“Open innovation is a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology” (Chesborough, 2003).

motivated to do so in real-time. This behavior is not consistent with the traditional culture of “every man for himself,” that is, a stance that other researchers in the field are competitors for publication priority or for scarce federal funding agency grants. Innovators working collaboratively across boundaries can share both the risks and rewards of their respective investments and tackle the most pressing problems that a lone actor would not attempt (Mimura, 2010).

The shift to viewing collaborators primarily as team members and as facilitators of a common goal lowers cultural barriers to even broader modes of distributed innovation that have long been the norm in other fields. Pre- or noncommercial research can be advanced through global networks that enable and facilitate sharing among relevant players without IP protection. Large, open, and IP-free collaboration strategies such as those employed by the Sage Bionetworks digital commons<sup>23</sup> and open-source drug discovery efforts in India,<sup>24</sup> for example, can provide insight into how the final costs of late-stage clinical trials are financed and proceeds (if any) are distributed, as well as indicate the effect on sustained participation and scaling (or not) of the model.

Formidable translation gaps between basic research and product development have been traversed through dozens of R&D partnerships and PDPs, such as those that have developed a low-cost synthetic form of artemisinin for use in artemisinin combination malaria therapy,<sup>25</sup> nutritionally fortified sorghum with enhanced bioavailability of nutrients, pesticide-free, disease-resistant crops,<sup>26</sup> MEMS-based hand-held point-of-care diagnostics,<sup>27</sup> a new cell phone-based diagnostic,<sup>28</sup> and a new meningitis A vaccine.<sup>29</sup> Adequate provisions to ensure access to these technologies, even for the poorest populations, have not always been ensured, but several encouraging examples exist.

Many R&D projects that are led by PDPs bridge translational research gaps by partnering “upstream” with academic, basic researchers on the one hand and “downstream” with pharmaceutical corporations on the other. PDPs bring vital funding and drug development expertise to partnerships that advance basic research projects to the developmental stage. PDPs often bridge the IP push mechanisms that are commonly employed by universities with pull-based, needs-driven research projects that are funded primarily by the public sector and/or philanthropic monies. This diversification of funding can accelerate the pace of innovation by enabling academics to stay more involved in the applied or translational R&D space than they typically would if their funding were limited solely to grants from federal funding agencies.

#### **BOX 4**

##### **Supplementary Information on Cultural Shifts and Evolving Academic Norms**

Product development is the paramount goal of PDPs and of other collaboration types. These and other influences are motivating subtle academic cultural shifts and academic norms are slowly evolving. For example, for basic researchers, understanding and wishing to facilitate “what comes next” in the

<sup>23</sup> See <http://sagebase.org/WP/com>.

<sup>24</sup> See <http://www.osdd.net/about-us>.

<sup>25</sup> See [http://ipira.berkeley.edu/sites/default/files/shared/3-Panel\\_Brochure\\_Final.pdf.pdf](http://ipira.berkeley.edu/sites/default/files/shared/3-Panel_Brochure_Final.pdf.pdf).

<sup>26</sup> See Mimura et al. (2011).

<sup>27</sup> See Bergman (2005).

<sup>28</sup> See <http://blumcenter.berkeley.edu/global-poverty-initiatives/mobile-phones-rural-health/remote-disease-diagnosis>.

<sup>29</sup> See <http://policycures.org/downloads/Saving%20lives%20and%20creating%20impact.pdf>.

value chain can motivate researchers to anticipate the (eventual) need (of others) to scale projects beyond “bench scale,” and, ultimately, to produce goods and services to a commercial standard. Scientists increasingly consider the ultimate cost of (future) large-scale production, or “freedom-to-operate” considerations revealed by IP landscape assessments, third-party property rights (such as cell lines), or the specific needs of in-country deployment (such as high heat, high humidity, or lack of refrigeration). Researchers in cooperative research extensions funded by the U.S. Department of Agriculture have long been accustomed to consider “end-user,” “needs-driven” factors when planning and executing R&D. Elements of the Cooperative Extension approach to financing, staffing, and expediting translational research in agriculture may provide insights into design considerations for other fields.

Moreover, academic researchers on “parallel tracks” in health research fields should be encouraged and supported by universities. Academic researchers pursuing fields that fall outside of “priority areas” (as periodically defined by USG funding agencies) often face funding obstacles and may also find it difficult to advance to tenured positions at universities. If the nature of a research program, for example, requires protracted scientific fieldwork in remote locations, thus compromising a researcher’s ability to serve on a university committee, or if the nature of a researcher’s contribution to a peer-reviewed journal article often results in being one author among many (and not the first author), or if one is a clinical trialist, then a departmental promotion or tenure review committee should be equipped with guidelines for commensurate evaluation of a given applicant’s record compared with others whose funding streams, daily duties, and publication records (and options) are different.<sup>30</sup>

To attract, support, and retain talented researchers, academic research institutions should apply nuanced approaches to evaluation in promotion and tenure decisions (but still base decisions on the three traditional pillars of teaching, publication, service), and global health research successes should be celebrated. To encourage and attract collaborative research projects, the academic research community can also participate in nascent efforts to develop and report “collaboration metrics” to indicate the relevance of individuals and institutions to team science and their willingness and ability to collaborate effectively.

## **Next Steps**

As mentioned in a previous section, in November 2012, WHO member states met to develop concrete steps for how to implement some of the recommendations of the CEWG report around which there was consensus. One action item, agreed to provisionally, asks the WHO Director General to

facilitate through regional consultations and broad engagement of relevant stakeholders the implementation of a few health R&D demonstration projects to address identified gaps which disproportionately affect developing countries, particularly the poor and for which immediate action can be taken. (WHO 2012)

We suggest that these pilot/demonstration projects be supported only if they explicitly operationalize the key principles described above, namely, if the products developed through the pilots are considered public goods; the concept of delinkage is implemented to ensure affordability; licensing terms (and management of IP more generally) abide by norms that ensure access; and open, collaborative approaches to data and knowledge sharing are utilized.

## **SUMMARY: MOVING FORWARD**

### **Role of the U.S. Department of State**

---

<sup>30</sup> Such as when a research grant requires real-time dissemination of data and results.

The USG, through its Department of State and its office of Global Health Diplomacy, can have an important international role in promoting science diplomacy for global health R&D. The State Department should embark on high-level discussions to exert diplomatic pressure on nations that have “underachieved” in their commitments to global health R&D and neglected disease research, with emphasis on specific high-income economies, emerging economies, and the large-GDP nations of Brazil, China, India, Indonesia, Japan, Mexico, and South Korea. These nations need to increase support for global health R&D and become international players on this front.

### **USG Contribution to Global Health R&D**

The USG has provided impressive leadership for support of global health R&D, especially for neglected diseases. However, there remains an urgency to find mechanisms to support late-stage product development, including clinical trials. *Depending on the specific needs of the global health R&D community*, the USG should consider committing annually to product development R&D up to 1 to 2 percent of the financial support currently allocated to global health overseas development assistance. These funds could place an estimated \$100-\$200 million into the system annually and would be transformative in providing new support for clinical trials and other late-stage product development activities. Potentially, these funds could be pooled with donor support from other countries.

### **Public Funding for Neglected Disease R&D**

Public financing of neglected disease R&D should include adequate support for product development and provide funds for both the private sector and PDPs/PPPs. There is a need for governments to collaborate in order to provide sufficient funds for this purpose. The following set of principles should be considered around public funding:

- Any public financing for neglected disease products should include support for academic scientists and for the lead organizations whose primary mission is to develop and test products (e.g., drugs, diagnostics, vaccines, and vector control agents), including PDPs, biotechnology companies, multinational pharmaceutical companies, and developing-country manufacturers. With public financing, though, must come strong conditions to ensure affordability and access for end-users.
- Flexibility in financing is paramount in order to foster partnerships among these different types of organizations, as well as for establishing PPPs among the organizations listed above and sovereign governments.
- PPPs might also include co-financing between governments and commercial investors, including venture capital funds.
- Accelerating innovation will require a “blurring” of the traditional boundaries and firewalls that exist among industry, universities, and governments. We recognize the challenges of implementing public financing for the private sector. The United States has successfully accomplished this with its SBIR program, in which 3 percent of the budget of an organization like NIH is reserved for the SBIR program, with the potential for a successful (i.e., profitable) product being the primary reason for funding. This type of

program could be expanded to include funds for neglected diseases, in which a successful “outcome” in reducing the burden of disease would be the primary outcome variable. In addition, an SBIR type of mechanism could be set up for nonprofit organizations, including PDPs, engaged in product development for neglected diseases. Such a program could be a model for other countries. Again, public funding for private companies and other entities must be tied to conditions that will ensure affordability and access for patients.

- Targets should be set around specific R&D and product needs (including those established through a Global Health R&D Observatory or similar mechanisms), in addition to specific financial targets.
- The use of FTTs is a promising mechanism to raise funds for global health R&D.

### **A Global Health R&D Observatory**

Establishing a Global Health R&D Observatory represents an important first step in prioritizing global health R&D needs and products. A well-managed and transparent observatory will be essential if funding pools are established. At present, there is no politically legitimate system for R&D priority setting at the global level, so an observatory would be a key starting point. While by itself an observatory will not address all of the challenges posed in the CEWG report, WHO member states, including the United States, will need to allocate resources to ensure that a Global Health R&D Observatory can flourish. At a minimum, the observatory needs to perform two critical functions: one that is primarily technical (monitoring) and one that is more “political,” namely, priority setting and coordination. In regard to priority setting, the structure, governance, and accountability mechanisms are critical and need to be carefully designed. Finally, a clear link to financing mechanisms should be established to ensure that resources are allocated according to identified and agreed-upon priorities, needs, and gaps.

### **Other Nonfinancial Assistance**

There are several key areas in which governments need to provide nonfinancial mechanisms of assistance, especially in the areas of human resources, regulatory science, and capacity building for research laboratories. In the area of regulatory science, the U.S. FDA can share acquired enormous regulatory experience with global health products that it has acquired over the last decade. The USG needs to identify specific mechanisms by which it can promote regionalization of regulatory processes for LMICs as opposed to country-based approaches; adoption of streamlined and harmonized requirements, including dossier content and format; work sharing, including dossier assessment, inspections, and product testing to improve efficiency in resource utilization; and an agreed-upon framework for post-assessment decision making.

### **Intellectual Property and Open Innovation**

Given the lack of rules around collaboration and innovation, to ensure equitable access to R&D outputs, a new normative framework is needed. We believe such a framework should include the following principles: (1) global health R&D as a public good, (2) “delinkage” of product pricing and the financing of R&D, (3) IP/licensing norms that ensure access, and (4)

more open, collaborative approaches to R&D and knowledge sharing. These principles should be operationalized in pilot/demonstration projects and funded accordingly.

**Suggested citation:** Hotez, P. J., R. Cohen, C. Mimura, T. Yamada, and S. L. Hoffman. 2013. *Strengthening mechanisms to prioritize, coordinate, finance, and execute R&D to meet health needs in developing countries*. Discussion Paper, Institute of Medicine, Washington, DC. <http://nam.edu/wp-content/uploads/2015/06/StrengtheningMechanismsRD>

## REFERENCES

- Bergman, B. 2005. Research patently in the public interest. *Berkeleyan*, December 2.
- Chesbrough, H. W. 2003. *Open innovation: The new imperative for creating and profiting from technology*. Boston: Harvard Business School Press.
- Chirac, P., and E. Torreele. 2006. Global framework on essential health R&D. *Lancet* 367:1560-1561.
- Feletto, M., and S. A. Matlin. 2009. *Global R&D financing for communicable and noncommunicable diseases. A report to the WHO Expert Working Group on R&D Financing*. Geneva: World Health Organization.
- GFHR (Global Forum for Health Research). 2000. *The 10/90 report on health research*. Geneva: GFHR.
- Hoffman, S., and J.-A. Røttingen. 2012. Assessing implementation mechanisms for an international agreement on research and development for health products. *Bulletin of the World Health Organization* 90:854-863.
- Hotez, P. J. 2010. Neglected tropical disease control in the “post-American world.” *PLoS Neglected Tropical Diseases* 31:e812.
- Hotez, P. J. 2011. New antipoverty drugs, vaccines, and diagnostics: A research agenda for the US President’s Global Health Initiative (GHI). *PLoS Neglected Tropical Diseases* 5:e1133.
- Hotez, P. J. 2012. Engaging a rising China through neglected tropical diseases. *PLoS Neglected Tropical Diseases* 6:e1599.
- Hotez, P. J., and A. S. Daar. 2008. The CNCDs and the NTDs: Blurring the lines dividing noncommunicable and communicable chronic diseases. *PLoS Neglected Tropical Diseases* 2:e312.
- Hotez, P. J., A. Fenwick, L. Savioli, and D. H. Molyneux. 2009. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* 373:1570-1575.
- Hotez, P. J., D. H. Molyneux, A. Fenwick, E. Ottesen, and J. Sachs. 2006. Incorporating a rapid impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis and malaria: A comprehensive pro-poor health policy and strategy for the developing world. *PLoS Medicine* 3:e102.
- Hotez, P. J., D. H. Molyneux, A. Fenwick, J. Kumaresan, S. E. Sachs, J. Sachs, and L. Savioli. 2007. Control of neglected tropical diseases. *New England Journal of Medicine* 357:1018-1027.
- Kiviat, B. and B. Gates. 2008. Making capitalism more creative. *Time*, July 31.
- Lomas, U. 2012. *France allocates 10% of FTT to fund development*. [http://www.tax-news.com/news/France\\_Allocates\\_10\\_Of\\_FTT\\_To\\_Fund\\_Development\\_\\_\\_57656.html](http://www.tax-news.com/news/France_Allocates_10_Of_FTT_To_Fund_Development___57656.html) (accessed January 9, 2013).
- Mimura, C. 2006. Technology licensing for the benefit of the developing world: U.C. Berkeley’s socially responsible licensing program. *Journal of the Association of University Technology Managers* 18(2): 15-28.
- Mimura, C. 2010. Nuanced management of IP rights: Shaping industry-university relationships to promote social impact. In *Working within the boundaries of intellectual property: Innovation policy for the knowledge society*. Rochelle Dreyfuss, Harry First, Diane Zimmerman, Eds. Oxford University Press, Pp. 269-295.
- Mimura, C., J. Cheng, and B. Penhoet. 2011. Socially responsible licensing, Euclidean innovation and the valley of death. *Stanford Journal of Law, Science and Policy*. Summer-Fall: 1-16.
- Molyneux, D. H., P. J. Hotez, and A. Fenwick. 2005. “Rapid impact” interventions: How a policy of integrated control for Africa’s neglected tropical diseases could benefit the poor. *PLoS Medicine* 2:e336.
- Moolani, Y., G. Bukhman, and P. J. Hotez. 2012. Neglected tropical diseases as hidden causes of cardiovascular disease. *PLoS Neglected Tropical Diseases* 6:e1499.
- Moran, M., J. Guzman, K. Henderson, R. Liyanage, L. Wu, E. Chin, N. Chapman, L. Abela-Oversteegen, D. Gouglas, and D. Kwong. 2012. *G-FINDER 2012. Neglected disease research and development: A five year review*. Sydney: Policy Cures.

- MSF (Médecins Sans Frontières). 2001. *Fatal imbalance: The crisis in research and development for neglected diseases*. Geneva: MSF.
- MSF/DNDi (Drugs for Neglected Diseases initiative). 2012. *Medical innovation for neglected patients*. <http://www.doctorswithoutborders.org/publications/reports/2012/Medical%20Innovations%20for%20Neglected%20Patients.pdf> (accessed January 9, 2013).
- Murray, C. J. L., T. Vos, R. Lozano, et al. 2012. 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* 380:2197-2223.
- Pécoul, B., P. Chirac, P. Trouiller, and J. Pinel. 1999. Access to essential drugs in poor countries: A lost battle? *JAMA* 281:361-367.
- Røttingen, J.-A., S. Moon, V. Tangcharoensathien, and S. J. Hoffman. 2012. Multi-Stakeholder Technical Meeting on Implementation Options Recommended by the WHO Consultative Expert Working Group on Research & Development (CEWG): Financing and Coordination. Meeting Report, Thai Ministry of Public Health/International Health Policy Program and Harvard Global Health Institute.
- Stevens, A.J. and A. Effort. 2008. Using Academic License Agreements to Promote Global Social Responsibility. *Les Nouvelles* 43 (2): 85-101.
- Trouiller, P., P. Olliaro, E. Torreele, J. Orbinski, R. Laing, and N. Ford. 2002. Drug development for neglected diseases: A deficient market and a public-health policy failure. *Lancet* 359:2188-2194.
- WHO (World Health Organization). 2006. *Report of the Commission on Intellectual Property, Innovation and Public Health*. Geneva: WHO.
- WHO. 2008. *Global strategy and plan of action on public health, innovation, and intellectual property*. Geneva: WHO.
- WHO, 2010. *Working to overcome the global impact of neglected tropical diseases. First WHO report on neglected tropical diseases*. Geneva: WHO.
- WHO. 2012a. *Research and development to meet health needs in developing countries: Strengthening global funding and coordination. Report of the Consultative Expert Working Group on Research and Development*. Geneva: WHO.
- WHO. 2012b. *Report of the open-ended meeting of member states on the follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva, 26-28 November 2012*. Geneva: WHO.