

## Better, Cheaper, Faster: Strategies for Sustainable Treatment Access for the World's Poorest

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### INTRODUCTION

Technological advances in diagnostics and therapeutics have the potential to revolutionize health care and improve the lives of millions of people. However, many of these technologies remain out of reach for those who need them, particularly the poor in low- and middle-income countries. The reasons for this inaccessibility vary, depending on the disease at issue and whether it is also endemic in affluent countries, the quality and availability of local healthcare services, and the type of technology and its current stage of development.<sup>1</sup> To be effective, strategies to improve the accessibility of a treatment must address the particular reasons for its inaccessibility.

Neglected diseases are a group of mostly infectious conditions that afflict the world's poorest people, almost exclusively in low- and middle-income countries.<sup>2</sup> Strategies to stimulate

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<sup>1</sup> See LAURA J. FROST & MICHAEL R. REICH, ACCESS: HOW DO GOOD HEALTH TECHNOLOGIES GET TO POOR PEOPLE IN POOR COUNTRIES? 2 (2009).

<sup>2</sup> This paper defines neglected diseases broadly to refer to malaria, tuberculosis, dengue fever, treponematoses, leptospirosis, strongyloidiasis, foodborne trematodiasis, neurocysticercosis, scabies, thirteen parasitic and bacterial infections, three soil-transmitted helminth infections (ascariasis, hookworm, and trichuriasis), lymphatic filariasis, onchocerciasis, dracunculiasis, schistosomiasis, Chagas disease, human African trypanosomiasis, leishmaniasis, Buruli ulcer, leprosy, and trachoma. This definition accords roughly with the definition of “neglected diseases of the developing world” under U.S. law. See U.S. Food, Drug, & Cosmetic Act § 524(a)(3), 21 U.S.C. § 360n(a)(3) (2008). With the arguable exception of tuberculosis, the neglected diseases discussed in this paper are all “Type III”

research and development (R&D) of effective therapies for neglected diseases have focused on subsidizing R&D costs (“push” programs), improving the expected revenues after product launch (“pull” programs), or a combination of both. Backed by substantial resources from the Bill & Melinda Gates Foundation, the U.S. National Institutes of Health (NIH), and other donors, these efforts have met with unprecedented success. There are now dozens of candidate technologies in the pipeline for neglected diseases.

As these candidate technologies for neglected diseases move to late-stage clinical development, however, significant challenges loom, which the push and pull strategies currently employed are ill-suited to address. The clinical research and regulatory capacity in many developing countries is not adequate to support the clinical trials that need to occur there in order to complete development of neglected disease products. Even with expected rates of attrition in the product pipeline, current levels of funding for neglected disease R&D are insufficient to support the clinical development and delivery of these candidate products under current cost assumptions. Registration of a neglected disease product for use requires navigating multiple, poorly coordinated regulatory processes, which can add years to neglected disease R&D efforts. Product delivery must occur in the resource- and infrastructure-poor settings where patients live.

New approaches are needed to address these challenges and sustainably improve access to treatment for the world’s poorest. While it is not easy to improve the incomes of the millions of people suffering from one or more neglected diseases, the costs of responding to their health needs can be lowered by improving the efficiency of clinical development, which represents the bulk of the expense and time required to develop a drug or a vaccine.<sup>3</sup> While there is no simple solution to building adequate clinical research and regulatory capacity in a desperately poor country, research and regulatory capacity may be pooled across such countries, creating regional platforms for sustainable capacity building. While improving health systems and product delivery platforms will take time, the success of these efforts can be improved by better engaging innovators in emerging economies, which may have more favorable cost structures, better ability to respond to domestic markets, and more incentives to address the diseases that are endemic in their own countries.

This paper proceeds in four parts. First, it describes the global neglected disease burden and the tremendous potential of the current pipeline of candidate health technologies to reduce that burden. Second, this paper provides an overview of the difficult challenges that loom as these candidate technologies move to late-stage clinical development, regulatory review, and product introduction. Third, it examines the sufficiency of the intellectual property system and other push and pull strategies for neglected disease R&D to address the current challenges facing neglected disease product developers. Finally, this paper proposes strategies to help bring the costs and financing of neglected disease product R&D into a more sustainable balance.

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diseases in the World Health Organization’s (WHO) Commission on Intellectual Property, Innovation and Public Health (“CIPIH”) classification—diseases almost exclusively endemic in low-income countries. *See* WORLD HEALTH ORG., REPORT OF THE COMMISSION ON INTELLECTUAL PROPERTY RIGHTS, INNOVATION AND PUBLIC HEALTH: PUBLIC HEALTH, INNOVATION AND INTELLECTUAL PROPERTY RIGHTS 26 (2006). This article does not address Type I diseases—diseases like diabetes and heart disease for which the burden is global—or Type II diseases—diseases such as HIV/AIDS for which there is some burden in high-income countries, but where most patients reside in low-income countries.

<sup>3</sup> *See* RUTH LEVINE ET AL., CTR. FOR GLOBAL DEV., MAKING MARKETS FOR VACCINES: IDEAS TO ACTION 3 (2005).

## I. NEGLECTED DISEASES AND THEIR TREATMENT

A. *The Burden of Neglected Diseases*

More than one billion people, including 400 million children, suffer from one or more neglected diseases.<sup>4</sup> These diseases include malaria, tuberculosis (TB), and a dozen other parasitic, soil-transmitted, bacterial, and tropical infections.<sup>5</sup> Neglected diseases disproportionately affect the world's poorest and most politically marginalized in urban and rural areas alike.<sup>6</sup> They are endemic to Africa, Asia, tropical regions of Latin America, and parts of the Middle East.<sup>7</sup>

Neglected diseases have a staggering impact on afflicted people and communities. Malaria and tuberculosis (TB) alone kill an estimated 2.6 million people annually, almost exclusively in low and middle-income countries.<sup>8</sup> Other neglected diseases disable and deform, adversely affect pregnancies and child development, undermine worker productivity, and perpetuate the cycle of poverty, insecurity, and infirmity in the communities in which they are endemic.<sup>9</sup> In short, neglected diseases rob the world's poorest communities of their hope for a better future.

Neglected diseases are not, however, just a challenge for low- and middle-income countries. Diseases like TB and dengue fever cross borders with trade and travel; the health and economic consequences of outbreaks are significant.<sup>10</sup> Other neglected diseases pose risks to the Americans who travel to disease-endemic environments and the women and men of the U.S. military who serve there.<sup>11</sup> Neglected diseases undermine the security of U.S. allies and the economic development of potential trading partners.<sup>12</sup>

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<sup>4</sup> WORLD HEALTH ORG., WORKING TO OVERCOME THE GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES iii (2010).

<sup>5</sup> U.S. Food, Drug, & Cosmetic Act § 524(a)(3), 21 U.S.C. § 360n(a)(3) (2008).

<sup>6</sup> See generally GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 5; Kenneth Gustavesen & Christy Hanson, *Progress in Public-Private Partnerships to Fight Neglected Diseases*, 28 HEALTH AFF. 1745 (2009).

<sup>7</sup> Philip Musgrove & Peter Hotez, *Turning Neglected Tropical Diseases into Forgotten Maladies*, 28 LANCET 1691, 1693 (2009).

<sup>8</sup> GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 3, 41, 77, 94, 132 (reporting the annual mortality for visceral leishmaniasis (50,000), schistosomiasis (41,000), Chagas' disease (10,000), and dengue fever (1 to 5% mortality out of a million annual cases)).

<sup>9</sup> Peter J. Hotez et al., *The Antipoverty Vaccines*, 24 VACCINE 5787, 5789 (2006); see also GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at iv, 3 (describing the terrible and debilitating effects of individual neglected diseases).

<sup>10</sup> Ruth Levine, *Healthy Foreign Policy: Bring Coherence to the Global Health Agenda* in CTR. FOR GLOBAL DEV., WHITE HOUSE AND THE WORLD, 43-45 (Birdsall ed., 2008). See also Donald G. McNeil, Jr., *Tropical Diseases: Outbreak of Dengue Fever Is Reported in Florida*, *Health Officials Say*, N.Y. TIMES (May 24, 2010), <http://www.nytimes.com/2010/05/25/health/25glob.html>; U.S. CTRS. OF DISEASE CONTROL AND PREVENTION, REPORTED TUBERCULOSIS IN THE UNITED STATES, 2009 3-6 (2010).

<sup>11</sup> GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 3 (noting that the spread of many neglected diseases is restricted by climate and the distribution of their vectors and hosts).

<sup>12</sup> Where data exist, they demonstrate that the economic impact of neglected diseases is significant. See, e.g., GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 15-16, 89 (reporting, *inter alia*, that lymphatic filariasis causes almost US\$1 billion in lost productivity; the annual global expenditure for rabies prevention and control exceeds US\$1 billion; the economic cost of trachoma in terms of lost productivity is estimated at US\$2.9 billion annually; and that Africa loses US\$1.5 billion annually in agricultural income as a result of African trypanosomiasis).

### B. *New and Improved Treatment Options Needed*

Historically, there has been little investment in developing new treatments for neglected diseases because most people who suffer from them are desperately poor. Since drug development costs and risks for neglected diseases are comparable to those for affluent diseases, the interest of pharmaceutical firms in investing in neglected diseases has been understandably small. Accordingly, if a disease or condition does not have a significant presence in high-income markets, a treatment usually does not exist. Infectious and parasitic diseases account for one-third of the disease burden in low-income countries and nearly half of the disease burden in Africa, but less than three percent of the disease burden in developed countries.<sup>13</sup> Fewer than 40 of the nearly 1400 new chemical entities approved between 1975 and 1999 were for neglected diseases.<sup>14</sup> Many neglected diseases have no effective treatments at all.<sup>15</sup>

If significant disease burden exists in low- and high-income countries alike, a treatment is more likely to exist, but may not be adapted for use in impoverished settings with limited refrigeration and health-care infrastructure. Most drugs, vaccines, and diagnostics used for neglected diseases were developed for wealthier country markets and other purposes. Many date back to the colonial era.<sup>16</sup> Others are new uses of existing drugs and veterinary products, or were developed for use by the U.S. military serving in disease-endemic areas.<sup>17</sup> Many of these treatments are prohibitively expensive, toxic, and otherwise ill-suited for use by target populations and in environments with few trained healthcare personnel.<sup>18</sup>

Implementation and compliance with current prevention and control strategies is often inadequate, particularly in resource-poor settings.<sup>19</sup> Effective, safe, affordable, and simple-to-use treatment, prevention, and diagnostic tools for neglected diseases are urgently needed. New vaccines are needed to lower the burden of neglected diseases.<sup>20</sup> Drug resistance is already a

<sup>13</sup> EMMANUEL HASSAN ET AL., RAND EUROPE, INTELLECTUAL PROPERTY AND DEVELOPING COUNTRIES 30 (2010).

<sup>14</sup> *Drug Approvals for Neglected Diseases Increase Along With More R&D Funding*, 11(6) IMPACT REPORT (Tufts Ctr. for the Study of Drug Dev., Boston, Mass.), Nov./Dec. 2009.

<sup>15</sup> See, e.g., GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 151 (citing the lack of effective treatments for leishmaniasis, trypanosomiasis, and dengue); Sarah E. Frew et al., *A Business Plan to Help the 'Global South' in Its Fight Against Neglected Diseases*, 28 HEALTH AFF. 1760, 1761 (2009) (reporting that there are no effective treatments for Buruli ulcer or Chagas disease).

<sup>16</sup> Solomon Nwaka et al., *Advancing Drug Innovation for Neglected Diseases—Criteria for Lead Progression*, 3 (e440) PLOS NEGLECTED TROPICAL DISEASES 1, 2 (2009).

<sup>17</sup> See HASSAN ET AL., *supra* note 13, at 30; see also Patrice Troullier et al., *Drug Development for Neglected Diseases: A Deficient Market and a Public Health Failure*, 359 LANCET 2188, 2188, 2192 (2002).

<sup>18</sup> See, e.g., Robert Hecht, Paul Wilson, & Amrita Palriwala, *Innovative Health R&D Financing for Developing Countries: A Menu of Innovative Policy Options*, 28 HEALTH AFF. 974, 975 (2009) (reporting that the treatments for TB require six months' administration and the treatments for Chagas disease and leishmaniasis are toxic); Monique F. Mrazek & Elias Mossialos, *Stimulating Pharmaceutical Research and Development for Neglected Diseases*, 64 HEALTH POL'Y 75, 78 (2003) (reporting that treatments for many neglected diseases are toxic; cannot be used by pregnant women, the elderly, or children; or require administration and treatment protocols that are ill-suited for resource- and infrastructure-poor settings).

<sup>19</sup> GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at ix (noting that program coverage targets for lymphatic filariasis, schistosomiasis, soil-transmitted helminthiases, and trachoma will not be met, especially in Africa and Southeast Asia, and that only 8% of people with schistosomiasis had access to high-quality medicines); see also Mrazek & Mossialos, *supra* note 18, at 76-79 (describing the low rates of implementation for many malaria preventative strategies).

<sup>20</sup> Over a twenty-year period, even a partially effective malaria vaccine could avert 10,000 deaths and 16,000 severe cases of malaria per million people in malaria-endemic countries. A vaccine to prevent dengue fever would reduce

serious threat to the efficacy of treatments for malaria and TB and will likely emerge as a problem for other neglected diseases as well.<sup>21</sup>

### C. Tremendous Progress

Over the last decade, there has been a substantial increase in the attention on global health, including developing new and improving existing treatments for neglected diseases. Most of this increased attention has taken two forms.

First, funding for neglected disease R&D has increased dramatically, with annual funding reaching almost \$1.5 billion in 2007.<sup>22</sup> The majority of that funding has come from two sources: the Bill & Melinda Gates Foundation and the NIH.<sup>23</sup> The biopharmaceutical industry contributed 14 percent of that funding, mostly in the form of in-kind transfers of technology, expertise, and training.<sup>24</sup> The majority of neglected disease R&D funding has gone to two diseases: malaria and TB.<sup>25</sup> The remaining neglected diseases continue to receive relatively little funding for R&D.<sup>26</sup>

Second, new partnerships have formed between private, philanthropic, and government actors seeking to meet the health needs of the world's poor. Product development partnerships (PDPs) are structured collaborations between commercial and public sector partners that combine drug and biotech company expertise with public sector funding and understanding of the developing country health needs and regulatory requirements.<sup>27</sup> Collaboration between the biopharmaceutical industry and public sector entities has existed for some time, but the current generation of PDPs represents a more systematic attempt to develop and adapt a portfolio of health technologies for neglected diseases.<sup>28</sup> PDPs are now responsible for most neglected disease R&D.<sup>29</sup> Some PDPs are disease-, technology-, and even product-specific; others have broader mandates and manage a sizable portfolio of drug, vaccine, and diagnostic candidates.<sup>30</sup>

82% of the mortality and morbidity of a mosquito borne viral disease that causes tens of millions of illnesses and thousands of deaths annually. An improved typhoid vaccine could help reduce the estimated 216,000 deaths that occur annually, mostly in school age children and adults. Hecht et al., *supra* note 18, at 974-75.

<sup>21</sup> Preventative chemotherapy is increasingly being used to prevent the spread of certain neglected diseases. As the use of this treatment expands, drug resistance is likely to become a problem. GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 148. See generally RACHEL NUGENT, EMMA BACK, & ALEXANDRA BEITH, THE RACE AGAINST DRUG RESISTANCE, A REPORT OF THE CTR. FOR GLOBAL DEV. DRUG RESISTANCE WORKING GROUP (2010) (describing, in detail, the challenge presented by drug resistance to global health).

<sup>22</sup> This data has been adapted from the George Institute's G-Finder Report to exclude HIV/AIDS funding. See MARY MORAN ET AL., THE GEORGE INST. FOR INT'L HEALTH, G-FINDER REPORT: NEGLECTED DISEASE RESEARCH AND DEVELOPMENT—HOW MUCH ARE WE REALLY SPENDING 13 (2008).

<sup>23</sup> *Id.* at 13, 41.

<sup>24</sup> *Id.* at 13, 38-40.

<sup>25</sup> *Id.* at 13.

<sup>26</sup> In 2007, R&D funding for leprosy, Buruli ulcer, trachoma, rheumatic fever, and typhoid and paratyphoid fever ranged between US\$1 to 9 million. *Id.* at 43.

<sup>27</sup> CHRISTOPHER J. ELIAS, CTR. FOR STRATEGIC AND INT'L STUDIES, POLICIES AND PRACTICES TO ADVANCE GLOBAL HEALTH TECH.: GLOBAL HEALTH POL. CTR. REPORT 6-7 (2009).

<sup>28</sup> LEVINE ET AL., *supra* note 3, at 19.

<sup>29</sup> See MARY MORAN ET AL., WELLCOME TRUST, THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG DEVELOPMENT 8 (2005) (reporting that PDPs manage more than three-quarters of the neglected disease drug development projects).

<sup>30</sup> See generally Roy Widdus, *Public-Private Partnerships for Health: Their Main Targets, Their Diversity, and Their Future Directions*, 79 BULL. OF THE WORLD HEALTH ORG. 713 (2001) (reporting the significant variation in the structure of PDPs and their purposes). Examples of PDPs include Aeras Global TB Vaccine Foundation ([www.aeras.org](http://www.aeras.org)), Drugs for Neglected Diseases Initiative (DNDi) ([www.dndi.org](http://www.dndi.org)), Global Alliance for Tuberculosis

Most PDPs are based in developed countries, but several partner with research institutions and manufacturers in Brazil, China, India, and other middle-income countries.<sup>31</sup>

As a result of the hard work of the PDPs and the support of the Bill & Melinda Gates Foundation, NIH, and other donors, dozens of new candidate technologies for neglected diseases are now in the pipeline.<sup>32</sup> There is, for example, a malaria vaccine candidate in late-stage clinical testing which, if approved, will be the first vaccine against malaria (a disease that kills 900,000 annually) and the first vaccine against a parasite approved for use in humans. There are nine new TB vaccine candidates in clinical trials worldwide, including the first late-stage infant study of a TB vaccine in over 80 years. These therapies could help reduce the 8 million new TB infections and 1.7 million TB-related deaths that happen each year.<sup>33</sup> Several promising vaccine candidates are in late-stage clinical development for dengue fever, which results in substantial morbidity and productivity losses in millions of people worldwide.<sup>34</sup> The PATH Meningitis Vaccine Project, a Bill & Melinda Gates Foundation-funded partnership between PATH and the World Health Organization, successfully developed and introduced a meningococcal A conjugate vaccine, which could prevent more than 1 million cases of illness over the next decade in sub-Saharan Africa.<sup>35</sup> These drug, vaccine, and diagnostic candidates could be, for many neglected diseases, the first new therapies and prevention tools in a generation and, for others, simply the first.<sup>36</sup>

## II. GAPS AND INEFFICIENCIES IN THE DEVELOPMENT AND DELIVERY PATHWAY

Health technology R&D is a multi-step process. The discovery of a novel drug or vaccine candidate that may be effective against a target disease is only the first step. Developers must next demonstrate the safety and efficacy of that candidate technology in a series of clinical trials and register it for use in disease-endemic settings. Finally, the product must be manufactured, distributed, and supported for effective use by target populations.

As the candidate technologies for neglected diseases move to late-stage clinical

Drug Development ([www.tballiance.org](http://www.tballiance.org)), Institute for One World Health ([www.oneworldhealth.org](http://www.oneworldhealth.org)), Malaria Vaccine Initiative ([www.mmv.org](http://www.mmv.org)), the Medicines for Malaria Venture ([www.mmv.org](http://www.mmv.org)), and the Pediatric Dengue Vaccine Initiative (PDVI) ([www.pdvi.org](http://www.pdvi.org)).

<sup>31</sup> Peter J. Hotez, *Neglected Tropical Disease Control in the 'Post-American World,'* 4(e812) PLOS NEGLECTED TROPICAL DISEASES 1, 2-3 (2010).

<sup>32</sup> See Joshua Cohen et al., *Development of and Access to Products for Neglected Diseases,* 5(e10610) PLOS ONE 1, 4 (2010) (concluding that, as of July 2009, there were 69 drugs, vaccines, and diagnostics in the pipeline for neglected diseases, not including those for HIV/AIDS); David de Ferranti et al., *Innovative Financing for Global Health: Tools for Analyzing the Options* 15-16 (Brookings Institution: Global Health Financing Initiative Working Paper No. 2, 2008) (describing the product candidates for neglected disease in greater detail).

<sup>33</sup> L.F. Barker et al., *New Tuberculosis Vaccines: What is in the Pipeline?,* in THE ART & SCIENCE OF TUBERCULOSIS VACCINE DEVELOPMENT (Norazmi, Acosta, & Sarmorto eds., 2010) (available at <http://tbvaccines.usm.my/?q=chapter/23/new-tuberculosis-vaccines-what-pipeline>).

<sup>34</sup> Bruce Y. Lee et al., *Economic Value of Dengue Vaccine in Thailand,* 84 AM. J. TROP. MED. HYG. 764 (2011).

<sup>35</sup> See, e.g., Samba O. Sow et al., *Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans,* 364 NEW ENG. J. MED. 2293 (2011) (describing the successful development by the PATH Meningitis Vaccine Project of the meningitis vaccine).

<sup>36</sup> *FDA's Role in Improving the Development Pathway for Neglected Disease Therapies: Hearing to Discuss the FDA's Review Process for Products to Treat Rare Diseases and Neglected Tropical Diseases Before the Subcomm. on Agriculture, Rural Development, the Food and Drug Administration, and Related Agencies of the U.S. Senate Comm. on Appropriations,* 111th Cong. (2010) (testimony of Thomas J. Bollyky).

development, several challenges loom. These challenges threaten not only the promise of the current candidate products for those in need, but call into question the long-term sustainability of neglected disease R&D generally.

*A. Insufficient Funding for Clinical Development and Product Introduction*

Clinical trials to support the registration of drugs and vaccines have generally become increasingly expensive and steadily less productive in recent years.<sup>37</sup> The reasons are manifold, but two factors bear emphasis here as they apply with equal force to neglected disease trials.<sup>38</sup>

First, changes in clinical trial regulation have contributed to the growth of clinical trial duration and cost.<sup>39</sup> Regulation of clinical trials is essential for ensuring the safety, well-being, and rights of clinical trial subjects and the validity of clinical data. However, since 1962, when the U.S. Food and Drug Administration (FDA) and other national regulators began regulating the clinical development process, the number of regulations has ballooned, with new regulations adopted in response to specific scandals.<sup>40</sup> There has been little subsequent streamlining of these regulations to address scientific advances.<sup>41</sup> Consequently, costs have risen significantly.<sup>42</sup>

Second, commercial practices, adopted to reduce the risk of regulatory non-compliance of new product development trials, have transformed clinical trial practices, increasing their cost and complexity.<sup>43</sup> A successful trial completed rapidly in patients with a common condition in the developed world can lead to revenues of tens or hundreds of millions of dollars a year for a pharmaceutical company. Under this commercial model, reductions in the risk of regulatory noncompliance are a greater priority than the costs of the trial.

These regulatory models and clinical practices are being imported into developing countries and adopted for clinical trials for neglected disease drugs and vaccines. Developing country governments adopt the regulations and guidance of the FDA and the European Medicines Agency (EMA) because their rules are publicly available and familiar to the commercial clinical trial sponsors that developing country governments hope to attract. Likewise, the same commercial clinical trial practices are employed broadly, including in highly cost-sensitive clinical trials in neglected disease-endemic countries, because they are familiar and

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<sup>37</sup> See GOV'T ACCOUNTABILITY OFFICE (GAO), *NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS*, GAO-07-49 15 (2006) (indicating that the rate of NDAs fell over 38% between 1994-2004).

<sup>38</sup> See Thomas J. Bollyky, *Bridging the Gap: Improving the Clinical Development and Regulatory Pathway for Health Products for Neglected Diseases* 3-6 (Ctr. for Global Dev. Working Paper No. 217, 2010) for a longer discussion of these reasons.

<sup>39</sup> See Lelia Duley et al., *Specific Barriers to the Conduct of Randomized Trials*, 5 *CLINICAL TRIALS* 40, 44 (2008) (arguing that clinical trial regulations have made even "low cost" trials expensive).

<sup>40</sup> See GOV'T ACCOUNTABILITY OFFICE, *supra* note 37, at 31 (citing industry analyst reports and a European Commission study that determined that FDA began to demand more complex regulatory requirements in response to series of high-profile drug withdrawals between 1997 and 2001).

<sup>41</sup> See generally Robert M. Califf, *Clinical Trials Bureaucracy: Unintended Consequences of Well-Intentioned Policy*, 3 *CLINICAL TRIALS* 496 (2006); see also Seth Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 *NEW ENG. J. MED.* 816, 818 (2009).

<sup>42</sup> Bollyky, *supra* note 38, at 5 (describing how data monitoring requirements, which were adopted in response to specific instances of fraud, now frequently comprise a third to two-thirds of a clinical trial's total cost).

<sup>43</sup> *Id.* at 6 (describing the proliferation of new business models to intermediate clinical trials including contract research organizations (CROs), site management organizations (SMOs), and data management organizations (DMOs)).

accepted practice.<sup>44</sup>

The clinical development costs for neglected disease therapies therefore remain high, despite the expertise, commitment, and improved efficiencies that PDPs have brought to neglected disease R&D.<sup>45</sup> Three quarters of R&D costs are incurred after drugs and vaccines enter pre-clinical testing.<sup>46</sup> One of the developers of the most advanced and promising malaria vaccine candidate estimated that as much as \$400 million had been spent on its development and further clinical trials would yet be needed.<sup>47</sup> Another recent report estimated that \$6 to 10 billion would be needed to complete the clinical development of all the candidate drugs for neglected diseases, even with expected rates of attrition in the product pipeline.<sup>48</sup> That estimate did not include vaccines, which represent three-quarters of the products in development to treat neglected diseases.<sup>49</sup> Manufacturing, distribution, and administration costs are additional and can be substantial, particularly if they include the development of new facilities and functioning health service delivery platforms.<sup>50</sup> Estimates of the funding required to sustain neglected disease R&D under current cost assumptions are daunting.<sup>51</sup>

The funding available for neglected diseases is insufficient to complete the clinical development, manufacturing, and delivery of all the candidate products in the neglected disease pipeline under current cost assumptions, even with expected attrition in that pipeline.<sup>52</sup> NIH and

<sup>44</sup> See, e.g., MORAN ET AL., *supra* note 29, at 25-26 (noting that, in 2005, one-third of PDPs used CROs to support their R&D process, which generally charged full commercial rates for their services).

<sup>45</sup> The true cost of new drug development is a subject of considerable debate. Compare Donald W. Light, Jon Kim Andrus, & Rebecca N. Warburton, *Estimated Research and Development Costs of Rotavirus Vaccines*, 27 VACCINE 6627, 6632 (2009) (estimating actual R&D costs for a rotavirus vaccine could be as low as \$172 million) with Joseph A. DiMasi, Ronald W. Hasen, & Henry G. Grabowski, ASSESSING CLAIMS ABOUT THE COST OF NEW DRUG DEVELOPMENT: A CRITIQUE OF THE PUBLIC CITIZEN AND TB ALLIANCE REPORTS 15 (2004) (defending studies that estimated R&D costs per new drug to be \$802 million, including the cost of failure). The costs of neglected disease R&D may be lower than other drug development projects due, in part, to the lower costs of capital for philanthropic funded programs. Mary Moran, *A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need*, 2 PLOS MEDICINE 828, 830-31 (2005).

<sup>46</sup> GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT, *ECONOMICS OF TB DRUG DEVELOPMENT* 38 (Pekar ed., 2001).

<sup>47</sup> Susan Dentzer, *Eliminating Neglected Diseases in Poor Countries: A Conversation with Andrew Witty*, 28 HEALTH AFF. w411, w413 (2009).

<sup>48</sup> See Paul L. Herrling, *Making Drugs Accessible to Poor Populations: A Funding Model*, in GLOBAL FORUM UPDATE ON RESEARCH FOR HEALTH 152, 152 (2008) (citing a study, commissioned by International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Novartis).

<sup>49</sup> *Drug Approvals for Neglected Diseases Increase*, *supra* note 14.

<sup>50</sup> See LEVINE ET AL., *supra* note 3, at 3, 18 (most R&D costs occur in clinical development and during the start-up of the manufacturing process); see also PATH & the International AIDS Vaccine Initiative, *HPV Vaccine Adoption in Developing Countries: Cost and Financing Issues* 21 (2007) (estimating that the cost of rolling out the human papillomavirus (HPV) vaccine to 80% of those requiring it would be between US\$180 million and US\$300 million by 2016), available at [http://www.rho.org/files/IAVI\\_PATH\\_HPV\\_financing.pdf](http://www.rho.org/files/IAVI_PATH_HPV_financing.pdf) (last visited Oct. 25, 2010).

<sup>51</sup> See Gerard F. Anderson, *Spurring New Research For Neglected Diseases*, 28(6) HEALTH AFF. 1750, 1750 (2009) (reporting that the WHO has estimated that nearly \$150 billion is needed over the next six years for R&D on neglected diseases to treat or protect the one billion people susceptible to these conditions).

<sup>52</sup> See Hecht et al., *supra* note 18, at 976 (reporting that only 40% of the funding that is needed to develop safe and effective TB vaccines by 2015 has actually been committed); MARY MORAN ET AL., THE GEORGE INST. FOR INT'L HEALTH, *THE MALARIA PRODUCT PIPELINE: PLANNING FOR THE FUTURE* 6-7 (2007) (estimating based on current portfolios, approaches, and policies, that approximately US\$561 million to US\$639 million will be needed to cover just the outstanding costs of clinical development and manufacture of new malaria drugs and vaccines in the next five years); LEVINE ET AL., *supra* note 3, at 20 (reporting that, even at the lowest estimates, pursuing a single malaria candidate vaccine through the later phases of clinical trials, regulatory approval, and production would exceed the total public and philanthropic funds presently available for the development of malaria vaccines generally).



the Bill & Melinda Gates Foundation already provide the bulk of the nearly \$1.5 billion in annual funding for neglected disease R&D.<sup>53</sup> With government budgets tightening and new donor funding scarce, that figure is unlikely to increase significantly in the near term.<sup>54</sup>

Charity and corporate social responsibility have motivated some pharmaceutical company investment in neglected diseases, mostly into internal R&D programs co-funded by external partners such as PDPs. Increased private investment in neglected disease R&D will depend on the prospects for a commercial return, the probability of success, and the timeframe in which that success may be achieved.<sup>55</sup> This calculus does not currently favor increased investment in part because of the gaps and inefficiencies, described below, in the development and delivery of these health technologies to the patients.

### *B. Limited Understanding of Neglected Diseases and the Affected Populations*

The probability of successfully developing health technologies to address neglected diseases and generating revenues from having done so are limited by our poor understanding of the diseases at issue and the populations that these diseases afflict.

Drug and vaccine development is an inherently uncertain endeavor, with few candidate therapies ever reaching market.<sup>56</sup> In the neglected disease context, that probability is diminished by our limited understanding of the populations involved and the diseases at issue.<sup>57</sup> The genetic characteristics of the populations and socioeconomic settings in which neglected diseases are endemic can differ in substantial ways from those encountered in the developed world.<sup>58</sup> We lack basic understanding of the causation and epidemiology of some neglected diseases.<sup>59</sup> Research into neglected diseases and the populations they afflict may be improving but remains modest.<sup>60</sup>

<sup>53</sup> Again, this data is adapted from the George Institute's G-Finder to exclude HIV/AIDS funding. See G-FINDER REPORT, *supra* note 22, at 13.

<sup>54</sup> See Gerard F. Anderson, *Spurring Mew Research for Neglected Diseases*, 28 HEALTH AFF. 1750, 1752 (2009) (reporting that NIH spends less than 4% of its total budget on neglected diseases, other industrialized countries spend approximately the same percentage, and international aid agencies such as the WHO, United Nations Children's Fund (UNICEF), U.S. Agency for International Development (USAID), and the World Bank have focused primarily on getting vaccines, drugs, and biologics to the people who need them, not developing them); Henry Grabowski, *Increasing R&D Incentives for Neglected Diseases*, in INTERNATIONAL PUBLIC GOODS AND TRANSFER OF TECHNOLOGY UNDER A GLOBALIZED INTELLECTUAL PROPERTY REGIME, 472 (Maskus & Reichman eds., 2005).

<sup>55</sup> HANNAH E. KETTLER, U.K. OFFICE OF HEALTH ECON., NARROWING THE GAP BETWEEN PROVISION AND NEED FOR MEDICINES IN DEVELOPING COUNTRIES 30 (2000).

<sup>56</sup> LEVINE ET AL., *supra* note 3, at 18 (reporting that for one drug to be approved by the FDA, a firm typically screens 5,000–10,000 compounds. Of these, an average of 250 compounds survive preclinical testing, only 5 are approved for clinical testing, and only 1 succeeds in obtaining FDA approval).

<sup>57</sup> KETTLER, *supra* note 55, at 30 (arguing that the probability of successful drug or vaccine development depends on the existing science, technology, and research base involved and the risks associated with the target use and population for the product).

<sup>58</sup> Bollyky, *supra* note 38, at 1.

<sup>59</sup> See, e.g., GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES, *supra* note 4, at 62 (noting that basic research is still needed to understand the biology and epidemiology of the causative agent of Buruli ulcer, a fast-emerging disease).

<sup>60</sup> Compare Jean O. Lanjouw & Iain M. Cockburn, *New Pills for Poor People? Empirical Evidence after GATT*, 29 WORLD DEV. 265, 275-79 (2001) (finding that less than one and a half percent of all biomedical research papers published between 1980 and 1999 made any reference to tropical diseases) with Carlos M. Morel et al., *Health Innovation Networks to Help Developing Countries Address Neglected Diseases*, 309 SCIENCE 401 (2005) (reporting

Under these circumstances, it is likely that the outcome for vaccine and drug development for neglected diseases will be, at best, a partial success.

Revenues for a drug or vaccine depend on the market size, the expected market share for the product, and the price that can be charged.<sup>61</sup> The poverty of those afflicted with neglected diseases will continue to limit the price that may be charged for the treatment in the foreseeable future.<sup>62</sup> Even where neglected disease treatments with a low per-dose cost are available, we have limited understanding of how to reach the millions of patients in need of those products. Health systems in many low-income countries are rudimentary; there are few health care professionals in these settings. In some of these countries, the percentage of patients with access to medical care facilities is as low as 10 percent.<sup>63</sup>

### C. *Insufficient Clinical Research and Regulatory Capacity*

Definitive studies of the safety and efficacy of a drug or vaccine must be conducted in settings where individuals suffer from the target disease and under the circumstances in which the product will be ultimately used. For neglected diseases, these settings are generally in low- and middle-income countries with, in many cases, limited clinical research capacity and underdeveloped regulatory systems.<sup>64</sup>

Weak clinical research and regulatory capacity block access to drugs and vaccines in many of the countries where they are needed most.<sup>65</sup> Many neglected disease-endemic countries, particularly in Africa, have weak or no national regulatory authorities (NRAs) and little ethical review capacity.<sup>66</sup> It can be difficult to conduct ethical, sufficiently regulated trials in such environments. The lack of regulatory and ethics capacity undermines the safety of subjects and

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increases in research and patenting in developing countries and the indications that innovative capacity is being directed toward neglected disease R&D ).

<sup>61</sup> KETTLER, *supra* note 55, at 34.

<sup>62</sup> John H. Barton, *TRIPS and the Global Pharmaceutical Market*, 23 HEALTH AFF. 146, 148-49 (2004).

<sup>63</sup> KETTLER, *supra* note 55, at 34.

<sup>64</sup> Neglected diseases are endemic primarily in Africa, Asia, and tropical regions of the Americas, with a lower prevalence in the Middle East. Musgrove & Hotez, *supra* note 7, at 1693. *See also* Bollyky, *supra* note 38, at 7-9 (conducting an analysis of the clinical trials registered on the international clinical trials registry, Clinicaltrials.gov, which revealed that two-thirds of the clinical trials for neglected diseases that initiated subject recruitment between 2003 and 2009 occurred in disease-endemic regions, with nearly a third of the total occurring in Africa—a proportion that only increases for later state trials).

<sup>65</sup> Andrew Witty, *New Strategies for Innovation in Global Health: A Pharmaceutical Industry Perspective*, 30 HEALTH AFF. 118, 123 (2011).

<sup>66</sup> *See* Diadié Maïga et al., *Regulatory Oversight of Clinical Trials in Africa: Progress Over the Past 5 Years*, 27 VACCINE 7249, 7250 (2009) (citing a WHO Regional Office for Africa (WHO/AFRO) study that determined 36% of its member states lack IRBs); WORLD HEALTH ORG., ASSESSMENT OF MEDICINES REGULATORY SYSTEMS IN 22 WHO MEMBER STATES: A SUMMARY OF RESULTS (2009) (assessing 22 developing country NRAs in Asia, Africa, and Latin America between 2001 and 2005 and concluding that two-thirds of these countries had weak or no mechanisms for regulating clinical trials or exerting proper oversight on clinical investigation); WORLD HEALTH ORG., REPORT ON WORKSHOP ON REGULATORY PROCEDURES FOR CLINICAL EVALUATION OF VACCINE, ADDIS ABABA, SEPT. 21-23, 2005 6-11 (2005) (concluding that only four of thirteen attending governments had national regulatory authorities involved in clinical trials review, authorization of importation of clinical batches, and/or inspection of clinical trial sites); NETWORKING FOR ETHICS ON BIOMEDICAL RESEARCH IN AFRICA, FINAL REPORT 94 (2006) (determining that that 10 of 15 African countries assessed either lacked legal or regulatory requirements for the ethical conduct of human clinical research or had not implemented the legislation that existed).

the validity and integrity of clinical data.<sup>67</sup> Unclear laws and regulatory requirements hinder trial planning, initiation, and patient recruitment. The risk of non-compliance and harm to subjects deters private investment. Even in neglected disease-endemic countries with sophisticated NRAs, the regulation and ethical review of clinical trial applications is frequently delayed due to limited resources and regulatory backlogs.<sup>68</sup> The shortcomings of these regulatory environments are compounded by the complexity of the diseases and products involved and the frequent need to conduct neglected disease product trials with pediatric subjects and in multiple countries.<sup>69</sup>

*D. Product Registration Processes are Protracted and Poorly Coordinated*

After a long and costly development process, a substantial delay in products reaching market would be an obvious deterrent to drug and vaccine development.<sup>70</sup> Unfortunately, this is often the case for neglected disease R&D where product registration requires navigating multiple, poorly coordinated regulatory processes, which can add years of delay to product introduction.

Before a drug or vaccine may be sold, distributed, or marketed, the appropriate regulatory authority for that jurisdiction must confirm the safety, quality, and efficacy of that product. Neglected disease product registration typically involves three regulatory processes. First, sponsors submit their novel therapy for marketing approval by a developed country regulator, like the FDA, in order to minimize the risk of liability and to take advantage of that regulator's resources, experience in assessment, and clear protocols and rules.<sup>71</sup> Upon receiving that regulatory approval, the sponsor will next submit its product to the World Health Organization (WHO) prequalification program, which ensures that drugs, vaccines, and diagnostics meet prescribed standards of quality, safety, and efficacy and are appropriate for procurement by United Nations agencies.<sup>72</sup> The WHO is not a regulatory authority; a novel therapy must first be approved by an NRA which the WHO deems to be "fully functional" (such as the FDA) in order to be eligible for prequalification. Nevertheless, many developing country regulators will not approve a novel therapy without WHO prequalification. Finally, once the WHO has prequalified a novel drug or vaccine, the sponsor can finally submit it to the NRA in the target neglected disease-endemic country for its approval.

These processes are sequential, poorly coordinated, and plagued by limitations in the relevant expertise and capacity at each step. The FDA may be unfamiliar with the neglected disease at issue (since it is not endemic in the United States) and the conditions and patient populations in which the product will be used. These gaps in expertise often delay and reduce the

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<sup>67</sup> 21 C.F.R. § 312.120 (2009) (requiring, for admissibility, that foreign data come from clinical trials in which subjects gave their informed consent, an institutional review board (IRB) approved and monitored the trial, and internationally recognized GCP were followed).

<sup>68</sup> See Bollyky, *supra* note 38, at 9 & n. 35; Deborah Cook et al., *Randomized Trials in Vulnerable Populations*, 5 CLINICAL TRIALS 61, 66 (2008) (noting that it took 9-18 months in some developing country trials to obtain import licenses as well as national regulatory approval). See, e.g., Kathryn Senior, *Experts Warn of Regulatory Hurdles Stalling Drug Trials* 8 LANCET INFECTION 281, 281 (2008) (reporting that tuberculosis-related trials were delayed due to regulatory hurdles in South Africa and Tanzania by two years and one year, respectively).

<sup>69</sup> Bollyky, *supra* note 38, at 11-16.

<sup>70</sup> Grabowski, *supra* note 54, at 463.

<sup>71</sup> See Bollyky Testimony, *supra* note 36.

<sup>72</sup> *Prequalification of Medicines Programme*, WORLD HEALTH ORG.: ESSENTIAL MEDICINES AND PHARMACEUTICAL POLICIES, <http://apps.who.int/prequal/> (last visited Oct. 10, 2011).

value of the FDA's assessment.<sup>73</sup> The assembly of an *ad hoc* assessment team can slow WHO prequalification; the average time for the WHO to prequalify drugs and vaccines is 18 and 24 months, respectively.<sup>74</sup> Many NRAs have limited experience, resources, and mandates for assessing, approving, and registering innovative products. The average time required for a novel drug or vaccine to advance through this multistep regulatory pathway is approximately three years.<sup>75</sup>

### III. THE INSUFFICIENCY OF PUSH AND PULL STRATEGIES TO ADDRESS THESE GAPS

To be effective, strategies to improve access to neglected disease treatments must address the root causes of their inaccessibility. Much of the attention to treatment access has focused on the international regulation of intellectual property, new incentives for R&D, and innovative financing strategies. The long-term sustainability of neglected disease R&D may require initiatives in all of these areas, but none is well-suited to address the aforementioned gaps and inefficiencies in the product development and delivery pathway that threaten to keep neglected disease therapies out of the hands of patients.

#### A. *The Role of Intellectual Property in Neglected Disease R&D*

Intellectual property (IP) rights, which have long dominated treatment access scholarship and debates,<sup>76</sup> are at present neither the cause nor the solution for the inaccessibility of neglected disease treatments.<sup>77</sup> In recent years, pharmaceutical firms have been willing to donate or voluntarily license their IP relevant to diseases and products for which there is little demand in affluent markets.<sup>78</sup> The NIH Technology Transfer Office and many major universities have likewise adopted humanitarian licensing policies that apply to neglected diseases.<sup>79</sup> Many of the

<sup>73</sup> Bollyky Testimony, *supra* note 36.

<sup>74</sup> GEORGE INST., REGISTERING NEW DRUGS: THE AFRICAN CONTEXT 13, 18 (2010).

<sup>75</sup> *Id.*

<sup>76</sup> Much of the legal and economic literature on improving treatment for the poor has focused on compulsory licensing and alternative strategies for improving access to neglected disease-relevant IP. *See, e.g.*, Leticia Orti et al., *A Kernel for Open Source Drug Discovery in Tropical Diseases*, 3(e418) PLOS NEGLECTED TROPICAL DISEASES 1 (2009) (open source drug development); Andrew L. Hopkins, Michael J. Witty, and Solomon Nwaka, *Mission Possible*, 449 NATURE 166, 169 (2007) (patent clearinghouses and public patent databases); Kevin Outterson, *Patent Buy-Outs for Global Disease Innovations for Low- and Middle-Income Countries*, 32 AM. J.L. & MED. 159 (2006) (patent buyouts); Jean O. Lanjouw, *A Patent Policy for Global Diseases*, 16 HARV. J.L. & TECH. 86 (2002) (territorial segmentation of essential medicine-related patent rights with preferential terms for developing country markets).

<sup>77</sup> It should be emphasized that the foregoing discussion applies to neglected diseases only, as defined in this paper, not HIV/AIDS or other diseases that have a substantial presence in developed country markets.

<sup>78</sup> Dentzer, *supra* note 47, at w411 (describing the launch of a GlaxoSmithKline (GSK)-led patent pool for neglected diseases, which the CEO Andrew Witty described as very unlikely to include patents relating to the discovery or development of particular molecules for neglected disease because "if [GSK] had molecules that worked in the disease, presumably we would have developed them."); Witty, *supra* note 65, at 120 (describing Pfizer and Astra-Zeneca programs to open their compound libraries of molecular entities to support research into African sleeping sickness, visceral leishmaniasis, Chagas disease, and the malaria caused by *Plasmodium falciparum*).

<sup>79</sup> *See, e.g.*, *Neglected Diseases: Technologies Available for Licensing from NIH/FDA and Non-Profit Institutions*, U.S. NAT'L INSTS. OF HEALTH, TECH. TRANSFER OFFICE, [http://www.ott.nih.gov/Technologies/NegDis\\_ovrvw.aspx](http://www.ott.nih.gov/Technologies/NegDis_ovrvw.aspx) (last visited Dec. 17, 2010); Carol Mimura, *Nuanced Management of IP Rights: Shaping Industry-University*

health technology candidates for neglected diseases are based on IP licensed from private firms or universities on preferential terms.<sup>80</sup>

Conversely, IP rights do not appear to have tilted health R&D priorities towards the needs of the poor.<sup>81</sup> Harmonization and strengthened protection for pharmaceutical patents under the World Trade Organization Agreement of Trade Related Aspects of Intellectual Property Rights (TRIPS) has not improved the effective demand for health technologies in developing countries.<sup>82</sup> As stated in a recent Rand Corporation study on IP and developing countries, “where market demand is small and accumulated knowledge is weak, evidence on the ability of IP measures to alter the direction of innovations is difficult to find.”<sup>83</sup> High-income country governments and philanthropic foundations have continued to need to heavily subsidize neglected disease research and development.<sup>84</sup>

The role of IP in neglected disease product development may well change with the continued economic development of low- and middle-income countries. Industry, governments, and academic institutions may become less willing to share neglected disease- relevant IP if it could be used to generate commercial returns. For the time being, however, IP is a second order issue when persistent challenges of clinical development, registration, and product introduction are hindering the development and delivery of neglected disease treatments now.

### B. *New Incentives for Neglected Disease R&D*

There has been significant interest recently in strategies to stimulate neglected disease R&D. These strategies may be divided into two categories: “push” and “pull.” Push strategies fund pharmaceutical R&D directly—for example, with research grants and subsidies<sup>85</sup>—or

*Relationships to Promote Social Impact, Chapter 9 in WORKING WITHIN THE BOUNDARIES OF INTELLECTUAL PROPERTY* 269-95 (Rochelle Dreyfuss, Harry First, & Diane Zimmerman eds., 2010).

<sup>80</sup> For example, the most advanced and promising malaria vaccine candidate, RTS,S, was invented and developed by GlaxoSmithKline in collaboration with the United States Walter Reed Army Institute of Research and licensed to the PATH Malaria Vaccine Initiative, with the support of the Bill & Melinda Gates Foundation, for pediatric clinical development in Africa. See *RTS,S Frequently Asked Questions*, PATH MALARIA VACCINE INITIATIVE, [http://www.malariavaccine.org/files/UpdatedPublicFAQ\\_21April2010.pdf](http://www.malariavaccine.org/files/UpdatedPublicFAQ_21April2010.pdf) (last visited Oct. 1, 2011).

<sup>81</sup> See Jean O. Lanjouw & Margaret MacLeod, *Statistical Trends in Pharmaceutical Research for Poor Countries*, in WHO COMMISSION ON INTELLECTUAL PROPERTY RIGHTS, INNOVATION AND PUBLIC HEALTH 2, <http://www.who.int/intellectualproperty/studies/stats/en/index.html> (last visited Oct. 1, 2011); Lanjouw & Cockburn, *supra* note 60, at 286-87.

<sup>82</sup> See AIDAN HOLLIS & THOMAS POGGE, *THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL 5* (2008); Joseph E. Stiglitz, in *Economic Foundations of Intellectual Property Rights*, 57 DUKE L.J. 1693, 1720-21 (2008); Grabowski, *supra* note 54, at 472.

<sup>83</sup> HASSAN ET AL., *supra* note 13, at 32.

<sup>84</sup> Intellectual property, however, has played a modest but important role as a tool with which foundations, governments, and PDPs have structured and managed collaborations in neglected disease R&D. See *Medicines for Malaria Venture*, MMV AND INTELLECTUAL PROPERTY RIGHTS, [http://www.mmv.org/sites/default/files/uploads/docs/policy\\_documents/MMV\\_and\\_Intellectual\\_Property\\_Rights.pdf](http://www.mmv.org/sites/default/files/uploads/docs/policy_documents/MMV_and_Intellectual_Property_Rights.pdf) (last visited Dec. 18, 2010); ANTONY TAUBMAN, INITIATIVE ON PUBLIC-PRIVATE PARTNERSHIPS FOR HEALTH, PUBLIC-PRIVATE MANAGEMENT OF INTELLECTUAL PROPERTY FOR PUBLIC HEALTH OUTCOMES IN THE DEVELOPING WORLD: THE LESSONS OF ACCESS CONDITIONS IN RESEARCH AND DEVELOPMENT AGREEMENTS (2004).

<sup>85</sup> There is a long history of public medical research councils like the U.S. National Institutes of Health, philanthropic foundations, and NGOs funding basic medical research. The U.S. government alone spent over \$100 billion in 2008 on R&D. See Mark Boroush, *New NSF Estimates Indicate that U.S. R&D Spending Continued to Grow in 2008*, INFOBRIEF (National Science Foundation), Jan. 2010, at 1, available at <http://www.nsf.gov/statistics/infbrief/nsf10312/nsf10312.pdf>. The U.S. National Institute of Allergy & Infectious

reduce its costs and risks—through vehicles such as expedited regulatory review, tax credits,<sup>86</sup> and liability protection.<sup>87</sup> Pull strategies motivate private sector engagement in pharmaceutical R&D by improving the size and/or certainty of the potential return on investments. Pull mechanisms include intellectual property rights,<sup>88</sup> prizes,<sup>89</sup> grants of market exclusivity,<sup>90</sup> advance market commitments (AMCs),<sup>91</sup> transferable vouchers for priority regulatory<sup>92</sup> or patent application review,<sup>93</sup> and purchase funds.<sup>94</sup> Some programs, like the U.S. Orphan Drug Act, incorporate both push and pull strategies.<sup>95</sup> A few push and pull programs have been

Diseases is the originator of the vast majority of U.S. federally funded grants for neglected disease research. *See* Lanjouw & Cockburn, *supra* note 60, at 275-79.

<sup>86</sup> *See, e.g.*, Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (consolidating and expanding the FDA's expedited development and accelerated approval regulations to allow for fast-track designation for drugs with the potential to address unmet medical needs for serious or life-threatening conditions). Fast-track development programs can take advantage of accelerated approval based on surrogate end points, rolling submissions of applications for marketing approval, and priority review.

<sup>87</sup> Mechanisms exist in the United States to address potential liability for childhood and avian influenza vaccines, but do not yet exist or cover the neglected disease products for use in the developing world. *See National Vaccine Injury Compensation Program*, U.S. DEPT. OF HEALTH & HUMAN SERVICES, HEALTH RESOURCES & SERVICES ADMIN. (HRSA), <http://www.hrsa.gov/vaccinecompensation> (last visited Nov. 27, 2010); Public Readiness and Emergency Preparedness Act of 2005 (PREPA), 42 U.S.C. §§ 247d-56d (2008).

<sup>88</sup> The intellectual property system promotes innovation by giving firms that create new inventions a temporary, exclusive right over their products. This right allows them to sell their products at higher prices than would be possible in a competitive market. That potential for supracompetitive profits spurs innovation.

<sup>89</sup> There has been explosion of interest in the potential use of prizes instead of intellectual property to encourage innovation in pharmaceuticals. *See generally* Benjamin N. Roin, *Intellectual Property Versus Prizes: A Policy-Lever Analysis* 13-15 (Feb. 25, 2010) (unpublished manuscript) (on file at [http://isites.harvard.edu/fs/docs/icb.topic619738.files/Paper\\_06\\_03-02\\_Roin.pdf](http://isites.harvard.edu/fs/docs/icb.topic619738.files/Paper_06_03-02_Roin.pdf)) (providing an overview of recent interest in prizes among policymakers, legislators, and academics in economics, law, philosophy, and medicine); HOLLIS & POGGE, *supra* note 82, at 5 (proposing a fund that would reward products based on a global assessment of that product's impact relative to the health impact of other products registered with that fund); James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHICAGO-KENT L. REV. 1519 (2007) (proposing an international research treaty to finance pharmaceutical innovation with a prize-like fund).

<sup>90</sup> The U.S. Orphan Drug Act (ODA) of 1983 uses market exclusivity, among other incentives, to stimulate R&D on products for diseases that are rare in the United States (defined as those that afflict fewer than 200,000 Americans). Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (current version at 21 U.S.C. §§ 360aa-60dd (2000)). Neglected diseases, which have little presence in the U.S., qualify as rare under ODA.

<sup>91</sup> The AMC, developed by Michael Kremer, the Center for Global Development, and others, is a contractual commitment between donors and drug or vaccine manufacturers in which donors agree to subsidize the provision of products that meet defined technical specifications and demand requirements in low- and middle-income countries. *See* LEVINE ET AL., *supra* note 3.

<sup>92</sup> *See generally* David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313 (2006) (proposing that firms that successfully develop a new product for neglected diseases be rewarded with a transferable voucher for an expedited regulatory review of another drug product that is submitted for FDA approval).

<sup>93</sup> Request for Comments on Incentivizing Humanitarian Technologies and Licensing Through the Intellectual Property System, 75 Fed. Reg. 57261 (Sept. 20, 2010).

<sup>94</sup> The Global Fund to Fight AIDS, TB, and Malaria ([www.theglobalfund.org/en/](http://www.theglobalfund.org/en/)) and the Global Alliance for Vaccines and Immunization ([www.gavialliance.org](http://www.gavialliance.org)) fund purchases of already licensed drugs and vaccines and existing health technologies. There have been calls to expand the mandates of these organizations to fund health technology R&D. Hecht et al., *supra* note 18, at 980.

<sup>95</sup> In addition to market exclusivity (a pull mechanism), the U.S. Orphan Drug Act provides grants, tax incentives for clinical development, and other push mechanisms to stimulate R&D in rare diseases. *See* Orphan Drug Act, *supra* note 90.

implemented specifically for neglected diseases;<sup>96</sup> most remain in the concept phase.

Incentives make it more attractive for private actors to put their minds to the problems of the poor, but are unlikely to be sufficient on their own. Prizes, AMCs, and innovation funds must be backed by donor and government resources, which are scarce. Other incentives which require little upfront funding such as extended market exclusivity have worked well in the United States because qualifying drugs, once they receive FDA approval, are subsequently reimbursed by private insurance companies as well as by the Medicare and Medicaid programs.<sup>97</sup> Government and private health insurance programs in many low-income countries remain modest and are still insufficient to address the needs of the poor.<sup>98</sup> The state of Connecticut spends more on health than the 38 low-income countries in sub-Saharan Africa combined.<sup>99</sup>

If the recent pneumococcal vaccine AMC and other recent prize fund proposals are any guide, mobilizing the funding required for neglected disease R&D prizes and incentives schemes will be daunting.<sup>100</sup> A 2008 report by the Dalberg Advisors, for example, estimates that while \$500 million had been spent building the current pipeline of candidate drugs for neglected diseases, an estimated \$6 to \$10 billion would be needed to complete their clinical development.<sup>101</sup> Other projections of development costs for the neglected disease product

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<sup>96</sup> In February 2007, the Bill & Melinda Gates Foundation and five governments (Canada, Italy, Norway, Russia, and the United Kingdom) committed \$1.5 billion to launch the first AMC to encourage private firms to manufacture and supply pneumococcal vaccines for strains prevalent in low and middle-income countries. See *Pneumococcal AMC—Funding & Finance*, GAVI ALLIANCE, <http://www.gavialliance.org/funding/pneumococcal-amc/> (last visited Oct. 2, 2011). The Food and Drug Administration Amendments Act of 2007 empowered the FDA to award a transferable “priority review voucher” to any company that gains FDA approval for a new pharmaceutical or biological targeted to a defined list of neglected tropical disease. See 21 U.S.C. § 360n (2007). In April 2009, FDA awarded the first priority review voucher to Novartis for Coartem tablets to treat malaria. Press Release, United States Food and Drug Administration, FDA Approves Coartem Tablets to Treat Malaria (Apr. 8, 2009) (available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149559.htm>). At the time of writing, Novartis had not used, transferred, or sold its voucher, nor had it released an internal valuation of its worth; and the FDA had not yet awarded any other priority review vouchers.

<sup>97</sup> Accordingly, the U.S. Orphan Drug Act has not spurred significant R&D investment in neglected diseases, even though these diseases qualify as rare under the statute due to their small presence in the United States. Grabowski, *supra* note 54, at 463, 472. Between 1983 and May 2008, the FDA granted approximately 2,000 orphan drug designations and approved 325 orphan drug products; only 10 of these products were for neglected diseases—all of which had limited or no value because their formulation and pricing were inappropriate for developing country settings. GEORGE INST., *supra* note 74, at 9.

<sup>98</sup> Chunling Lu et al., *Public Financing of Health in Developing Countries: A Cross-National Systematic Analysis*, 375 LANCET 1375, 1379-82 (2010) (reporting that domestic health spending is increasing in absolute terms in low- and middle-income countries in most regions of the world, particularly in parts of Latin America, the Middle East, and Asia, but less so in sub-Saharan Africa). See also A.K. Shiva Kumar et al., *Financing Healthcare for All: Challenges and Opportunities*, 377 LANCET 668, 668 (2011) (reporting that public spending on health in India is 0.94% of its gross domestic product, among the lowest in the world and the reason why private expenditures represent 78% of the Indian health spending).

<sup>99</sup> *World Development Indicators (2008)*, WORLD BANK, <http://data.worldbank.org/products/data-books/WDI-2008> (last visited Oct. 5, 2011). Overall, U.S. health spending in 1998 was US\$4,000 per person; sub-Saharan African nations’ spending constituted only US\$8 per person, with some countries spending as little as US\$2 per person. *Id.*

<sup>100</sup> The AMC scaling up manufacturing for pneumococcal vaccines required \$1.3 billion. GAVI ALLIANCE, *supra* note 96. See also HOLLIS & POGGE, *supra* note 82, at 10 (estimating the proposed Health Impact Fund would require substantial government upfront funding, including initial commitments of at least US\$6 billion per year).

<sup>101</sup> See Paul L. Herrling, *Making Drugs Accessible to Poor Populations: A Funding Model*, GLOBAL FORUM UPDATE ON RESEARCH FOR HEALTH 152 (2008) (citing a study, commissioned by International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Novartis).

pipeline are similarly daunting.<sup>102</sup>

Governments and foundations can employ contingent rewards, which pay only upon the achievement of successful neglected disease R&D outcomes, but these mechanisms are often unattractive to governments and funders with budgeting rules that require more certainty. Further, prizes and contingent rewards for neglected disease R&D are undermined by the same gaps and inefficiencies in the development and delivery of these health technologies as those described above. If regulatory gaps and inefficiencies continue to delay neglected disease product registration and delivery, potential rewards tied to their achievement will be discounted. Likewise, if potential investors perceive neglected disease technology R&D to be intractable due to limited understanding of the diseases and populations involved, then the size of a push or pull incentive to conduct that R&D becomes irrelevant.<sup>103</sup>

### C. *Innovative Financing*

Recent years have seen an explosion of interest in new ways to finance health services and products for the world's poor. Examples of innovative financing initiatives include the International Finance Facility for Immunization,<sup>104</sup> which uses long-term funding pledges by rich country governments to collateralize commercial debt financing, and UNITAID,<sup>105</sup> which uses revenues from levies on the purchase of airline tickets to subsidize and improve access to drugs, malaria bed nets, and nutritional supplements for children. There are also dozens of still unimplemented innovative financing proposals for global health R&D, including levies on financial transactions, bond funds, IP-backed securities, and various risk insurance schemes.<sup>106</sup>

While it is clear that additional funds are needed to develop and deliver the contents of the neglected disease product pipeline, there are limits to the funding that may be mobilized through innovative financing tools. The potential funding sources for neglected disease R&D are local governments, foreign government aid programs, philanthropic or intergovernmental institution donors, and private investors. Low- and middle-income country government health spending is increasing, particularly in the Middle East, Latin America, and Asia, but remains modest overall.<sup>107</sup> Developed country governments are constrained politically from imposing new taxes to address the health needs of individuals living in low-income countries, particularly

<sup>102</sup> See Hecht, Wilson, & Paliwala, *supra* note 18, at 976 (reporting that only 40% of the funding that is needed to develop safe and effective TB vaccines by 2015 has actually been committed); MORAN ET AL., *supra* note 52, at 6-7 (estimating based on current portfolios, approaches, and policies, that approximately US\$561 million to US\$639 million will be needed to cover just the outstanding costs of clinical development and manufacture of new malaria drugs and vaccines in the next five years); LEVINE ET AL., *supra* note 3, at 20 (reporting that, even at the lowest estimates, pursuing a single malaria candidate vaccine through the later phases of clinical trials, regulatory approval, and production would exceed the total public and philanthropic funds presently available for the development of malaria vaccines generally).

<sup>103</sup> HASSAN ET AL., *supra* note 13, at 31 (noting that the supply of invention is completely inelastic (zero output at all levels of prices) when there is insufficient science and technical capacity to make the sought-after technological leap).

<sup>104</sup> See *About IFFIm*, INT'L FINANCE FACILITY FOR IMMUNIZATION, [http://www.iff-immunisation.org/01\\_about\\_iffim.html](http://www.iff-immunisation.org/01_about_iffim.html) (last visited on Nov. 27, 2010).

<sup>105</sup> A tax on airline tickets sold in seven countries provides 72% of UNITAID's funding for malaria, HIV/AIDS, and TB programs. *How Innovative Financing Works*, UNITAID, <http://www.unitaid.eu/en/about/innovative-financing-mainmenu-105/163.html> (last visited Oct. 19, 2011).

<sup>106</sup> Ferranti et al., *supra* note 32, at 2-3 (listing the various outstanding proposals that existed as of 2008).

<sup>107</sup> Lu et al., *supra* note 98, at 1379. It is also unclear how much of that increased funding is being devoted to health technology R&D or drug or vaccine reimbursement.



if those taxes are on unrelated services and activities.<sup>108</sup> New philanthropic donor funding is scarce. Future revenues from health technologies can be front-loaded through bond offerings and other financial vehicles targeting private investors, but this approach reduces future incentives for product introduction and delivery and may have modest potential benefits for health technologies for which there will be limited returns.<sup>109</sup>

#### IV. BETTER, CHEAPER, FASTER: A MORE SUSTAINABLE STRATEGY FOR TREATMENT ACCESS FOR NEGLECTED DISEASES

Vision, strategic investments, and hard work built the current pipeline of candidate technologies for neglected diseases. Realizing the promise of that pipeline and ensuring its future vitality will require not only new incentives and increased funding, but also greater attention to how clinical development, registration, and introduction of these technologies can be improved to reduce unnecessary costs, delays, and risks. This section describes four complementary and relatively inexpensive approaches for bringing the costs and finances for neglected disease R&D into a more sustainable balance.

##### A. *Sensible Clinical Trial Practices*

Insistence on approximating rich-country clinical development models under difficult poor-country conditions will only lead to a consequent escalation of delays, complications, and costs. More efficient approaches to clinical development in resource-poor settings are needed for neglected disease R&D projects to successfully and sustainably achieve their goals.

New initiatives—designed to reduce the cost of large, randomized clinical trials without sacrificing scientific rigor, quality assurance, or the safety of trial subjects—are underway. The FDA's Office of Critical Path Programs and Duke University have launched a public-private partnership, the Clinical Trials Transformation Initiative (CTTI), to research and develop practices that would increase the efficiency and quality of clinical trials.<sup>110</sup> Clinical research groups from McMaster, Duke, and Oxford Universities have initiated the Sensible Guidelines for the Conduct of Clinical Trials Project to advocate for the simple design of large-scale trials in order to reduce costs and improve patient participation in these trials.<sup>111</sup> One study performed by the Sensible Guidelines group using these large, simple trial design strategies demonstrated a 35 percent clinical trial cost reduction when modeled against a commercial design of a large-scale, late-stage trial.<sup>112</sup> Considering such trials frequently cost several hundred million dollars, these practices could generate substantial savings.

While this research is exciting and promising, it has focused on the demands of

<sup>108</sup> Hecht et al., *supra* note 18, at 977.

<sup>109</sup> Ferranti et al., *supra* note 32, at 9.

<sup>110</sup> Currently, over 50 organizations comprise CTTI, including U.S. government and international agencies, industry representatives (pharmaceutical, biotech, device, and clinical research organizations), patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties. *See* CLINICAL TRIALS TRANSFORMATION INITIATIVE, <https://www.trialstransformation.org/> (last visited Sept. 30, 2011).

<sup>111</sup> *Sensible Guidelines for the Conduct of Clinical Trials*, UNIV. OF OXFORD CLINICAL TRIAL SERVICE UNIT & EPIDEMIOLOGICAL STUDIES UNIT, <http://www.ctsu.ox.ac.uk/projects/sg> (last visited Oct. 16, 2011).

<sup>112</sup> *See generally* Eric Eisenstein et al., *Sensible Approaches for Reducing Clinical Trials*, 5 *CLINICAL TRIALS* 75 (2008) (focusing on selective site visits combined with electronic data capture, centralized monitoring, and statistical sampling techniques).

cardiovascular, cancer, and other industrialized world products. It may not be applicable to clinical trials for vaccines or drugs for neglected diseases where highly vulnerable subjects and limited research and regulatory capacity may require more elaborate safeguards and low-technology solutions. Clinical practices and procedures should reflect the scientific and policy goals of the trial and be well-adapted to the particular demands of the setting, subjects, and intervention at issue.

The Clinical Trials and Regulatory Pathways Working Group at the Center for Global Development is working to adapt this emerging research on sensible trials to the needs of the neglected disease pipeline and the challenges of the clinical trials performed for regulatory approval.<sup>113</sup> The primary purposes of this effort are not to identify practices that should be adopted in all neglected disease trials, but to demonstrate that efficiencies are possible and to propose a practical and workable mechanism by which regulators, sponsors, and donors may collaborate on achieving those efficiencies on trial-by-trial basis.

### *B. Regional Regulatory Pathways for Neglected Disease Clinical Trials*

While philanthropists and private companies have increasingly seen the value in devising products for neglected diseases, a coherent plan for building the requisite regulatory infrastructure to develop and deliver these therapies to patients is lacking. With global health budgets tightening and new donor funding scarce, a country-by-country approach to regulatory capacity-building is not feasible.

A single, regional pathway with integrated regulatory and ethics reviews for clinical trials would have significant potential benefits for reducing the cost, delays, and risks of neglected disease product clinical development and for participating neglected disease-endemic countries.

First, it would improve the quality of clinical trial regulation and the protection of the clinical trial subjects in participating disease-endemic countries by pooling scarce regulatory resources. Such a regional pathway would also provide a platform for foundations, non-governmental organizations (NGOs), governments, and intergovernmental entities seeking to support clinical trial regulatory capacity building in disease-endemic regions and developing countries, but without the resources to duplicate those investments on a country-by-country basis.<sup>114</sup>

Second, a regional, integrated pathway for regulation of clinical trials would help reduce regional inconsistency in regulatory and ethics requirements and their interpretation, as well as limit the number of regulatory and ethics reviews and compliance obligations required for multi-country clinical trials. In doing so, such a pathway would expedite trial initiation and reduce the cost and uncertainty of conducting clinical trials in participating neglected disease-endemic countries.

Third, reductions in the cost, duration, and risks of conducting clinical trials in disease-endemic countries would improve the use of scarce existing resources for neglected disease

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<sup>113</sup> *The Clinical Trials and Regulatory Pathways for Neglected Diseases Working Group*, CTR. FOR GLOBAL DEV., [http://www.cgdev.org/section/initiatives/\\_active/ghprn/workinggroups/clinical\\_trials](http://www.cgdev.org/section/initiatives/_active/ghprn/workinggroups/clinical_trials) (last visited Oct. 16, 2011).

<sup>114</sup> See, e.g., OFFICE OF INSPECTOR GENERAL, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS, OEI-01-08-00510 (2010) (reporting on the FDA's interest in building the capacity of foreign regulators to help address the exponential growth in overseas clinical trial activity); Donald L. Barlett & James B. Steele, *Deadly Medicine*, VANITY FAIR, Jan. 2011, at 58 (describing the recent growth of clinical trials conducted internationally to support product registration in the United States and some of the concerns arising as a result).

product clinical development, reduce barriers to private sector investment, and expedite patients' access to treatments.

Finally, better protection for subjects and a more cost- and time-efficient regional regulatory approach with more certain review timelines and procedures would help attract private clinical trial activity to neglected disease-endemic regions and investment in local and regional research capacity.

Regional regulatory cooperation is not without its challenges. Governments value their sovereignty in regulatory affairs and the independence and local accountability of their regulatory authorities. Regional regulatory cooperation requires a supporting infrastructure—agreements and coordination mechanisms—to direct activities and support the exchange of confidential information, applications, and inspection reports. Generating multi-state regulatory architecture is already challenging; it may be doubly difficult for countries that may not have such regulatory infrastructure and legal frameworks domestically.

There are, however, precedents for such regional regulatory pathways involving both developed and developing countries. For example, the EMA offers a centralized procedure for pharmaceutical product registration with a single application, single evaluation, and a single review process allowing direct access to all national markets of the European Union (EU).<sup>115</sup> It is an intriguing model for several reasons. First, the principle motivation for establishing the centralized procedure was not regulatory harmonization, but rather the pooling of regional regulatory expertise on a difficult regulatory problem.<sup>116</sup> Second, the centralized procedure uses common documentation and regulatory requirements, but did not require the dissolution of participating NRAs, which is often a sensitive issue of national sovereignty and employment. Third, the centralized procedure has been scalable: it was initially mandatory only for high-technology products and expanded over time.

These features have contributed to the success of the EMA centralized procedure. In contrast to other more protracted international regulatory harmonization efforts, the centralized procedure required just six years to move from concept to implementation.<sup>117</sup> Within its first year of formal operation, two-thirds of the centralized procedure applications filed by industry were done so voluntarily.<sup>118</sup> The U.S. Government Accountability Office estimates that the centralized procedure saved an estimated 40 percent of the cost and much of the time required to obtain separate marketing authorizations in, at that time, the 15 EU member states.<sup>119</sup>

Another example is the African Vaccine Regulatory Forum (AVAREF), a network of 19 countries that the WHO identified as likely settings for clinical trials of priority vaccines. In

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<sup>115</sup> Council Regulation 726/2004, 2004 O.J. 136 (L 214) (EC).

<sup>116</sup> European Community (EC) NRAs lacked expertise in the novel techniques needed to assess biotechnology products. The centralized procedure enabled these regulators to work together on biotechnology product registration applications with the intention of achieving a common decision. It was initially known as the “concertation procedure.” See Council Directive 87/22, 1986 O.J. 38 (L 015) (EEC); see also GOV'T ACCOUNTABILITY OFFICE, REPORT TO THE CHAIRMAN, UNITED STATES SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES, EUROPEAN UNION DRUG APPROVAL: OVERVIEW OF NEW EUROPEAN MEDICINES EVALUATION AGENCY AND APPROVAL PROCESS 4 (1996).

<sup>117</sup> In contrast, the EU mutual recognition process required more than 25 years to establish and has been far less popular than the centralized procedure. See Elaine M. Healy & Kenneth Kaitin, *The European Agency for the Evaluation of Medicinal Products' Centralized Procedure for Product Approval: Current Status*, 33 DRUG INFO. J. 969, 970 (1999).

<sup>118</sup> OVERVIEW OF NEW EUROPEAN MEDICINES EVALUATION AGENCY AND APPROVAL PROCESS, *supra* note 116, at 12.

<sup>119</sup> *Id.* at 10.

order to improve their lack of technical expertise and capacity, AVAREF countries have engaged in an *ad hoc* joint regulatory and ethics review process for several vaccine clinical trials in Africa.<sup>120</sup> While the results of that review have not been binding, the AVAREF process has been widely viewed as successful at improving the capacity and coordination of participating NRAs and ethics committees and encouraging the use of defined review timelines and common documentation.<sup>121</sup>

Finally, the United Kingdom's Integrated Research Application System (IRAS), which offers a single, integrated application point for ethics review of clinical trials in the UK, is another promising model.<sup>122</sup> In the UK and elsewhere, institutional review boards (IRBs) protect the rights and welfare of clinical trial subjects and ensure that clinical trials meet national and international standards for biomedical ethics.<sup>123</sup> Over the years, however, the number of IRBs has greatly proliferated and their role has substantially expanded.<sup>124</sup> With trials now often involving multiple sites and dozens of IRBs, the costs and time imposed by this IRB system can be substantial. Under the IRAS system, a single, national IRB performs the ethics reviews of clinical trials in the UK, leaving issues of local ethical concern to be assessed by local IRBs. The system reduces bureaucratic burden, particularly for multi-site studies. It helps eliminate duplication; study wide checks are performed only once. The system also improves national ethics review consistency and creates a single, secure online database and document repository.

Drawing from these three examples, a potential model for a regional cooperation on clinical trial regulation and ethics reviews of neglected disease technologies would be a centralized procedure/joint review model in which participating NRAs and IRBs jointly review clinical trial applications and perform inspections of trial sites.<sup>125</sup> A multilateral regulatory cooperation agreement between participating governments should create the centralized procedure/joint review process, which should be expanded to include more products and parties over time.<sup>126</sup> This agreement should establish the foundation for sustainable, predictable,

<sup>120</sup> See generally Diadié Maïga et al., *Joint Reviews and Inspections: Strategic Forms of Collaboration for Strengthening the Oversight of Vaccine Clinical Trials in Africa*, 28 VACCINE 571 (2009).

<sup>121</sup> See generally *id.*

<sup>122</sup> UNITED KINGDOM INTEGRATED RESEARCH APPLICATION SYSTEM, <http://www.myresearchproject.org.uk> (last visited Oct. 20, 2011).

<sup>123</sup> FDA investigational new drug regulations define institutional review boards as the oversight bodies "designated by an institution to review, approve initiation of and conduct periodic review of biomedical research involving human subjects. [Their p]rimary purpose is to assure protection of rights and welfare of human subjects." 21 C.F.R. § 56 (2010).

<sup>124</sup> IRBs once only assessed whether clinical testing met ethical standards; today, IRBs examine trial protocols to ensure written consent forms are sufficiently simple and clear, monitor the progress of testing, and maintain substantial records of activities. Each IRB imposes its own ethical standards, consistent with its mandate to protect local community standards. See Bollyky, *supra* note 38, at 4-5; Duley, *supra* note 39, at 44.

<sup>125</sup> The Clinical Trials and Regulatory Pathways Working Group at the Center for Global Development ([http://www.cgdev.org/section/initiatives/\\_active/ghprn/workinggroups/clinical\\_trials](http://www.cgdev.org/section/initiatives/_active/ghprn/workinggroups/clinical_trials)) is in the midst of developing such a model.

<sup>126</sup> Bilateral and plurilateral regulatory cooperation agreements are not a new idea. See Keith Maskus and Yin He, *Trans-Atlantic Regulatory Cooperation in Pharmaceuticals: An Intellectual Property and Trade Perspective* 19-22 (May 8-9, 2008) (unpublished manuscript) (on file with the German Marshall Fund Academic Policy Research Conference, Ford School, University of Michigan, [http://www.fordschool.umich.edu/news/event\\_details/reg\\_coop\\_and\\_comp\\_08/documents/Maskus\\_Paper.pdf](http://www.fordschool.umich.edu/news/event_details/reg_coop_and_comp_08/documents/Maskus_Paper.pdf)) (describing the 1997 U.S.-EU Mutual Recognition Agreement on pharmaceutical regulatory cooperation, which included a framework agreement and six sectoral annexes). The approach of an international agreement on deep substantive engagement on a few matters, which can then be expanded and increasingly legalized over time, also has precedent in regional economic cooperation, regional trade agreements, and plurilateral approaches to agricultural

plurilateral cooperation on the regulation of clinical trials for neglected disease products, consistent with the domestic and international legal obligations of the parties.<sup>127</sup>

Participation in this agreement should be voluntary and its results, at least initially, non-binding. Governments should have the opportunity to participate and gain confidence in regional clinical trial regulation before being bound by its results. Participation should likewise not require the harmonization or dissolution of underlying NRAs or IRBs, which would raise sensitive issues of national sovereignty and local employment that might deter participation in regional regulatory cooperation.

As in the AVAREF model, the regulatory and ethics review processes should be integrated to promote collaboration between NRAs and IRBs and avoid duplication in their efforts. As in the IRAS system, ethical reviews should be conducted by a regional IRB, leaving only issues of local relevance to national and local IRBs. In order to expedite the joint review process, participating governments should agree to use a common set of regulatory and ethics requirements and protocol and safety-monitoring report formats.<sup>128</sup> In order to address variations in the sophistication of participating NRAs, clinical trial application reviews should be conducted as a group or by pairing regulators with weaker capacities with regulators with stronger expertise and resources. The model should include a formal process for outside assistance, when requested by its constituents, from the FDA, the EMA, or other qualified regulatory authorities.<sup>129</sup>

At the outset, the process should be limited to only one category of products: vaccines for neglected diseases. There is a strong regional orientation to product development trials for

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and environmental standard setting. See Kenneth W. Abbott & Duncan Snidal, *Pathways to International Cooperation*, in *THE IMPACT OF INTERNATIONAL LAW ON INTERNATIONAL COOPERATION: THEORETICAL PERSPECTIVES* 57, 57-60 (Benvenisti & Hirsch, eds., 2004) (citing the formation of the European Union, the North American Free Trade Agreement, the Food and Agriculture Organization, and the UN Environment Program as examples).

<sup>127</sup> To accomplish this goal, the issues covered in such a Framework Agreement would need to include: the objectives, definitions, and scope of cooperation; the identity, responsibilities, and rights of state parties; product eligibility; the eligibility, responsibilities, and rights of applicant clinical trial sponsors; a process for development of common forms and technical, data, and document requirements; treatment of IP and protection of confidential data; the creation of any intermediary advisory or management structure; cooperation on tariffs or other relevant non-tariff barriers; and provisions for entry into force, withdrawal, termination, amendment, dispute resolution, enforcement, and sanctions. Such an agreement could take the form of a memorandum of understanding with key attachments. See Kenneth W. Abbott, *An International Framework Agreement on Scientific and Technological Innovation and Regulation* 2-3 (Jun. 4, 2009) (unpublished manuscript) (on file at [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1414430](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1414430)) (arguing that such international framework agreements have been useful in international environmental law because they are flexible, more easily negotiated than formal treaties, and facilitate the cooperation and involvement of three sets of actors: international (participating states), trans-governmental (constituent regulators and agencies of the state parties), and transnational (relevant private actors with issues at stake)).

<sup>128</sup> Participating NRAs, manufacturers, and trial sponsors seeking to use the regional regulatory pathway would need to enter into confidentiality agreements to allow sharing of proprietary information between national regulatory authorities. See generally Maïga et al., *supra* note 120.

<sup>129</sup> Julie Milstien & Lahouari Belharbi, *Regulatory Pathways for Vaccines for Developing Countries*, 82 *BULL. OF WORLD HEALTH ORG.* 128, 132 (2004) (arguing that a collective, expert committee approach would expand the ability of NRAs in this region to address the needs of the specific epidemiological situation of these countries). Ideally, the EMA and/or the FDA would enter into a memorandum of understanding with the participating governments to provide the necessary technical and/or financial support at expert committee level.

neglected disease.<sup>130</sup> The bulk of the products in development for neglected diseases are vaccines. These products present particularly difficult regulatory and ethical challenges to NRAs and IRBs and would benefit from the pooled regulatory resources of this regional pathway. Limiting the scope of regulatory cooperation would allow participating countries to assess the benefits of a regional approach to clinical trial regulation and address concerns before expanding the scope of that cooperation to other products. Like the EMA centralized procedure, this regulatory pathway could be expanded over time to include other products.

As the benefits of the model are demonstrated to its participants, the process should include the option to become binding.<sup>131</sup> In order to accomplish this goal, the multilateral agreement should include a provision by which the state parties commit that by agreeing to jointly review a clinical trial application, the parties will also abide by the results of that joint review process.<sup>132</sup>

Finally, such a regional regulatory pathway should be linked to clinical research networks, existing regional, intergovernmental economic or public health organizations,<sup>133</sup> or pooled procurement initiatives in order to minimize administrative costs.<sup>134</sup> The pathway would require technical support from the WHO and seed funding from donors, but should be self-supporting over the long-term.<sup>135</sup> A streamlined, regional regulatory pathway with more certain regulatory timelines would be materially valuable to pharmaceutical firms and their investors, who could be harnessed to generate private-sector funding or cross-subsidies for that pathway or

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<sup>130</sup> Bollyky, *supra* note 38, at 15 (conducting an analysis of the clinical trials registered on the international clinical trials registry, Clinicaltrials.gov, which revealed that the majority of multi-country product development trials for neglected diseases had all their sites within a single geographic region).

<sup>131</sup> Alar Irs et al., *Development of Marketing Authorization Procedures for Pharmaceuticals*, in *EVALUATING PHARMACEUTICALS FOR HEALTH POLICY AND REIMBURSEMENT 3* (Freemantle & Hill eds., 2004) (arguing that long-term, successful intergovernmental regulatory cooperation requires a binding legal framework).

<sup>132</sup> This mechanism would be analogous to an arbitration clause or optional protocol of an international treaty for the settlement of disputes. *See, e.g.*, *Optional Protocol Concerning the Compulsory Settlement of Disputes*, Vienna Convention on Consular Relations, Apr. 24, 1963, 21 U.S.T. 325, 596 U.N.T.S. 487 (establishing that parties agreeing to the Optional Protocol can require other parties of that Protocol to submit disputes arising out of the Vienna Convention on Consular Relations to International Court of Justice and agree to be bound by the outcome of that dispute resolution). In this instance, failure to abide with the result of the joint review process, after an appeal procedure, could lead to the state's expulsion from participation in the regional regulatory pathway, rather than financial penalties.

<sup>133</sup> *E.g.*, the Southern African Development Community, Pan American Health Organization, or the Association of Southeast Asian Nations.

<sup>134</sup> *See Procurement Support Services*, THE GLOBAL FUND, <http://www.theglobalfund.org/en/procurement/vpp/> (last visited Oct. 1, 2011); Fredrick M. Abbott & Jerome H. Reichman, *The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines Under the Amended TRIPS Provisions*, 10(4) J. INT'L ECON. L. 921, 921-22 (2007) (proposing a pooled procurement initiative to support treatment access for the poor).

<sup>135</sup> The WHO's technical support and convening power has been critical in launching the existing regional approaches to clinical trial regulation in low- and middle-income countries. *See generally* Maïga et al., *supra* note 120 (describing WHO's involvement in launching and facilitating the development of AVAREF). The U.S. government has multiple programs supporting science, innovation, and development, as well as clinical research capacity for global health that could be expanded to provide initial support to regional approaches to clinical trial regulation. *See, e.g.*, *Fact Sheet on Global Health Research Capacity*, U.S. NAT'L INSTS. OF HEALTH, <http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=74&key=B> (last visited Jan. 6, 2011); Dr. Rajiv Shah, Administrator, United States Agency on International Development, Remarks at USAID on July 13, 2010: *Transforming Development Through Science Technology and Innovation* (Jul. 13, 2010) (transcript available at <http://www.usaid.gov/press/speeches/2010/sp100719.html>) (describing USAID's increased focus and future programs on supporting science, technology, and development to meet global health needs).

development of products for neglected diseases.<sup>136</sup> Fees and the increased commercial clinical trial activity resulting from a more certain, expedited regional regulatory pathway could help induce country participation in the pathway.

### C. *Improved Cooperation on Product Registration*

Significant organizational and logistical challenges undermine the FDA's efforts to review neglected disease therapies intended for foreign use.<sup>137</sup> The challenges are twofold. First, resource limitations and FDA reviewers' unfamiliarity with neglected diseases and the conditions and patient populations in which the product will be used often delay and reduce the utility of the FDA's product assessment.<sup>138</sup> Second, FDA regulatory pathways and programs are not well coordinated with or sufficiently supportive of the other entities involved in developing and approving these products.

There are precedents for addressing these challenges. In 2004, the European Commission established a mechanism, "Article 58," to facilitate developing country registration of medicines for prevention or treatment of diseases of major public health interest but intended exclusively for use outside the EU.<sup>139</sup> Under Article 58, sponsors submit applications equivalent to those used for approval of a product for use in the EU. The EMA conducts a regulatory review that is identical to its review of products for EU marketing authorization. In the Article 58 process, however, the EMA incorporates input from WHO-recommended experts, including from developing countries, on the risks, benefits, and need for the candidate product. Observers from the WHO and relevant developing country NRAs are able to participate as non-voting observers and experts in the product's assessment. If the outcome of that review is positive, the EMA issues a scientific opinion that may be used by the sponsor to secure WHO prequalification of the drug or vaccine. After the scientific opinion is issued, sponsors are required to conduct post-marketing surveillance of the product and submit periodic safety update reports.<sup>140</sup> The EMA has

<sup>136</sup> The use of review fees, in exchange for more certain review timelines, was used to improve regulatory capacity in the U.S. The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and renewed in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV.) Under sections 735 and 736 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 379g-h, the FDA has the authority to assess and collect user fees for certain drug and biologics license applications that are submitted to the agency for review. The FDA sets these fees on a yearly basis.

<sup>137</sup> This section focuses on possible improvements to the U.S. FDA's support for registering neglected disease therapies intended for foreign use, but the strategies offered could be applied by other sophisticated national regulatory authorities with resources seeking to do the same.

<sup>138</sup> For a longer discussion of this issue, see Bollyky Testimony, *supra* note 36.

<sup>139</sup> Commission Regulation 726/2004, *supra* note 115, art. 58 (outlining Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency). Article 58 superseded an EU rule that required the withdrawal of an EU marketing authorization if the product was not marketed in Europe for three years. *See generally* Michael J. Brennan, *The U.S. Food and Drug Administration Provides a Pathway for Licensing Vaccines for Global Diseases*, 6(e1000095) PLOS MEDICINE 1 (2009) (describing the Article 58 process in detail). In order to be eligible for the Article 58 procedure, the product must be intended to prevent or treat diseases of major public health interest as defined by the WHO. *See Article 58 Applications: Regulatory and Procedural Guidance*, EUR. MEDICINES AGENCY, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000157.jsp&mid=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&mid=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d1) (last visited Oct. 1, 2011).

<sup>140</sup> EUR. MEDICINES AGENCY, EMEA PROCEDURAL ADVICE ON MEDICINAL PRODUCTS INTENDED EXCLUSIVELY FOR MARKETS OUTSIDE THE COMMUNITY UNDER ARTICLE 58 OF REGULATION (EC) NO. 726/2004 IN THE CONTEXT OF CO-OPERATION WITH THE WORLD HEALTH ORGANIZATION 19-20 (2009), *available at* [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/02/WC5000](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC5000)

considered only three pharmaceutical products and one vaccine under Article 58, but other products candidate are now in the pipeline.<sup>141</sup> Thus far, the Article 58 review process has required less than three months on average.<sup>142</sup> Incorporation of the WHO and relevant developing country NRAs into the Article 58 process is expected to reduce the time required for prequalification and target country registration.<sup>143</sup>

In conjunction with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the FDA instituted a program to review the safety, efficacy, and quality of HIV/AIDS medication manufactured in countries where they are off-patent, prior to the expiry of those patents in the United States.<sup>144</sup> In this context, the FDA works with eligible sponsors to help prepare applications for this program and for inspections. The FDA prioritizes review of PEPFAR-eligible submissions and, as part of its assessment process, engages with the WHO prequalification program and developing country NRAs to facilitate product registration and adoption.

Building on these precedents, the FDA should facilitate simultaneous, coordinated reviews by all the regulatory entities—the FDA, the WHO, and the developing country NRA—involved in the approval of a potential therapy to minimize duplication of scarce regulatory resources and reduce delays in product approval and introduction. This approach would combine the FDA's resources and expertise in assessing novel and complex therapies with the WHO and developing country NRAs' understanding of neglected disease presentation, local conditions, patient populations, and healthcare delivery platforms.

The FDA should work with the WHO to develop a formal collaborative process in which the FDA would commit to address the requirements for prequalification as part of its approval process and the WHO would commit to an expedited decision on prequalification after FDA approval. This collaborative process should be formalized and its details of operation made public in order to improve its predictability for prospective product developers.

FDA reviews of neglected disease products should include, with the consent of the clinical trial sponsor, WHO and developing country experts as formal observers. The FDA, WHO, and priority developing country NRAs should enter into agreements to share confidential data and inspections reports on neglected disease product submissions.<sup>145</sup> The budgets of FDA advisory committees should be sufficient to enable the active participation of developing country experts. The FDA should also hire more full-time reviewers with neglected disease expertise and experience.

At the same time, the United States and other donors should increase their support for the WHO and developing country NRA partners. The efficiency and productivity of the

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74039.pdf. The effectiveness of this approach is unclear in light of the few products that the EMA has assessed under Article 58.

<sup>141</sup> Julie Milstien & Michael Brennan, PDP Regulatory Discussion Paper: Regulatory Challenges in Ensuring Equitable Access to New Health Products in Low Income Countries 3-4 (2010) (on file at <http://www.conceptfoundation.org/files/PDP%20Regulatory%20Discussion%20Paper.pdf>).

<sup>142</sup> GEORGE INST., *supra* note 74, at 11.

<sup>143</sup> *Id.*

<sup>144</sup> *President's Emergency Plan for AIDS Relief, Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm> (last visited Oct. 1, 2011).

<sup>145</sup> *See, e.g., Memoranda of Understanding and Other Cooperative Arrangements*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm> (last visited Nov. 18, 2010).



development pathway for neglected disease therapies depends on the capacity of the WHO prequalification program and priority developing country NRAs. The FDA should commit additional experienced and qualified FDA reviewers to conduct prequalification assessments on behalf of WHO in priority neglected disease areas or agree to perform a fixed number of neglected disease product dossiers per year. The FDA should initiate a pilot project for one- to two-year rotations of mid-career FDA reviewers into developing country NRAs and WHO prequalification programs to help build the capacity of regulatory counterparts and improve mutual understanding.<sup>146</sup>

Finally, the FDA, the EMA, and other sophisticated national regulatory authorities should enhance their support and guidance for the PDPs and other nontraditional developers that may not have experience with late-stage clinical development or product registration.<sup>147</sup> The FDA should help attract more interest in neglected disease product development by issuing clear and detailed public guidance on the full menu of support services that the FDA offers for neglected disease drug, vaccine, and diagnostic candidate development and registration, including incentives, fee waivers, and accelerated reviews. Further, the FDA should institute a program to work with PDPs and other nontraditional product developers on their submissions to ensure that clinical development plans are both scientifically sound and cost-effective, and to ensure that those developers take full advantage of the tools, incentives, and expedited pathways available to them under FDA programs.<sup>148</sup>

#### D. *Engaging Innovators in Emerging Economies*

Multinational pharmaceutical and large biotechnology companies are making substantial contributions to global health, but may be ill-suited to sustainably address the health needs of the world's poorest over the long-term.<sup>149</sup> The business model of these companies is structured

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<sup>146</sup> If successful, this program could be expanded to other areas such as food and drug safety and serve as the foundation of an FDA version of the successful Epidemic Intelligence Service (EIS) at the U.S. Centers for Disease Control and Prevention. See *Epidemic Intelligence Service*, U.S. CTNS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/eis/index.html>; MARK PENDERGRAST, *INSIDE THE OUTBREAKS: THE ELITE MEDICAL DETECTIVES OF THE EPIDEMIC INTELLIGENCE SERVICE* (2010) (describing the history and tremendous accomplishments of the Epidemic Intelligence Service program).

<sup>147</sup> See *Advancing the Development of Medical Products Used in the Prevention, Diagnosis, and Treatment of Neglected Tropical Diseases: Public Hearing Before the Food & Drug Admin.* 7 (2010) (testimony of Kaitlin Christenson & Florence Kaltovich) (transcript available at <http://www.ghcoalition.org/files/FDAtestimony092310FINAL.pdf>).

<sup>148</sup> The Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997), consolidated and expanded the FDA's expedited development and accelerated approval regulations to allow for fast-track designation for drugs with the potential to address unmet medical needs for serious or life-threatening conditions. Fast-track development programs can take advantage of accelerated approval based on surrogate end points, rolling submissions of applications for marketing approval and priority review.

<sup>149</sup> Morel et al., *supra* note 60. Multinational pharmaceutical firms, however, are increasing their efforts to market existing products in and develop new products specifically for emerging country markets. See Shirley S. Wang & Jonathan D. Rockoff, *Drug Research Gets New Asian Focus*, WALL STREET J. (Dec. 14, 2010), <http://online.wsj.com/article/SB10001424052748703531504575623891891473992.html> (reporting Western pharmaceutical firms' efforts to create drugs for diseases prevalent in Asian markets); Avery Johnson, *Drug Firms See Poorer Nations as Sales Cure*, WALL STREET J. (Jul. 7, 2009), <http://online.wsj.com/article/SB124691259063602065.html> (reporting a push by multinational drug firms to sell already developed products to the working poor in middle-income countries); Thomas J. Bollyky, *Drug Marketing Push in Developing Countries Has Upside and Potential Downside for Poor People*, GLOBAL POL'Y BLOG, CTR.

around generating blockbuster returns on cost-intensive R&D and commercialization practices. Biopharmaceutical companies and institutions in emerging markets offer better long-term prospects for addressing the treatment needs of the world's poorest. The reasons are fourfold.

First, these firms have greater understanding of local markets and consumer needs. Emerging country manufacturers already represent significant shares of the low- and middle-income drug export market.<sup>150</sup> Potential markets for neglected disease technology remain untapped because potential producers and suppliers have not spent sufficient time or energy to understand the needs and limits of that market.<sup>151</sup> This is particularly true in markets where there is some existing and evolving infrastructure to deliver the product, and consumers or their government have some ability, however little, to pay for the product.<sup>152</sup> In these settings, existing medical technology may be modified or delivered in a cost-effective manner that better suits the needs of a patient population that currently has no access to it. For example, an existing vaccine may be modified so it does not require refrigeration (reducing storage and transport costs) or so it may be inhaled instead of injected (reducing the costs of its safe application).

Second, biopharmaceutical companies and institutions in emerging markets may have more incentives to address the diseases that are endemic in their own countries. The public sector in these countries funds and performs much of the health R&D and, thus, may be more motivated by public health goals.<sup>153</sup> Indeed, emerging country research institutions and manufacturers are already engaged in global health projects. This is particularly true in manufacturing and distribution. China is the world's leading producer of penicillin.<sup>154</sup> The Serum Institute of India has a 138-country global distribution network that provides one of every two doses of vaccines worldwide on behalf of United Nations Children's Fund (UNICEF) and Pan American Health Organization programs.<sup>155</sup> Manufacturers in Brazil, Cuba, and Indonesia meet a significant portion of the remaining vaccine requirements for UNICEF's Expanded Program on Immunization.<sup>156</sup>

Third, these emerging country actors have a comparative advantage over multinational corporations in performing lower cost drug, vaccine, and diagnostic manufacturing.<sup>157</sup> Many first

FOR GLOBAL DEV. (Jul. 10, 2009), <http://blogs.cgdev.org/globalhealth/2009/07/pharma-marketing-push-in-developing-countries-has-upside-and-downside-for-poor-people.php> (describing the potential positive and negative consequences of this marketing push for global health).

<sup>150</sup> See *id.* (reporting that, in dollar terms, two-thirds of India's exports and three-quarters of Brazilian drug exports go to other low- and middle-income countries).

<sup>151</sup> Bill Gates, Chairman, Microsoft Corporation, Speech at Davos 2008: Creative Capitalism (Jan. 2008) (transcript available at <http://www.egovmonitor.com/node/16877>).

<sup>152</sup> C.K. PRAHALAD, *THE FORTUNE AT THE BOTTOM OF THE PYRAMID* 23-46 (2006).

<sup>153</sup> See, e.g., Morel et al., *supra* note 60; Nandini K. Kumar et al., *Indian Biotechnology—Rapidly Evolving and Industry Led*, 22 *NATURE BIOTECH.* DC31 (2004) (noting that the Indian national government oversees the National Health Programs and provides policy direction and, together with state governments, funding for substantial amounts of biomedical research).

<sup>154</sup> Morel et al., *supra* note 60.

<sup>155</sup> Sarah E. Frew et al., *The Indian And Chinese Health Biotechnology Industries: Potential Champions Of Global Health?* 27 *HEALTH AFF.* 1029, 1030 (2008). See also Morel et al., *supra* note 60 (reporting that the Serum Institute is also the world's leading manufacturer of diphtheria-pertussis-tetanus vaccine); CHERI GRACE, DEPT. FOR INT'L DEV. HEALTH SYS. RESOURCE CENTRE, *THE EFFECT OF CHANGING INTELLECTUAL PROPERTY ON PHARMACEUTICAL INDUSTRY PROSPECTS IN INDIA AND CHINA: CONSIDERATIONS FOR ACCESS TO MEDICINE* 23 (2004).

<sup>156</sup> Morel et al., *supra* note 60.

<sup>157</sup> Hannah E. Kettler & Rajiv Modi, *Building Local Research and Development Capacity for the Prevention and Cure of Neglected Diseases: The Case of India*, 79 *BULL. OF THE WORLD HEALTH ORG.* 742, 743 (2001); *Indian and*

generation emerging country drug and vaccine manufacturers specialize in high-volume, low-margin production.<sup>158</sup> Lower manufacturing costs allows for more affordably priced treatments, an important factor in access to medicines for neglected diseases.<sup>159</sup>

Finally, firms in Argentina, Brazil, China, India, and other emerging markets have been rapidly improving innovative biopharmaceutical capacity with lower R&D costs than their affluent country counterparts.<sup>160</sup> Emerging country biopharmaceutical companies are responsible for the development of an increasing number of technologies for neglected diseases.<sup>161</sup> A recent survey of emerging country biopharmaceutical companies reported a collective pipeline of 123 products targeting neglected diseases, with 69 products already on the market.<sup>162</sup> Nearly half of this pipeline is diagnostics, many of which are low-cost and environment appropriate. Lower cost drug development and delivery of drugs, vaccines, and diagnostics reduce demands on scarce global health funds and improve the commercial viability of neglected disease R&D.<sup>163</sup>

Some PDPs have established partnerships with emerging country research institutions and manufacturers.<sup>164</sup> These partnerships have allowed PDPs to lower manufacturing costs, develop treatments appropriate for patients, and scale up production. For example, the Program for Appropriate Technology in Health (PATH)'s Meningitis Vaccine Project has partnered with the Serum Institute of India to produce vaccines at a fixed, low per-dose price many times lower than developed country bidders.<sup>165</sup> Most PDPs, however, do not yet have developing country

*Chinese Health Biotechnology Industries*, *supra* note 155, at 1039 (noting the large domestic talent pool and relatively low labor-costs in India and China).

<sup>158</sup> See generally PRAHALAD, *supra* note 152; *Indian And Chinese Health Biotechnology Industries*, *supra* note 155, at 1033 (reporting that generic products continue to account for the majority of China's \$3 billion biopharmaceutical market and India's \$2 billion biotechnology market).

<sup>159</sup> *Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 133.

<sup>160</sup> *See id.* at 1035-36 (describing ambitious Chinese and Indian government programs to develop their biotechnology sectors); *Frugal Healing*, *ECONOMIST* (Jan. 22, 2011), <http://www.economist.com/node/17963427> (describing the rapid growth of low cost medical technology innovation in China and India).

<sup>161</sup> *Id.* at 1030 (reporting that Shanghai United Cell Biotech has developed the only tablet formulation of cholera vaccine; India's first indigenously developed recombinant DNA product drove down the price of the hepatitis B vaccine from US\$15 per dose for the imported product to US\$0.50; Shanta Biotechnics has launched a new oral cholera vaccine that offers broader, longer-lasting protection at one-third the per dose price of the existing option).

<sup>162</sup> Frew et al., *supra* note 15, at 1764.

<sup>163</sup> *Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 1030; Kettler & Modi, *supra* note 157, at 745. *See, e.g.*, Morel et al., *supra* note 60 (reporting that innovative re-engineering of the manufacturing process in India, Cuba, and Brazil for the hepatitis B vaccine has greatly improved its cost-effectiveness and availability).

<sup>164</sup> The Drugs for Neglected Diseases Initiative was established by Médecins sans Frontières, Institut Pasteur, the Indian Council for Medical Research, the Kenya Research Institute, the Oswaldo Cruz Foundation in Brazil, and the Malaysian Ministry of Health. DRUGS FOR NEGLECTED DISEASES INITIATIVE, <http://www.dndi.org/> (last accessed Oct. 20, 2011). The Human Hookworm Vaccine Initiative works in collaboration with FIOCRUZ/Bio-Manguinhos and the Butantan Institute of Brazil on developing new treatments. *Partners*, SABIN VACCINE INSTITUTE, <http://www.sabin.org/vaccine-development/partners> (last visited Dec. 20, 2010).

<sup>165</sup> *See Developing a Meningococcal A Conjugate Vaccine*, MENINGITIS VACCINE PROJECT, <http://www.meningvax.org/developing-conjugate-vaccine.php> (last visited Dec. 20, 2010); *see also* MMV-supported Artesunate Receives WHO Prequalification, MEDICINES FOR MALARIA VENTURE, <http://www.mmv.org/newsroom/news/mmv-supported-iv-artesunate-receives-who-prequalification> (last visited Dec. 20, 2010) (reporting that a partnership with Guilin Pharmaceutical Co. Ltd in China helped MMV successfully develop an intravenous malaria treatment for severe malaria patients, who are often unconscious or too ill to consume an orally administered medication); *Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 1039 (noting that the GAVI Alliance funds Indian biotechnology firms Panacea Biotec, Serum Institute of India, and Shantha Biotechnics to increase sales of pentavalent, polio, measles, and hepatitis B vaccines).

partners and those that do often restrict that arrangement to manufacturing.<sup>166</sup>

While emerging country innovation for global health is promising, its sustainability is uncertain. As emerging country companies and institutions build their capacity for biopharmaceutical innovation, they are demonstrating diminished interest in investing in neglected disease technologies for which the market is unlikely to provide a high return.<sup>167</sup> Emerging country pharmaceutical R&D increasingly targets more lucrative markets with more defined regulatory processes and better-understood diseases (e.g., cancer, diabetes).<sup>168</sup>

Emerging country research institutions and manufacturers are the best hope for sustainable R&D for neglected disease treatments, but cannot be expected to pursue neglected disease R&D unless it is in their economic interest to do so and there is adequate support for their efforts. This support should be provided in three ways.

First, existing push and pull programs for encouraging neglected disease R&D should target the participation of emerging country biopharmaceutical firms. To do so, the design of these programs must be well-adapted to the distinct cost structures, skills, and strategic capabilities of low- and middle-income country biopharmaceutical companies.<sup>169</sup>

Second, governments, foundations, and other donors should offer incentives such as matching grants and technical support to encourage emerging country governments to target neglected diseases and the poor, locally and abroad, in their industrial and regulatory policies. Emerging country governments should, conversely, join the U.S. and other governments that support neglected disease R&D with grants, market exclusivity, tax credits, expedited regulatory approval, and other rewards for neglected disease research.<sup>170</sup> No one country or philanthropic foundation can or should bear the burden of building incentives and carrying out research for neglected disease products.

Third, foundations and other donors should establish and fund an advisory network to provide business support to emerging firms seeking to develop and manufacture health technologies for neglected diseases.<sup>171</sup> Strategic investments and incentives to encourage joint ventures and other collaborations between multinational research-based firms, capable emerging manufacturers, and global health financing vehicles should facilitate greater inclusion of emerging market companies.<sup>172</sup>

Finally, expanded efforts are needed to help strengthen the capacity of regulators in developing countries that are responsible for increasing pharmaceutical exports to developed and

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<sup>166</sup> *Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 1039.

<sup>167</sup> Morel et al., *supra* note 60. A recent survey revealed a decline in Indian pharmaceutical R&D expenditure directed toward products specifically suited for developing country markets, from 16% in 1998 to 10% in 2003. Lanjouw & MacLeod, *supra* note 81, at 2-3.

<sup>168</sup> HASSAN ET AL., *supra* note 13, at 33; *Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 1035-36; *see also* Kettler & Modi, *supra* note 157, at 745.

<sup>169</sup> *See* Kettler & Modi, *supra* note 157, at 746; *see, e.g.*, Frew et al., *supra* note 15, at 1770-72 (noting that innovative emerging economy companies, particularly smaller firms, tend to lack upfront risk capital and international business expertise).

<sup>170</sup> *See also* Witty, *supra* note 65, at 123 (arguing that developed country public sector institutions such as the UK Department for International Development, the U.S. Trade Representative and USAID should encourage emerging economies to speed their investment in the pharmaceutical sector).

<sup>171</sup> Frew et al., *supra* note 15, at 1769-73 (proposing a “Global Health Accelerator” which would provide these business support services by matching emerging firms working on neglected disease projects to pro bono, high-quality consulting, accounting, and business support services).

<sup>172</sup> *See Indian and Chinese Health Biotechnology Industries*, *supra* note 155, at 1030; *see also* Morel et al., *supra* note 60.

developing countries alike. The FDA, the EMA, and other developed country regulators cannot establish the necessary regulatory control, oversight, and surveillance of the pharmaceutical products that their own countries import from these markets, let alone those exported to poor country markets.<sup>173</sup> The inspections and quality control of drug products will depend on local regulatory authorities and industry. The regulatory authorities or local businesses in many developing countries, however, do not have the resources and expertise to conduct the necessary stringent regulatory reviews or establish adequate quality and safety management systems. Out of self-interest as well as in support of global health objectives, the FDA and other developed country regulators must devote sufficient resources to pursuing regulatory cooperation and capacity-building efforts with developing countries that export the highest volume of drug products.<sup>174</sup>

## CONCLUSION

A combination of philanthropic and governmental generosity, NGO perseverance, and industry charity has built a pipeline of neglected disease treatments that is fuller than ever before. These candidate products provide hope for the millions who suffer from neglected diseases without another prospect of relief.

Manifold challenges, however, threaten the potential of this product pipeline and the current momentum behind neglected disease R&D. Late-stage clinical development of these candidate products is slow and expensive, perhaps prohibitively so. Trials must be conducted with highly vulnerable subjects in environments with limited research and regulatory capacity and, often, across multiple jurisdictions with conflicting rules, standards, and procedures. Product registration is protracted, deterring investment in neglected disease R&D and delaying patient access to treatment. Product delivery efforts to resource- and infrastructure-poor settings are costly and often ineffective.

No single incentive scheme, R&D innovation model, or innovative financing mechanism will address these challenges. Prizes, grants, and open-source drug development models can stimulate creative research and fill the product pipeline for neglected diseases, but are less useful in achieving the process efficiencies most needed to realize and sustain neglected disease R&D efforts.<sup>175</sup> Increased funding for neglected disease R&D is certainly needed, but the prospects are dim for innovative financing schemes satisfying the substantial resource demands of neglected disease R&D under current cost assumptions.

Much greater attention must be paid to the process improvements, practices, and collaborations that can improve access to neglected disease treatments by making their development, registration, and introduction cheaper, faster, and less uncertain. This paper

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<sup>173</sup> See THOMAS J. BOLLYKY, CTR. FOR STRATEGIC & INT'L STUDIES GLOBAL HEALTH POL'Y CTR., GLOBAL HEALTH INTERVENTIONS FOR U.S. FOOD AND DRUG SAFETY 7 (2009) (reporting that 20% of finished generic and over-the-counter drugs sold in the United States and more than 40% of the active ingredients in U.S.-made medications are produced in China and India).

<sup>174</sup> The Institute of Medicine of the National Academies of Science has recently launched a project on "Strengthening Core Elements of Food and Drug Regulatory Systems in Developing Countries," which will examine many of these issues. See *IOM Current Activities and Recent Reports, Ongoing Studies and Activities*, INST. OF MED., <http://www.iom.edu/~media/Files/About%20the%20IOM/December%202010%20CARR.pdf> (last visited Dec. 20, 2010).

<sup>175</sup> Stephen M. Maurer, *Choosing the Right Incentive Strategy for Research and Development in Neglected Diseases*, 84(5) BULL. OF THE WORLD HEALTH ORG. 376, 376-79 (2006).

describes four strategies that would help achieve these goals and have compound benefits.<sup>176</sup> More efficient trial practices and regulatory streamlining would encourage donor and private investment in addressing diseases of the poor. Regional, sustainable approaches to clinical trial research and regulation in disease-endemic countries would better engage and equip local regulators and ethics committees to support the development of health products for neglected diseases and protect trial subjects. More favorable regulatory environments and prospects for product registration in developing countries may encourage indigenous innovation in health technologies to meet local needs. Finally, ensuring that public investments, policies, and regulations facilitate the participation of emerging country innovators would help engage new potential sources of government funding and actors with the cost structures and ability to respond to domestic markets in ways that global players may not.

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<sup>176</sup> The four strategies put forth in this paper are not meant to be exhaustive. Other initiatives also encourage better spending and reductions in global health costs and deserve support. *See, e.g.*, RENA EICHLER & RUTH LEVINE, CTR. FOR GLOBAL DEV., *PERFORMANCE INCENTIVES FOR GLOBAL HEALTH: POTENTIAL AND PITFALLS* (2009) (describing the potential of results-based financing to achieve global health objectives).