Orphan Drug Programs, Public-Private Partnerships and Current Efforts to Develop Treatments for Diseases of Poverty

By Dan Phair

In July 2007, the World Health Organization (WHO) announced an initiative to eliminate Chagas disease by 2010.1 The initiative brings together a “global network” of public and private groups and is backed by contributions from the pharmaceutical industry.2 Common in South America, Chagas disease is caused by a form of trypanosomiasis, an insect-borne parasite.3 The primary vector for the disease is the triatoma protracta, a nocturnal insect, commonly known as the “kissing bug,” so named because of the way it attacks its victims.4 The most recognizable symptom is severe inflammation around the eyes, as described by Brazilian physician Carlos Chagas.5 Chagas disease is one of several diseases of poverty, sometimes referred to as tropical or neglected diseases.6 Diseases of poverty are accurately thought of as a subset of neglected diseases.7 Unlike other neglected diseases, such as acquired immune

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2 Id.
3 See Center for Disease Control and Prevention (CDC), Chagas Disease Fact Sheet, available at http://www.cdc.gov/chagas/factsheet.html [hereinafter Chagas Disease Fact Sheet].
5 See Chagas Disease Fact Sheet, supra note 3.
7 See Milne, Kaitin & Ronchi, supra note 4, at 2 (describing the category of neglected disease that includes Chagas disease). This category of neglected diseases that are sometimes referred to as diseases of poverty includes Chagas disease, African trypanosomiasis, leishmaniasis and other diseases “with significant worldwide morbidity and mortality.” Id.
deficiency syndrome (AIDS), tuberculosis, and malaria, diseases of poverty are generally confined to “less industrialized countries or... impoverished sub-populations.”\(^8\) Chagas disease, for example, is most common in rural areas of Central America and Mexico.\(^9\) Chagas disease poses little threat to the wider global community because it is transmitted primarily by insects inhabiting rural parts of South America.\(^10\)

That said, the impact of diseases of poverty in areas where they are endemic is significant.\(^11\) According to the public-private partnership Drugs For Neglected Disease Initiative (DNDi), approximately eight million people are infected with Chagas disease.\(^12\) Of these people, between ten and thirty percent will develop the chronic and typically fatal stage of the disease.\(^13\) The two drugs commonly used to treat Chagas disease are only effective in the early stages of infection and both have “serious and frequent side effects.”\(^14\)

Numerous sources, including the WHO’s Commission on Macroeconomics and Health, have proposed using orphan drug legislation as platforms for producing

\(^8\) See Milne, Kaitin & Ronchi, supra note 4, at 2.

\(^9\) Carlos Franco-Paredes et al., Chagas Disease: an Impediment in Achieving the Millennium Development Goals in Latin America, 7 BMC INT’L HEALTH AND HUM. RTS. 1, 2 (2007), at http://www.biomedcentral.com/1472-698X/7/7. Due to the way it vectors, it does not pose a significant health threat to developed countries in the northern hemisphere. Cf. Milne, Kaitin & Ronchi, supra note 4, at 43 (discussing transmission of African Sleeping Sickness, which, like Chagas Disease, is transmitted primarily by biting insects).

\(^10\) See Milne, Kaitin & Ronchi, supra note 4, at 32 (discussing diseases of poverty). The category of neglected diseases that includes Chagas disease is “of public health importance in the developing world, but of little public health and economic significance in the developed world.” Id.

\(^11\) See Milne, Kaitin and Ronchi, supra note 4, at 32. (noting that characteristics of the disease include “significant morbidity and mortality”).

\(^12\) See DNDi, supra note 6, at 7 (providing statistical information about Chagas disease). In addition to the number of people who have the disease, 100 million people are at risk of contracting it. See id.

\(^13\) See DNDi, supra note 6, at 7. But see Franco-Paredes et al., supra note 9, at 2. Other estimates suggest that 10-13 million people have chronic Chagas disease; of these, only 20-30 percent are symptomatic. See id. The disease causes significant cardiovascular damages as well as “progressive dilation of the esophagus and colon and gastrointestinal dysmotility.” See id.

\(^14\) Special Programme for Research and Training in Tropical Diseases, UNICEF/UNDP/World Bank/WHO, Strategic Direction for Research: Chagas Disease 2 (2002) (describing drugs available for treatment of Chagas disease). See also Franco-Paredes et al., supra note 9, at 5. Franco-Paredes et al., note that “[c]urrently, there is no adequate treatment for chronic late cases, which are associated with most of the morbidity and mortality of Chagas disease. Nifurtimox and benznidazole are effective only in the treatment of acute and chronic early phase cases...” Id.
treatments for diseases of poverty. Since 1983, when the United States (U.S.) passed its Orphan Drug Act (ODA) in an effort to spur research and development of treatments for conditions considered rare in the U.S., many developed countries and the European Union (E.U.) have passed similar legislation. Orphan drug legislation creates incentives, such as grants, tax breaks, and government assistance with clinical trial protocols, in order to make the development of treatments for rare conditions more lucrative.

Despite the apparent availability of orphan drug incentives, they have not been used extensively to support the development of treatments for diseases of poverty. This is due in part to the fact that even with incentives available under orphan drug programs, producing treatments for conditions such as Chagas disease is unlikely to yield a financial profit. Instead, there has been a proliferation of partnerships between publicly-funded research groups and private industry, known as public-private partnerships. Though they are a recent development, these philanthropic unions have shown significant promise. This note is an attempt to assess what role orphan drug

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15 See generally Milne, Kaitin & Ronchi, supra note 4. See also Patricia C. Kuszler, Balancing the Barriers: Exploiting and Creating Incentives to Promote Development of New Tuberculosis Treatments, 71 WASH. L. REV. 919, 965 (1996) (suggesting the possibility that Congress might expand the scope of the ODA to include drugs developed as part of public health initiatives). Kuszler looked specifically at ways to compel research and development of treatments for tuberculosis. See id. at 919-21. In fact, several drugs for the treatment of tuberculosis have been granted orphan status. See Food and Drug Administration (FDA) List of Orphan Designations and Approvals, at http://www.fda.gov/orphan/designat/list.htm (last visited Apr. 8, 2008).


18 See FDA, Cumulative List of All Orphan Designated Products That Have Received Marketing Approval, at http://www.fda.gov/orphan/designat/allap.rtf (last visited Apr. 8, 2008). See also European Commission, Register of Designated Orphan Medicinal Products (by number), at http://ec.europa.eu/enterprise/medicinal-products/register/orphreg.htm (last visited Apr. 8, 2008).

19 Cf. Milne, Kaitin & Ronchi, supra note 4, at 45 (recognizing that market-based incentives are unlikely to compel development of treatments for diseases of poverty).


programs could play in this new environment dominated by public-private partnerships.

Part I will look at some of the historical problems in developing treatment for tropical disease and current efforts to address these problems. Part II will compare and describe some common features of orphan drug legislation and look at how conditions that are rare in developed countries are similar to diseases of poverty that are prevalent in developing countries. Part III will consider modest changes at the international and national levels that might better enable orphan drug manufacturers to contribute to existing disease of poverty initiatives. Partly for the sake of economy, the focus of the proposed changes to national regulation will be confined to the U.S., the E.U. and disease-endemic countries. The core position of this note is that even without revision, orphan drug programs could provide incentives for manufacturers seeking to contribute to tropical disease initiatives, though changes to the way cross-border research is conducted and incentivized may make orphan incentives more useful in this regard. To that end, this note proposes modest statutory, regulatory and policy changes that may better allow drug manufacturers to unify their research efforts with those of public-private partnerships.

I. Efforts to Address Tropical Disease: Past Efforts to Address Tropical Disease, Current Initiatives and the Role of Public-Private Partnerships

The array of medicines brought to market in developed countries since World War II is a testament to the power of market forces to compel innovation. This expansion was complemented by public health initiatives that were largely successful in


But see Andrew Creese et al., The World Medicines Situation 7, 23-26 (WHO 2004) (providing national drug production, export, and import statistics), available at http://www.searo.who.int/LinkFiles/Reports_World_Medicines_Situation.pdf. Collectively, the U.S. and countries within the E.U. comprise a very large proportion of worldwide drug production, exportation and importation. Id. The top 5 producers are the United States, Germany, Japan, France and the United Kingdom. Id. The top five exporters are Germany, Switzerland, the United States, the United Kingdom and France. Id. at 23. While Japan is one of the major producers, most of its drugs are manufactured for use in its own market. Id. at 24. The United States is the largest single importer of pharmaceutical products, though the other major producers and exporters also rank near the top of the list. Id. at 26.

See infra, Part II.C.

See infra, Part III.C-F.

See M. N. Graham Dukes, The Law and Ethics of the Pharmaceutical Industry 7 (Elsevier 2006) (explaining that like other technological industries, the pharmaceutical industry expanded after World War II). The pharmaceutical industry, however, expanded more rapidly than other industries because of "vigorous public demand." Id.
preventing the most lethal infectious pandemics from spreading to much of the world, especially to developed countries.\textsuperscript{26} Against this, the relative absence of treatments to address conditions endemic to impoverished areas of the world stands in marked contrast.\textsuperscript{27} Despite the prevalence and high rate of morbidity for diseases of poverty, the pipeline of treatments for these conditions has been largely fallow.\textsuperscript{28} For example, of the 1,223 new chemical entities developed between 1975 and 1997, only thirteen were developed to treat tropical disease.\textsuperscript{29}

Despite this history, in recent years considerable effort and attention have been given to the plight of persons affected by diseases of poverty.\textsuperscript{30} In April 2007, the WHO announced its intent to expand its efforts to eliminate Chagas disease, thanks in part to contributions from Bayer HealthCare, the manufacturer of one of the treatments

\textsuperscript{26}See Kuszler, \textit{supra} note 15, at 938 (reviewing public health achievements). Unfortunately, because of success in eradicating many public health threats, much of the infrastructure used to combat the epidemics of the early and middle twentieth century has atrophied from lack of need. \textit{Id.}


\textsuperscript{28}Cf. DUKES, \textit{supra} note 25, at 264 (noting role of pharmaceutical industry in developing countries). “Over a long period, the international pharmaceutical industry played no role of any significance in the development of Africa or various other parts of the third world. While it vigorously sought growth opportunities in other new markets it found little reason to look to the tropics and certainly no moral ground for doing so.” \textit{Id.}

\textsuperscript{29}Milne, Kaitin & Ronchi, \textit{supra} note 4, at 17. “From 1910 to 1970, the pharmaceutical industry led the charge in the fight against microbial and parasitic disease. Yet, from 1975 to 1997, only 13 of 1223 new chemical entities were developed specifically for tropical disease.” \textit{Id. But see} Lipkus, \textit{supra} note 20, at 410 (noting increase in neglected disease drug development since 1999).

Several months later, the WHO announced that it had formed a coalition to eradicate the disease by 2010. These initiatives mark the WHO's renewed focus on Chagas disease; the organization originally began focusing on issues related to this disease and others over thirty years ago. In 1975, acting in collaboration with the United Nations Children's Fund, the United Nations Development Programme and the World Bank, the WHO established the Special Programme for Research and Training in Tropical Disease (TDR). In the 1990s, TDR achieved remarkable success in reducing the number of Chagas cases in South America by helping to establish vector-control initiatives.

Given its limited budget, however, TDR has been forced to focus on vector control, rather than drug research and the development of treatments. TDR has also worked to promote and foster research by other organizations, including several public-
private partnerships. In a recent report, TDR noted that, “while the new environment of multiple players in research and increased resources is to be warmly embraced, there is a danger of fragmentation of effort.” In light of this potential problem, TDR emphasized that one of its goals would be to “provide a collaborative framework” and a “neutral platform for partners to discuss and harmonize activities.”

The recent development of public-private partnerships has brought new life to some efforts to combat tropical disease. Prominent partnerships include the Drugs for Neglected Disease Initiative (DNDi) and Medicines for Malaria Venture (MMV). The partnerships bring together researchers from both public and private sectors to facilitate the development of treatments for neglected disease and to harness the strengths of both types of research. For example, often publicly funded initiatives are better equipped to undertake basic and field research and can do so more cost effectively than private industry. Conversely, it is generally recognized that private industry is better able to translate basic research into actual drug therapies. Accordingly, DNDi minimizes the cost of its development projects by channeling most of its research

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37 See EIGHTEENTH PROGRAMME REPORT, supra note 34, at 14 (noting initial support from TDR for several public-private partnerships). In describing TDR’s ability to network with public-private partnerships, the Eighteenth Programme Report mentions, in particular, its work with the Medicines for Malaria Venture (MMV) and DNDi. Id. at 59.

38 EIGHTEENTH PROGRAMME REPORT, supra note 34, at 14 (describing analysis that informs the organization’s current “vision statement”).

39 EIGHTEENTH PROGRAMME REPORT, supra note 34, at 15. In addition to “provid[ing] a collaborative framework and information service for research partners,” TDR has also committed itself to “empower[ing] scientists from [disease endemic countries] as research leaders; and support[ing] research on neglected priority needs.” Id.


41 Cf. EIGHTEENTH PROGRAMME REPORT, supra note 34, at 59 (noting work with public-private partnerships and noting, specifically, work with MMV and DNDi).

42 See Lipkus, supra note 20, at 423. While much of DNDi’s research is being undertaken by public sector participants, they have also been able to secure agreements with private sector companies to facilitate drug development. Id. DNDi minimizes the cost of its development projects by channeling most of its research through the public sector, using private contributions for specific tasks. Id.

43 See Lipkus, supra note 20, at 390-91 (noting weakness of private industry in this regard). See also CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 3 (2006) (describing primary role government research plays in development of drug therapies). This report indicates that a significant portion of the National Institute of Health’s research spending goes toward basic research. Id. at 28.

44 See Lipkus, supra note 20, at 397 (describing inability of public sector to translate research into drug development). Lipkus notes that “the $36 million dollar drug development budget allocated by the WHO to [TDR]... is scarcely sufficient for the development of even one drug.” Id.
through the public sector, using private contributions for specific tasks. By allocating development tasks to the parties that can perform the task most efficiently, public-private partnerships maximize the usefulness of all available resources.

Despite the recent uptake in funding, relative to the very high costs of pharmaceutical research even high profile public-private partnerships are constrained by a shortage of resources. Additionally, because private industry is largely beholden to shareholder interests, their ability to contribute to charitable projects depends on their doing so without sapping company profits. However, efficiency is sometimes a tall order for researchers working across national and even continental borders. In addition to logistical problems related to distance, substantial obstacles, such as a lack of infrastructure and uncertain regulation, can make conducting clinical trials in developing countries very difficult. Fortunately, organizations like DNDi and MMV have established connections within the communities where they operate, helping them minimize cultural and logistical complications in conducting research.

See Lipkus, supra note 20, at 423-24. A significant part of DNDi's research process is undertaken by public sector researchers. Id. As Lipkus notes "By minimizing contact with the private sector, transaction costs of collaboration can be minimized." Id.

See Lipkus, supra note 20, at 424 (describing methods of cost containment). Public-private partnerships must find ways to keep transaction costs down and, to keep private sector partners interested in contributing, find ways to "creatively expand[ing] the value proposition." Id. at 415. See also EIGHTEENTH PROGRAMME REPORT, supra note 34, at 58 (describing cost reduction efforts including establishment of "specialist networks" and "partnerships").

See Bryan Mercurio, Resolving the Public Health Crisis in the Developing World: Problems and Barriers of Access to Essential Medicines, 5 NW. U. J. INT'L HUM. RTS. 1, 65 (2006) (noting that the majority of initiatives . . . remain underfunded"). See also Congressional Budget Office, supra note 43, at 20 (noting that it takes an average of $802 million dollars to bring a drug to market in the United States). But see DNDi, supra note 6, at 37. Public funds contributed to DNDi amounted to EUR 4,902,153. Id. Additionally, the organization received private grants in the amount of EUR 5,398,048. Id. Note however, because of their structure, public-private partnerships can develop treatments in a cost effective manner. See Lipkus, supra note 20, at 415 (noting cost of $150 million dollars to develop an anti-malarial treatment).

See Lipkus, supra note 20, at 389-90. "Since for-profit corporations require the maximization of shareholder value as their organizational imperative, we cannot expect them to voluntarily solve public crises via underperforming investments." Id.

See also Christopher-Paul Milne, Racing the Globalization of Infectious Diseases: Lessons From the Tortoise and the Hare, 11 NEW ENG. J. INT'L & COMP. L. 1, 11 (2004) (noting problems in communication between administrators of polio vaccination program and intended recipients).

See DUKN, supra note 25, at 271-72. In addition to a lack of governing regulation, regulation in some countries is corrupt. Id. See also Lipkus, supra note 20, at 390-91 (noting problems that lack of infrastructure poses for pharmaceutical manufacturers).

See Lipkus, supra note 20, at 422-23 (describing network of partners involved in DNDi). Since its beginning, DNDi has involved both regional collaborators as well as partners from developed
II. Using Orphan Drug Programs to Diseases of Poverty

A. Common Characteristics of Orphan Drug Systems and the Possibility of Using Orphan Drug Systems to Foster Research and Development of Treatments for Diseases of Poverty

An article written about DNDi defined its objectives as an initiative to address “three ‘orphan’ diseases . . . African sleeping sickness, its Latin American relative Chagas' [sic] disease and leishmaniasis.” This was not the first time diseases of poverty were referred to as orphan conditions. However, laws dealing with orphan diseases, which have been enacted in the U.S., the E.U., Japan and other countries, typically do not explicitly include diseases of poverty, that is, diseases that are prevalent in developing countries, but rare in developed countries. Rather, orphan drug laws define orphan conditions primarily—if not exclusively—in terms of domestic prevalence.

The incentives and public assistance provided by orphan drug programs are an effort to compel private manufacturers to undertake ventures that might otherwise be unprofitable. The basic reality underpinning orphan drug legislation is that, all things

53 See generally Milne, Kaitin & Ronchi, supra note 4. The Commission on Macroeconomics and Health paper proposes modification to the E.U. and U.S. orphan drug laws to make them more effective in fostering treatments for diseases of poverty. Id. See also Kuszler, supra note 15, at 954-58 (proposing use of the ODA as a way to stimulate research and development of new tuberculosis treatments).
55 See id.
56 See H.R. REP. NO. 97-840(I), at 5-6 (1982), as reprinted in 1982 U.S.C.C.A.N. 3577, 3577-78 (discussing need for legislation to compel manufacturers to research and develop treatments for rare conditions). The Committee on Energy and Commerce noted that, for some rare diseases there is “virtually no commercial value to any drug that is useful against them.” Id. at 3578. See also 21 U.S.C.A. § 360ee(b)(2) (2007). The definition of “rare disease or condition” in §360ee(b)(2) also includes conditions affecting over 200,000 people in the United States for which sales of a successful treatment in the United States will not allow the manufacturer to recover its costs. Id. In both cases, without incentives, market forces alone would not compel
being equal, market forces will compel research and development for conditions that represent the greatest stream of potential revenue.\textsuperscript{57} Orphan drug programs typically feature research grants, clinical protocol assistance, tax incentives and market exclusivity provisions.\textsuperscript{58} The effect of these incentives is to reduce or even remove many of the initial costs of bringing drugs into the market, thereby allowing manufacturers to justify, in financial terms, the development of life saving treatments for conditions that would not otherwise represent significant revenue.\textsuperscript{59}

Although orphan drug laws have been used primarily to foster the development of treatments for "rare" conditions, there is an obvious similarity between conditions considered rare in developed countries and tropical disease, a category of diseases that includes diseases of poverty as well as pandemic conditions like malaria and tuberculosis.\textsuperscript{60} Persons afflicted by rare conditions in developed countries and persons

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\textsuperscript{57} See Rohde, supra note 17, at 126-27 (describing market realities). When it enacted the ODA, the U.S. Congress "believed that unless drug development for rare diseases was incentivized, the market would continue to operate in favor of larger patient populations to the detriment of smaller groups." \textit{Id.}

\textsuperscript{58} See The Orphan Drug Act, 21 U.S.C.A. § 360aa-ee (2007). The ODA combines several types of incentives meant to foster research and development. \textit{Id.} The final subsection of the U.S. ODA provides, in relevant part, that the government . . . may make grants to and enter into contracts with public and private entities and individuals to assist in (1) defraying the costs of qualified clinical testing expenses incurred in connection with the development of drugs for rare diseases and conditions, (2) defraying the costs of developing medical devices for rare diseases or conditions, and (3) defraying the costs of developing medical foods for rare diseases or conditions.


\textsuperscript{59} H.R. REP. NO. 97-840(I), at 3582-84 (discussing disincentives for conducting research and incentives to encourage private manufacturers to engage in development of treatments for orphan conditions). \textit{See also} Regulation on Orphan Medicinal Products, Regulation 141/2000, 2000 O.J. (L18) 1, 2 (EC) (discussing purpose of European Union Regulation on Orphan Medicinal Products).

\textsuperscript{60} See H.R. REP. NO. 97-840(I), at 3578 (discussing lack of commercial value derived from development of treatment for certain conditions). The committee points out that for disease like Lou Gehrig’s disease and Huntington’s disease, the cost of development is disproportionate to
suffering from tropical disease simply do not have the combined wealth to attract the attention of for-profit pharmaceutical manufacturers. Some have argued that, since tropical diseases are rare in developed countries, the fact that many orphan drug programs define orphan conditions in terms of domestic prevalence suggests that they may well be used for development of treatments for conditions like malaria. This reading is supported by actual practice under both the U.S. ODA and the E.U. orphan drug regulation. A number of treatments for conditions which have a significant impact on developing countries, like AIDS, tuberculosis and malaria, have been developed under the auspices of both the U.S. ODA and the E.U.’s orphan products program. To date, however, the programs have not been used extensively to develop treatments for the most neglected subcategory of tropical disease, diseases of poverty.

the likely financial return from bringing a successful treatment to market. Id. But see Milne, Kaitin & Ronchi, supra note 4, at 21-23. One key impediment to compelling research and development of treatments for tropical disease is that “[t]he poor have no purchasing power.” Id. See also Making a Difference, supra note 21, at 11 (noting that initial focus of TDR included Chagas and malaria). Though tuberculosis was not part of TDR’s initial focus, it reemerged as a public health threat in the 1980s. Id.

61 See H.R. REP. NO. 97-840(I), at 3578. Cf Milne, Kaitin & Ronchi, supra note 4, at 21-23 (describing plight of persons suffering from diseases of poverty). The WHO’s Commission on Macroeconomics and Health argued that neglected diseases fall within the definition of orphan condition under both the U.S. ODA and the E.U.’s orphan program. See generally id.

62 See H.R. REP. NO. 97-840(I), at 3581 (indicating support for use of the ODA as a means to foster development of treatments for diseases which occur commonly in developing countries). See also Milne, Kaitin & Ronchi, supra note 4, at 10-11.


64 See Milne, Kaitin & Ronchi, supra note 4, at 36 (noting extent to which ODA has contributed to R&D for treatment of AIDS virus). After 1993, AIDS was reclassified by the CDC. Id. As a result, some treatments are not eligible for orphan status. Id. See also FDA, Lists of Orphan Designation and Approvals, at http://www.fda.gov/orphan/designat/list.htm (last visited Apr. 8, 2008). See also European Commission, Register of Orphan Medicinal Products (by Number), available at http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm (last visited Apr. 8, 2008).

65 See Milne, Kaitin & Ronchi, supra note 4, at 43-46 (noting absence of treatments for diseases of poverty). See also id. at 2 (defining diseases of poverty).
B. A Brief Comparison of Orphan Drug Legislation: Several Prominent Orphan Drug Programs in Order of Enactment

In 1983, Congress passed the Orphan Drug Act to provide incentives for research and development of treatments for diseases considered rare in the U.S.66 Under the ODA, an orphan condition is one afflicting fewer than 200,000 nationwide or one for which a manufacturer is able to demonstrate that it is unlikely to recoup its development costs through sales in the U.S.67 This 200,000 mark is the highest prevalence limit among existing orphan drug programs.68 In most cases, the grant of market exclusivity is the most significant incentive for manufacturers seeking orphan designation under the U.S. program.69 Under the ODA, over 1,700 orphan products have been designated to treat a range of rare and serious conditions.70 Because the ODA has no novelty requirement, unlike the requirements for patent protection, manufacturers can obtain a seven-year grant of market exclusivity for reformulations of old medications.71

In the U.S., the public support afforded by the ODA has been a blessing for start-up biotech companies.72 The tax incentives and grants provide crucial operating

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66 The Orphan Drug Act, 21 U.S.C.A. § 360aa-ee (2007) (establishing U.S. orphan drug program). The ODA was the first legislative act directed at fostering development of treatments for orphan conditions. See DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 23 (comparing orphan drug programs chronologically by date of enactment).

67 21 U.S.C.A. § 360ee(b)(2) (defining "rare disease or condition"). See also Drusilla L. Scott et al., Orphan Drug Programs/Policies in Australia, Japan and Canada, 35 DRUG INFO. J. 1, 3 (2001) (describing ways a manufacturer can obtain orphan designation).

68 See DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 23 (noting prevalence limit).

69 See 21 U.S.C.A. § 360cc(a)(2) (setting out market exclusivity provision). See also Rohde, supra note 17, at 132. It is generally acknowledged that the grant of market exclusivity is, for manufacturers, the most important incentive offered under the ODA. See id. See also Mut. Pharm. Co. v. Ivax Pharm. Inc., 459 F. Supp.2d 925, 930 (D. Cal. 2006) (describing benefits available to drug sponsors under the ODA, including seven-year market exclusivity term).

70 See FDA, LIST OF ORPHAN DESIGNATION AND APPROVALS (listing treatments receiving orphan product designation including Pompe disease, Gaucher's disease and various cancers), available at http://www.fda.gov/orphan/designat/list.htm (last visited Apr. 8, 2008).

71 See Mut. Pharm. Co. v. Ivax Pharm. Inc., 459 F. Supp.2d 925, 928-30 (D. Cal. 2006) (discussing whether marketing approval for quinine sulfate to treat malaria preempted other manufacturers from marketing quinine sulfate). Quinine sulfate had been distributed previously by various manufacturers, though the FDA removed its approval for over the counter sales of the drug in 1998. Id. Manufacturers continued to distribute quinine sulfate through prescription. Id. When Mutual obtained approval under the ODA, it brought a claim against manufacturers that had continued to distribute quinine sulfate. Id.

72 Diedtra Henderson, '83 Law Called Big Boost for Rare-Disease Drugs, BOSTON GLOBE, May 1,
capital to fledgling biotech companies for research and development in niche markets.73 Government assistance in devising clinical trial protocols is also important for small-scale companies that may lack the experience and infrastructure of more established manufacturers.74 This assistance makes obtaining approval from the Food and Drug Administration (FDA) more efficient and less costly for the manufacturer, eliminating the need to revise clinical trials to satisfy FDA requirements.75 Additionally, the market exclusivity provision provides a form of intellectual property protection that is less costly and easier to obtain than full patent protection.76 Though some large-scale companies have been attracted by the possibility of the grant of seven years of market exclusivity, biotech companies and smaller manufacturers remain the driving force behind the ODA.77

Ten years after U.S. enactment of the ODA, Japan became the second country to develop an orphan products regime.78 Under the Japanese program, an orphan

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2006, at E1 (discussing effect of ODA on drug manufacturers and persons with rare diseases). Some biotech companies start out in the orphan market in order to gain a foothold before moving into development of treatments for more common conditions. Id.

73 Syamala Ariyanchira, BioMarket Trends: Orphan Drug Arena Driven by Biologics, GENETIC ENGINEERING AND BIOTECHNOLOGY NEWS, Jan. 1, 2008 (describing biotech industry's embrace of orphan drug market), available at http://www.genengnews.com/articles/chitem.aspx?aid=2318&chid=0. When the ODA was first passed, mainstream pharmaceutical companies were more focused on developing blockbuster treatments and this lack of competition allowed biotech and small pharmaceutical companies to establish a niche within the orphan market. Id. Even now, large pharmaceutical companies typically only become involved in the later stage of product development, often by acquiring or partnering with the original sponsors. Id.

74 See Rohde, supra note 17, at 132 (describing impact of the ODA on product development, including its impact on less established pharmaceutical companies).

75 See Rohde, supra note 17, at 132 (describing ODA incentives). The FDA's direct involvement in devising the clinical trial prevents "time consuming and costly revisions." Id. This in turn "encourages smaller, less experienced pharmaceutical manufacturers to seek NDA [new drug application] approvals..." Id.

76 See 21 U.S.C.A. §360cc, ee (2007). See also Rohde, supra note 17, at 133 (discussing market exclusivity provision). It is generally acknowledged that the grant of market exclusivity is, for manufacturers, the most important incentive offered under the ODA. See id. at 130. See also Milne, Kaitin & Ronchi, supra note 4, at 8-9 (explaining appeal of market exclusivity provision for biotech firms). In contrast with obtaining patent protection, obtaining orphan designation and, with it, a grant of market exclusivity is a straightforward process. Id.

77 See Ariyanchira, supra note 73 (noting that large firms usually become involved later in the research and development process).

78 See DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 46 (describing Japan's orphan drug program). Japan enacted its orphan drug program in 1993. Id. The program is modeled on the U.S. ODA. Id.
condition is a "rare and serious" condition that affects only 0.05% of the domestic population.\textsuperscript{79} In 1998, Australia passed its Orphan Drug Program following discussions with the U.S. Office of Orphan Product Development.\textsuperscript{80} Both the Japanese and Australian programs are modeled after the U.S. ODA.\textsuperscript{81} Unlike the U.S.'s program, the Australian program does not feature market exclusivity, tax credits or research grants.\textsuperscript{82} One notable feature of the Australian Orphan Drug Program is that prior marketing approval by the U.S. FDA may provide a basis for marketing approval.\textsuperscript{83}

In 2000, the E.U. enacted its Regulation on Orphan Medicinal Products.\textsuperscript{84} This legislation defines orphan conditions as either those affecting less than five in ten thousand people or those for which the likely return on investment from sales within the

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  \item \textsuperscript{79} Department of Health and Aged Care, supra note 54, at 46 (providing details about Japan's orphan drug laws). See also Scott et al., supra note 67, at 5 (describing Japan's orphan drug laws). As Scott notes, the prevalence limit in Japan is roughly half that of the United States. Id. Unlike the U.S. program, the mere fact that a drug is unlikely to generate returns on investment is not a basis for obtaining orphan designation. Id. (indicating orphan drug criteria under Japanese program). If a treatment developed under an orphan program yields profits exceeding 100 million yen, the producers must pay back a portion of grants received during the development phase. See Department of Health and Aged Care, supra note 54, at 46-47, 57 (indicating key aspects of Japanese program). See also Marlene E. Haffner, Orphan Drug Development—International Program and Study Design Issues, 32 Drug Information Journal 93, 95 (1998). While the Japanese government subsidized R&D of orphan products, where a manufacturer extracts significant profit from a product, it must pay part of the subsidy. Id. The U.S. program has been criticized as providing a platform for developing treatments that later generate significant revenue, thus conferring a windfall. See Kuszler, supra note 15, 956-57 (citing instances where manufacturers had generated significant profits through sales of orphan products).
  \item \textsuperscript{80} See Department of Health and Aged Care, supra note 54, at 48 (providing brief history of Australia's Orphan Drug Program).
  \item \textsuperscript{81} See Department of Health and Aged Care, supra note 54, at 48 (noting history of orphan drug programs). The program was initiated following discussions with the U.S. Office of Orphan Product Development and was largely modeled on the U.S. program. Id. Japan's orphan drug program is similar in this regard. Id. at 46.
  \item \textsuperscript{82} See Department of Health and Aged Care, supra note 54, at 48 (distinguishing Australian program from the U.S. program).
  \item \textsuperscript{83} See Scott et al., supra note 67, at 4 (explaining key feature of Australian orphan drug program). But see Department of Health and Aged Care, supra note 54, at 14-15 (noting reality of regulatory process). Approval based on U.S. FDA evaluation is allowable only on review of an unedited report. Id. Unfortunately, the FDA has been reluctant to provide unedited version where doing so may reveal "commercially sensitive information." Id.
  \item \textsuperscript{84} Regulation on Orphan Medicinal Products, Regulation 141/2000, 2000 O.J. (L18) (EC) (establishing E.U. orphan products program). Article 1 provides that the purpose of the regulation is to "lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products." Id. at Art. 1.
\end{itemize}
Union would not justify development.\textsuperscript{85} Approval for orphan designation is granted by the Committee for Orphan Medicinal Products, a committee established within the European Agency for the Evaluation of Medicinal Products.\textsuperscript{86} The E.U. orphan products regime allows a ten-year grant of market exclusivity.\textsuperscript{87} However, the grant of market exclusivity may be curtailed by four years if a product is "sufficiently profitable."\textsuperscript{88} In a recent development, the U.S. FDA and European Medicines Agency agreed to use a common application form for submission to both the regulatory bodies in pursuance of orphan designation of a medicinal product.\textsuperscript{89}

C. Compatibility of Orphan Drug Programs with Initiatives to Address Diseases of Poverty

In much the same way that public-private partnerships leverage the strengths of individual participants to make drug development more efficient and less costly, orphan drug systems leverage government resources to make product development more efficient and less costly.\textsuperscript{90} Fundamentally, orphan drug programs and public-private

\textsuperscript{85} Id. at Art. 3 (providing "Criteria for designation"). As with the U.S. ODA, the EC program also provides for orphan designation where a sponsor demonstrates that "without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment." Id.

\textsuperscript{86} See Reg. 141/2000, art. 4, (EC) (establishing the Committee for Orphan Medicinal Products). Committee approval requires a two-thirds majority. Id. at Art. 5(6). A manufacturer may appeal the committee's decision to reject an application for orphan status. Id. at Art. 5(7).

\textsuperscript{87} Id. at Art. 8. But cf. 21 U.S.C.A. § 360cc(a)(2) (2007) (setting out market exclusivity provision). The U.S. system provides a maximum of 7 years of market exclusivity. Id.

\textsuperscript{88} Reg. 141/2000, Art. 8 (EC). Article 8 provides that an individual member state may provide evidence to the European Medicines Agency that a given product no longer meets the criteria for orphan designation. Id. The sponsor then may bring evidence justifying the product's designation as an orphan product. Id. at Art. 8, 5(2)(d), 3(1). In this way the procedure allows the sponsor to appeal any action taken by a member state. Id.


\textsuperscript{90} Compare Mine, Kaitin & Ronchi, supra note 4, at 5 (describing incentives provided under U.S. ODA) with DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 14 (describing incentives under E.U. orphan drug program). See also Rohde, supra note 17, at 132 (noting, in particular, the benefit of FDA assistance in designing clinical trial protocols). Protocol assistance, for example, allows manufacturers to design clinical trials in a matter that ensures compliance with FDA requirements. Id.
partnerships are framework systems. A one article analyzing public-private partnerships noted that “[p]ublic-private partnerships are essentially not-for-profit facilitators of value between public and private parties in the interest of mobilizing the resources and capabilities of both parties toward the development of drugs.” Under orphan drug systems, tax incentives and grants provide financial support while assistance in developing clinical protocols ensures that clinical trials are designed efficiently and effectively. Like public-private partnerships, orphan drug systems create value, allowing manufacturers to participate in the development and eventual production and distribution of treatments for persons with diseases considered rare in developed countries.

As previously discussed, both the U.S. and E.U. have granted orphan designation for medicinal products to treat diseases that occur more commonly in developing countries, but orphan incentives have not been used extensively to foster development of treatments for diseases of poverty. However, the development of the drug miltefosine illustrates that orphan incentives could be used to foster development of treatments for diseases of poverty. Miltefosine received orphan designation in 2002 for the treatment of visceral leishmaniasis, a disease that causes “abnormal functioning

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92 Lipkus, supra note 20, at 414 (characterizing public-private partnerships).
93 See Mut. Pharm. Co. v. Ivax Pharm. Inc., 459 F. Supp.2d 925, 930 (D. Cal. 2006) (describing ODA incentives). See also Rohde, supra note 17, at 132 (noting benefit of FDA assistance in designing clinical trial protocols). “Without the assistance of the FDA in defining the clinical profile, additional time consuming and costly revisions to the clinical trial often are required.” Id.
94 See Lipkus, supra note 20, at 390-1 (noting that for-profit companies exist to create value for investors). See also Haffner, supra note 79, at 98 (describing benefits of U.S. ODA). But see Lipkus, supra note 20, at 414 (noting role of public-private partnerships in creating value for participants).
of the blood and immune system abnormalities and frequent infection.”

Visceral leishmaniasis is fatal if left untreated. Like Chagas disease, it is considered a disease of poverty. As grounds for considering leishmaniasis eligible for orphan designation, the European Medicines Agency’s public summary of opinion notes that the disease only affects about 4,000 people in Europe. But, while it affects only a small number of people in Europe, the disease is much more prevalent in other parts of the world, affecting roughly 100,000 people per year in India, Nepal and Bangladesh. The task force that carried out the clinical investigation of miltefosine for visceral leishmaniasis involved both public and private researchers working in close collaboration with TDR. While it is not clear what effect receiving orphan designation had on the development of miltefosine, the fact that the drug received orphan designation clearly meant that it was eligible for fee reductions and clinical protocol assistance, as well as government funding.

The development of dihydroartemisinin-piperaquine for malaria suggests the potential value of obtaining orphan designation in public-private partnerships. Following successful completion of Phase III clinical trials involving the public-private partnership Medicines for Malaria Venture (MMV) and a European pharmaceutical company, Sigma Tau, the pharmaceutical company sought and obtained orphan


99 See, e.g., Milne, Kaitin & Ronchi, supra note 4, at 2 (describing the category of neglected disease that includes Chagas disease and leishmaniasis).

100 See MILTEFOSINE OPINION, supra note 63 (indicating prevalence of visceral leishmaniasis in Europe).

101 See EIGHTEENTH PROGRAMME REPORT, supra note 34, at 26 (indicating concentration of visceral leishmaniasis in several states in India as well as Bangladesh and Nepal).

102 See SIXTEENTH PROGRAMME REPORT, supra note 96, at 25 (describing development of miltefosine).

103 See EUROPEAN MEDICINES AGENCY, ORPHAN INCENTIVES (indicating forms of assistance and providing link to inventory of incentives offered by member states), available at http://www.emea.europa.eu/htms/human/orphans/incentives.htm (last visited Apr. 8, 2008).

104 See Press Release, Sigma-Tau and Medicines for Malaria Venture, Dihydroartemisinin and Piperaquine Shows Promise as the Next Generation Artemisinin-based Combination Therapies (ACT) for the Treatment of Malaria (Sept. 30, 2005) (indicating that Medicines for Malaria Venture hopes orphan designation will facilitate registration), available at http://www.mmv.org/IMG/doc/PR_COST_B22_eurartekin_release_final.doc.
designation for the treatment. According to MMV, the hope is that obtaining orphan designation will speed up the registration process for dihydroartemisinin-piperaquine.

Orphan drug programs could contribute significantly to the charitable efforts of manufacturers working with public-private partnerships by providing an efficient framework for translating basic research into drug therapies. Given that orphan drug programs are a form of public-private collaboration, they might dovetail well with existing public-private partnerships. One way to make orphan drug laws more useful in this regard would be for intergovernmental organizations to provide incentives that complement those of national governments. For example, national governments could be given a partial credit toward their WHO dues based on the value of grants and tax incentives conferred through orphan drug programs to sponsors of research in

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105 See European Commission, Register of Designated Orphan Medicinal Products (by number), at http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm (indicating orphan designation for dihydroartemisinin-piperaquine on March 8, 2007) (last visited Apr. 8, 2008). See also Medicines for Malaria Venture, Orphan Drug Status for MMV Drug DHA-Piperaquine, at http://www.mmv.org/article.php3?id_article=378&recherché=orphan (indicating orphan designation, participating organizations, and benefit of dihydroartemisinin-piperaquine relative to other malaria treatments) (last visited Apr. 8, 2008). After development and registration in China, a subsequent clinical evaluation, was carried out in order to assess the safety and efficacy of the treatment. Id. The evaluation was a joint effort involving the public-private partnership, Medicines for Malaria Venture, two private companies, Chongqing Holley Holding (of China) and Sigma Tau (of Italy), the University of Oxford and Guangzhou University. Id.


107 Cf. Regulation on Orphan Medicinal Products, Regulation 141/2000, ¶ 3, 2000 O.J. (L18) 1 (EC). The principal of efficient, concerted effort is expressed in the E.U. Orphan Medicinal Products Regulation, which provides in relevant part, “...to avoid the dispersion of limited resources; action at Community level is preferable to uncoordinated measures...” Id. The E.U. Orphan Products Regulation conserves resources by creating a regulatory framework to coordinate product development. Id. But see Lipkus, supra note 20, at 423-24 (noting how DNDi minimizes transaction costs). Conversely, DNDi creates informational and logistical frameworks to coordinate research efforts. Id.


109 See infra Part III.D (proposing possible international agreements).
tropical disease. In turn, national governments might establish new ways to fund cross-border clinical trials and new ways to obtain marketing approval.

III. Proposals For Making Orphan Drug Legislation More Useful in the Context of Research and Development of Treatments for Tropical Disease

A. Cohesive Pharmaceutical Research and Development Efforts

Cohesive clinical trial procedures—that is, consistent, standardized procedures—meeting the regulatory standards applicable to all participants might allow for a more effective use of limited resources. In a typical public-private partnership, there are many participants operating across national borders. The fact that patients who suffer from diseases of poverty are generally confined to endemic countries means that the preclinical research and clinical trials must occur there. At the same time, U.S. and European regulatory and manufacturing infrastructures are ideally suited to performing some elements of clinical trials and for translating research into treatments. Allowing for data to be transferred across borders as part of a unified assessment of a treatment’s safety and effectiveness would ensure the efficient use of available resources.


\[ \text{See infra, Part III.D (discussing proposed national measures within the E.U. and in the U.S.).} \]

\[ \text{See Kuszler, supra note 15, at 966 (noting that manufacturers must answer to many regulatory authorities). One problem with a lack of regulatory harmony is the need to satisfy multiple regulatory authorities causes delays and increases the cost of bringing products to market. Id.} \]

\[ \text{See DNDi, supra note 6, at 9 (noting composition of DNDi).} \]

\[ \text{See DUKES, supra note 25, at 280 (noting incentive to conduct clinical trials in disease endemic countries).} \]

\[ \text{See ANDREW CREESE ET AL., WHO, THE WORLD MEDICINES SITUATION 5 (2004) (describing concentration of worldwide drug production). See also id. at 13 (describing concentration of worldwide research and development).} \]

\[ \text{See Michael J. Malinowski, Globalization of Biotechnology and the Public Health Challenges Accompanying It, 60 ALB. L. REV. 119, 160-2 (1996) (describing need to unify research at the international level). Malinowski notes that, specifically with respect to orphan drugs, eliminating regulatory barriers between countries would help to distribute philanthropy. Id.} \]
B. Previous Efforts to Harmonize Regulatory Standards and Impediments to Total Harmonization

Despite the fact that total harmonization of regulatory standards would allow clinical data and pharmaceutical products, like orphan drugs, to pass easily from country to country, the process of approving pharmaceuticals is not one that easily lends itself to fixed procedures.\textsuperscript{117} Regulatory harmonization refers to the establishment of common standards and procedures for testing and approving pharmaceutical products.\textsuperscript{118} In both the E.U. and the U.S., regulatory bodies have made considerable efforts to harmonize actual regulatory standards with the understanding that doing so makes transnational research more efficient.\textsuperscript{119} However, approaches to drug regulation are, in essence, value judgments.\textsuperscript{120} Nearly all pharmaceuticals entail some risk of side effects.\textsuperscript{121} As

\textsuperscript{117} See DUKES, supra note 25, at 122 (noting potential for different regulatory approaches). Regulatory approval is influenced by “tradition, topography, political and social beliefs.” \textit{Id.} In other words, cultural considerations may affect regulatory decisions. \textit{Id.} Much drug regulation arose in response to pharmaceutical disasters and resulting pressure to ensure public protection. \textit{Id.} at 106 (noting pharmaceutical disasters in the U.S., France and Germany which precipitated regulatory reform). \textit{See also} SAUWAKON RATANAWIJITRASIN \& ESHETU WONGDEMAGEGNEHU, WHO, EFFECTIVE DRUG REGULATION: A MULTICOUNTRY STUDY 8 (2002) (noting that actual regulation in countries studied may have changed since study was conducted). The WHO-sponsored study notes that “[d]rug regulatory functions are performed in response to a changing environment.” \textit{Id.}

\textsuperscript{118} See ICH GLOBAL COOPERATION GROUP, ICH INFORMATION BROCHURE (May 2001) at 3-4 (providing details about ICH), \textit{available at} http://www.ich.org/LOB/media/MEDIA410.pdf.

\textsuperscript{119} See Council Regulation 2309/93, 1993 OJ (L214) (EEC) (establishing the European Medicines Agency for the Evaluation of Medicinal Products). Following extensive early collaborations between regional groups of member states, the European Union established the European Medicines Agency for the purpose of coordinating regulatory oversight of pharmaceutical industry within the Union. \textit{Id.} \textit{See also} DUKES, supra note 25, at 120 (describing early collaboration between regulatory agencies of European countries). In addition to providing for harmonized regulatory standards, the European Medicines Agency also functions as a liaison between the E.U. and the WHO and the ICH conference. \textit{See Overview of European Medicines Agency, at} http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm (last visited Apr. 8, 2008) (indicating how the organization functions).

\textsuperscript{120} See RATANAWIJITRASIN \& WONGDEMAGEGNEHU, supra note 117, at 1 (providing background on the development of pharmaceutical regulation and describing drug regulation as “a public policy response to the perceived problems or perceived needs of society.”). \textit{See also} DUKES, supra note 25, at 122. Sociological differences will impact how countries regulate their pharmaceutical industry. \textit{See id.} Against the need to protect the public, there is competing public and industry pressure to allow treatments for life threatening conditions to reach the market, sometimes based on the argument that unnecessary delay is tantamount to murder. \textit{Id.} at 125 (noting past criticism
one author notes, "[s]ome aspects of the quality of a drug can be defined in exact mathematical terms, but neither safety nor efficacy can be so rigidly circumscribed ... [N]o drug can be expected to prove effective in 100% of the patients for whom it is prescribed, and no drug is entirely free of adverse reactions." In light of this consideration, it is unlikely that a comprehensive, uniform standard of regulatory approval will emerge in the near future.

Slow progress toward total harmonization of regulatory standards and procedures should not impede the use of orphan drug legislation to further existing efforts to combat tropical disease. At least with respect to the U.S. and E.U., there has been considerable effort to establish a workable degree of regulatory harmonization. In 1990, the U.S., E.U. and Japan established the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). Recognizing the international nature of the pharmaceutical industry, the participants sought to eliminate redundant testing and data production that arises during repeated regulatory review. Currently, although U.S.
federal regulation restricts the exportation of pharmaceutical products without prior safety assessment by the FDA, products can be exported if they have received marketing approval from regulatory authorities in the European Community. Additionally, in 2004, the U.S. and E.U. announced a program whereby the FDA and European Medicines Agency would provide parallel scientific advice to drug sponsors.

Regarding orphan drugs programs, it should be noted that the success of the U.S. and Japanese orphan drug programs inspired lawmakers in the E.U. to establish a similar program. Additionally, as mentioned, in 2007, the FDA and European Medicines Agency promulgated a common form for use in applying to both the FDA and European Medicines Agency for orphan designation. This suggests a willingness to collaborate in matters related to orphan approval.

C. Possible Course of Action at the International Level

One option for making orphan drug programs more useful in fostering the development of treatments for diseases of poverty might be to allow tax incentives and grants afforded under a given nation’s orphan drug program to be credited toward its assessed contributions to the WHO. Existing orphan drug programs are largely

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130 See Regulation 141/2000, ¶ 2, 2000 O.J. (L18) 1 (EC) (noting U.S. and Japanese orphan programs and need for similar program within the E.U.); see also DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 42-50 (describing common derivation from the U.S. ODA of Australian and Japanese orphan programs). The Australian program allows U.S. FDA approval of orphan drugs to serve as a basis for marketing approval in Australia. Id. See also Scott et al., supra note 67, at 4 (explaining key feature of Australian orphan drug program). See also DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 15 (indicating that an unedited FDA evaluation report to be utilized in Australia’s evaluation process). But see id. at 14-15. The U.S. FDA has been reluctant to provide unedited regulatory reports to Australian authorities. Id. See also infra, Part III.F (discussing FDA reluctance).
132 Id. See also Michael J. Malinowski, Globalization of Biotechnology and the Public Health Challenges Accompanying It, 60 ALB. L. REV. 119, 153 (describing establishment of European Medicines Agency and the potential for collaboration with the FDA).
133 See ASSESSED CONTRIBUTIONS, supra note 110 (describing assessed contributions and collection rates). See also Lipkus, supra note 20, at 408 (noting the “chronic under-funding” of
funded by national governments in order to develop treatments for individual citizens with rare conditions.\textsuperscript{134} Allowing expenditures made in support of tropical disease initiatives to be offset against past due or outstanding obligations to the WHO might encourage involvement by national governments.\textsuperscript{135} In the U.S., for example, with the threat of a recession, an ongoing war, and a rising tide of home foreclosures, it is unlikely that funding neglected disease initiatives will be one of Congress's top priorities.\textsuperscript{136} However, allocating money to fund research for diseases of poverty becomes more likely if such expenditures can be used to offset obligations to the WHO.\textsuperscript{137}

Another approach would be for the WHO to create new drug prequalification programs.\textsuperscript{138} The WHO established a prequalification program to assure importing countries that treatments for AIDS/HIV are manufactured according to international standards.\textsuperscript{139} It also established a similar tuberculosis prequalification program.\textsuperscript{140} If similar programs were implemented to cover diseases of poverty, prequalification could eliminate the need for costly monitoring by disease endemic countries.\textsuperscript{141}

\textsuperscript{134} See 21 U.S.C.A. § 360ee (2007) (providing for government funded incentives to compel development of treatments for orphan conditions).

\textsuperscript{135} Cf. Lipkus, supra note 20, at 413-14 (describing need for “Strategic Value Proposition” in the context of Public-Private endeavors). Lipkus describes the need to create value for all parties involved in a given effort. \textit{Id.} By extension, the WHO could create strategic value propositions to help induce members to contribute to its efforts to combat tropical disease. \textit{Id.}


\textsuperscript{137} Cf. Lipkus, supra note 20, at 413-14 (observing need to create value for parties involved in public-private partnership).

\textsuperscript{138} See WHO Prequalification Programme, \textit{at} http://www.who.int/prequal/ (describing objectives of prequalification program) (last visited Apr. 8, 2008); \textit{see also} CREES E ET AL., supra note 115, at 100 (describing prequalification program for AIDS drugs). According to Creese et al., in compiling a list of approved products, WHO inspectors “spent up to two weeks at each factory making inspections.” \textit{Id.}

\textsuperscript{139} CREESE ET AL., supra note 115, at 100 (describing prequalification program for AIDS drugs).

\textsuperscript{140} CREEESE ET AL., supra note 115, at 100.

\textsuperscript{141} CREESE ET AL., supra note 115, at 100.
D. Enhancing Clinical Standards in Disease Endemic Countries

For manufacturers from the U.S. or the E.U. to work effectively with researchers in developing countries, it is essential to establish common clinical standards. Both industry representatives and regulators have acknowledged that the absence of any regulatory or clinical infrastructure is a problem for researchers conducting clinical trials in developing countries. However, many countries simply do not have the resources to implement a comprehensive regulatory system. Even where countries have established legal standards that prescribe the manner in which clinical trials should be executed, regulatory authorities are sometimes unable to police clinical trials undertaken in their jurisdiction.

142 See PRECIOUS MATSOSO ET AL., WHO, HOW DOES THE REGULATORY FRAMEWORK AFFECT INCENTIVES FOR RESEARCH AND DEVELOPMENT? 53 (2005) (discussing clinical trials in developing countries and providing results of survey response by industry representatives and regulators in developing countries). One of the key difficulties for sponsors of clinical trials is “demonstrating [ing] reliability of data and confirming [ing] that clinical trials were conducted in accordance with good clinical practice.” Id. Regulatory authorities from disease endemic countries acknowledge that they lack the capacity to provide oversight for clinical research. Id. See also Joe Stephens, WHERE PROFITS AND LIVES HANG IN BALANCE, WASH. POST, Dec. 17, 2000, at A01 (describing conduct of clinical trial in Nigeria where doctors failed to switch course of treatment despite rapid decline of patient’s health).

143 See MATSOSO ET AL., supra note 142, at 24 (describing need for responsive regulatory process). "Pharmaceutical markets that are poorly regulated pose significant threats to public health.” Id. Frequently data produced in clinical trials conducted in developing countries is not sufficient to allow for marketing approval elsewhere. Id. at 53. Unfortunately, many developing countries lack trained staff to ensure the safety and efficacy of pharmaceutical products and in some developing countries there is no established procedure for approving clinical trials. See also Lipkus, supra note 20, at 390-91 (describing problems lack of infrastructure creates for private researchers in developing countries). Additionally, from a human rights perspective, the apparent absence of ethical review of clinical trials in developing countries is alarming. MATSOSO ET AL., supra note 142, at 54.

144 See RATANAWIJITRASIN AND WONGDEMEGEGNEHU, supra note 117, at 53 (noting common lack of human resources to carry out regulatory activity). While roughly 70% of WHO member countries have at least some level of pharmaceutical regulation, only 20% have comprehensive drug regulation programs. Id. Those that do are industrialized countries, not developing countries. Id. In fact, relatively few countries actually have regulatory systems that enable them to carry out independent reviews. Id. at 10 (providing statistics concerning regulatory capacity of WHO member states).

145 See Karen DeYoung and Deborah Nelson, LATIN AMERICA IS RIPE FOR TRIALS, and FRAUD, WASH. POST, Dec. 21, 2000, at A01 (noting difficulty on the part of regulatory authorities in policing clinical trials conducted in Latin America). It is apparent from DeYoung and Nelson’s article that many areas of Latin America do in fact have modern clinical infrastructure and laws which criminalize unethical clinical behavior. Id. Because of this modern infrastructure and because of the cost savings realized by conducting clinical trials in Latin America versus North America, as
In this regard, one of the key accomplishments of TDR is the development of the research capacity of endemic country researchers.\textsuperscript{146} To compensate for the lack of regulatory capacity found in many disease endemic countries, TDR and public-private partnerships have focused on creating research systems in disease endemic countries that meet international standards of Good Clinical Practice.\textsuperscript{147} Fostering research capacity among scientists from disease endemic countries provides ownership and a foundation for developing a sustainable means of addressing problems facing affected populations.\textsuperscript{148} The approach taken by public-private partnerships seeks to ensure the accuracy of research data, while protecting human rights despite the absence of fully operable regulatory systems.\textsuperscript{149} The intended effect is a cohesive research endeavor that involves participants from various sectors and regions.\textsuperscript{150} The additional step of establishing incentive systems that run from countries with orphan drug programs to disease endemic countries will help to translate research into actual drug therapies.\textsuperscript{151}

well as a host of other factors, multi-national pharmaceutical companies have begun flocking to Latin America to conduct clinical trials. \textit{Id.} The effect is that regulatory agencies are unable to fully monitor all trials. \textit{Id.} Additionally, in some instances they face pressure from major pharmaceutical companies to take unethical measures. \textit{See id.} According to an individual interviewed by DeYoung and Nelson, pharmaceutical companies try to pressure authorities to remove as many regulatory impediments as possible. \textit{Id.}

\textsuperscript{146} \textit{See} \textit{MAKING A DIFFERENCE, supra} note 21, at 5. Capacity building is one of the key goals of TDR. \textit{Id.} The goal is to spread scientific knowledge more equitably so that the benefit of medical technology reaches persons outside the wealthiest countries in the world. \textit{See id.}

\textsuperscript{147} \textit{See} \textit{MAKING A DIFFERENCE, supra} note 21, at 1 (describing organization of groups working on issues affecting developing countries). TDR and its affiliates were originally an open grouping of “governments, international organizations, the private sector, non-governmental organizations (NGOs) and other civil society groupings, brought together under a single organizational umbrella.” \textit{Id.} at 5. \textit{See also} Lipkus, \textit{supra} note 20, at 423. Part of what DNDi has accomplished since it was conceived is to “identify[] organizations with complementary competencies developed by countries and companies which have historically adapted to economic and political circumstances.” \textit{Id.}

\textsuperscript{148} \textit{MAKING A DIFFERENCE, supra} note 21, at 4-5. TDR has foregone a centralized approach in favor of a strategy that involves training groups of researchers from disease endemic countries and empowering them to “to identify their own problems, find novel solutions and press for the transformation of research knowledge into disease-control programmes.” \textit{Id.} \textit{But see} Lipkus, \textit{supra} note 20, at 408 (noting chronic under-funding of TDR).

\textsuperscript{149} \textit{Cf.} \textit{SIMON BELCHER ET AL., EUROPEAN AND DEVELOPING COUNTRIES CLINICAL TRIALS PARTNERSHIP, ANNUAL REPORT 18 (2006)} (describing efforts to ensure clinical trial compliance with Good Clinical Practice and simultaneous regulatory capacity development), \textit{available at} http://www.edctp.org/Publications.11.0.html.

\textsuperscript{150} \textit{See} \textit{MAKING A DIFFERENCE, supra} note 21, at 4 (describing efforts to bring together participants from different sectors).

\textsuperscript{151} \textit{See infra} Part II.A; notes 60-65 (discussing compatibility of orphan programs with public-private partnerships).
E. Actions by the European Union and Its Member States

Given the E.U.'s supranational nature, agencies and committees established by the E.U. must be capable of cross-border collaboration. Accordingly, legislation governing the European Medicines Agency requires the agency to "provide technical and scientific support in order to improve cooperation between the Community, its Member States, international organizations and third countries on scientific and technical issues relating to the evaluation of medicinal products. . ." With respect to tropical disease, Article 58 of Regulation 726/2004 authorizes the European Medicines Agency to provide scientific opinions on the safety and efficacy of medicinal products that are intended for use outside the European Community on behalf of the WHO.

Expanding the European and Developing Countries Clinical Trials Partnership (EDCTP) represents one way to enhance the effectiveness of the E.U.'s orphan drug regime. Incubated as part of the European Community's Sixth Framework Programme, the EDCTP was established in order to coordinate much of Europe's collective research aimed at developing treatments for AIDS/HIV, malaria and tuberculosis. Decision 1209/2003 commits the E.U. to provide financial support for

152 See James Thuo Gathii, Rights, Patents, Markets and the Global AIDS Pandemic, 14 FLA. J. INT'L L. 261, 342-43 (2002) (explaining how E.U. regulatory agency has facilitated sharing of clinical data). Collaboration between regulatory agencies in Europe has shortened drug approval times. Id. This has also given rise to cost savings. Id. This approach advanced by the European Medicines Agency can be contrasted against the FDA's approach which places strict limitations on acceptance of clinical data produced under the authority of other regulatory agencies. Id. at 342-43 (contrasting the approaches taken by the FDA and European Medicines Agency with respect to acceptance of foreign clinical data). See also 21 C.F.R. § 314.106 (2002), § 312.120 (2002) (providing limitations on acceptance of foreign clinical data).

153 Regulation 726/2004, art. 58, 2004 O.J. (L 136) 24 (EC) (providing that the European Medicines Agency may give scientific opinions regarding medicinal products for use outside the E.U.). Id. This allows the regulatory infrastructure of the European Medicines Agency to be used to assess the safety and efficacy of products for use in, for example, initiatives to combat malaria. Id.

154 Id. at 21 (describing relation of EDCTP to the Sixth Framework Programme). See also id. at 8-9 (describing need to coordinate the efforts of Member States in addressing AIDS/HIV, malaria and tuberculosis). The key objective underpinning Council Decision 1209/2003 is the development of new treatments for HIV/AIDS, malaria and tuberculosis. Id. at ¶ 11.
Several current EDCTP clinical trials involve researchers from Europe and Africa. As a condition for receiving funding, the partnership must support clinical trials in Sub-Saharan Africa and foster capacity development in developing countries. In particular, the Netherlands, as part of its EDCTP commitment, has collaborated with the WHO to “develop a regulatory framework to ensure appropriate oversight of clinical trials in Africa.” The ultimate goal is to create permanent regulatory infrastructure that meets international standards.

157 Id. at Art. 1(2) (providing support in the amount of EUR 200 million for EDCTP).
158 See SIMON BELCHLER ET AL., supra note 149, at 12. For example, two trials for malaria treatments for children involve researchers from Austria, Belgium, France, Germany, Spain and the UK. Id. They are working in collaboration with researchers in Burkina Faso, Gabon, Gambia, Ghana, Kenya, Malawi, Mozambique, Nigeria, Rwanda, Tanzania, Uganda and Zambia. Id. Interestingly, though the U.S. is not a member of the EDCTP, one of the trials is sponsored by the Office of the Army Surgeon General, Walter Reed Medical Hospital. Id. (indicating clinical trials receiving funding from EDCTP). Groups working with EDCTP, including the public-private partnership Medicines for Malaria Venture (MMV), successfully carried out several trials for artemisinin-derived products to treat malaria. See id. One of the drugs assessed was dihydroartemisinin-piperaquine. Id. See also infra Part II.C and notes 104-106. Based on the assessment, the manufacturer was able to obtain orphan designation for the product. See MMV, Orphan Drug Status for MMV Drug DHA-Piperaquine, available at http://www.mmv.org/article.php3?id_article=378&recherche=orphan (last visited Apr. 8, 2008). The hope in obtaining orphan designation is that this will speed up registration of the product. Id. See also infra Part II.C; notes 104-06.
159 Council Decision 1209/2003, art. 7 2003 O.J. (L169) (EC) (indicating that conditions for funding require compliance with Annex I of Decision 1209/2003). See also id. Annex I(2) (requiring support for clinical trials and capacity development). The decision granted approval and funding for a joint initiative aimed at combating HIV/AIDS, malaria and tuberculosis. Id. The intent was to unify efforts by Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom to combat the three pandemics. Id. at ¶ 9. Among the key goals, the participants seek to develop capacity in developing countries, to support clinical trials in developing countries and to coordinate efforts by member states. See id. at Annex I. The activities of the partnership also include capacity development. Id. See also BELCHER ET AL., supra note 149, at 2.
160 See MATSOSO ET AL., supra note 142, at 61-62 (noting objectives of the initiative). In the past, researchers from developed countries would conduct investigations in disease endemic countries, gather data and return home to report findings. Id. The new initiative aims to bring the capacity to ensure proper clinical research up to international standards, thereby providing a platform for ongoing research. Id. The text of Council Decision 1203/2003 clearly indicates that the trial procedures established should be consistent with recognized ethical and clinical standards. See Council Decision 1209/2003, at ¶ 19 (indicating that research efforts should “conform to basic ethical principles... and apply the best clinical practices”). In fact, funding for participants is
The text of the Council Decision indicates that the Council would consider funding a program based on the EDCTP model to treat diseases of poverty. Implementation of such a program would provide a clinical structure for developing treatments for diseases of poverty. Clinical data derived from program activities could then be used to support orphan designation, which would allow for access to other incentive sources.

F. Legislation and Regulation that Affects U.S. Orphan Drug Manufacturers’ Ability to Contribute to Public-Private Partnerships

A provision of the Food and Drug Administration Act of 2007 supports priority review of new drugs for the treatment “tropical diseases.” Under this provision, sponsors of tropical disease treatments may obtain “priority review vouchers,” entitling them to expedited regulatory review. Since many disease endemic contingent upon demonstrating compliance with scientific and ethical standards. Id. at Art 2. In light of existing standards established by the European Medicines agency, the implication is that these clinical procedures established with the support of Council Decision 1209/2003 should have specific criteria for the protection of participants in clinical trials and should comply with the requirements of good clinical practice. See Council Directive 2001/20, Art. 3, 2001 O.J. (L 121) 37 (EC) (providing that clinical trials may only be carried out based on risk analysis and, generally, only after the participant has given informed consent). See also Commission Directive 2005/28, ¶ 8, 2005 O.J. (L 91) 35 (EC) (instructing member states to enact legislation reflecting the standards of Good Clinical Practice agreed upon through the International Conference on Harmonization). Under the E.U.'s regulatory system, compliance with the ICH’s guidelines for good clinical practice is mandatory for member states, meaning all members must implement similar clinical standards. Id. But see CREESE ET AL., supra note 115, at 99. Some studies suggest that the degree of regulatory assessment of products to be exported from E.U. member states is not equivalent to the assessment given to products for use inside the E.U. Id. According to the WHO, not all countries in the E.U. condition export on eventual regulatory review in the importing country. Id.

See Council Decision 1209/2003, at ¶ 11 (indicating that the Council would also consider supporting a similar initiative aimed at diseases of poverty).

Cf. BECHER ET AL., supra note 149 (describing EDCTP efforts, including support for establishment of permanent clinical trial capacity in developing countries).


§ 360n(a)(1)-(2). Under this provision, the applicant is issued a voucher for review of a
countries lack the regulatory infrastructure to carry out independent evaluations, FDA review provides a valuable assessment. Additionally, for pharmaceutical products exported from the U.S., U.S. law generally requires marketing approval by the FDA or by a national regulatory body with standards similar to those of the FDA.

The FDA's stringent conditions on acceptance of foreign clinical data may create an impediment for U.S. manufacturers seeking priority review vouchers. Because few people in the U.S. suffer from diseases of poverty, significant portions of clinical trials must occur in disease-endemic countries. For FDA approval based on foreign data alone, federal regulation requires that,

1. The foreign data must be applicable to the U.S. population and U.S. medical practice;
2. The studies have been performed by clinical investigators of recognized competence; and
3. The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means.

Some scholars have argued that these conditions "do not facilitate the easy exchange of clinical data." The European Medicines Agency, for example, generally treatment for a tropical disease treatment, which "entitles the holder of such voucher to priority review of a single human drug application..." §360n(a)(2). As defined by the amendment, tropical diseases include "infectious diseases for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations..." §360n(a)(3)(Q).

Cf. DUKES, supra note 25, at 272. "[T]he regulatory authorities of industrialized countries have... assumed much of the de facto responsibility for ensuring that the medicines available attain satisfactory standards as regards their quality and the suitability for the purpose for which they are to be sold." Id.


See Gathii, supra note 152, at 342-43 (describing stringent FDA requirements for foreign clinical data).

See DUKES, supra note 25, at 280 (noting incentive to conduct clinical trials in developing countries when a treatment is aimed at treating conditions which are rare elsewhere).

21 C.F.R. § 314.106 (2002). See also Gathii, supra note 152, at 342 (discussing FDA requirements).

Gathii, supra note 152, at 342-43 (comparing FDA approach to foreign clinical data to E.U. approach). The FDA's reluctance to share clinical data also is evident in its protective approach to clinical data submitted by U.S. manufacturers pursuant to orphan drug approval. See DEPARTMENT OF HEALTH AND AGED CARE, supra note 54, at 15 (describing lack of FDA cooperation). Australia's orphan drug program was drafted to allow an unedited FDA evaluation
places fewer restrictions on the acceptance of foreign data. Because most clinical research on diseases of poverty must occur in disease endemic countries, the European Medicines Agency's more collaborative regulatory approach allows it to serve as a more efficient reviewing body than the FDA.

The ODA actually provides a remedy to this problem. Orphan designation is available for products aimed at treating diseases of poverty. Because orphan designation allows for protocol assistance by the FDA, manufacturers and public-private partnership developing treatments for diseases of poverty can seek guidance from the FDA in designing clinical trial procedures. If acceptable to the FDA, clinical data obtained by researchers in disease endemic countries could make collaboration between U.S. manufacturers and public-private partnerships more efficient.

report to serve as a surrogate for regulatory review in Australia. While the FDA makes its evaluation reports available to the public, it redacts them to avoid disclosing "commercially sensitive information." To request the unedited report, both the manufacturer and the Australian agency must submit a prescribed set of documents and requests and, because of the delays that frequently attend this process and statutory the requirement obligating Australian regulatory authorities to review applications for marketing approval within 255 days, they are forced to carry out an independent clinical trial. 173

See Gathii, supra note 152, at 342 (noting that E.U. regulation is less restrictive). According to Gathii, unlike the FDA, the European Medicines Agency is aimed at both protecting the public and also fostering trade. In fairness, the conditions the FDA places on the acceptance of foreign data are intended to ensure that assessment of the safety and efficacy of a drug is based on accurate data and that clinical trials are conducted in accordance with recognized human rights standards, in particular the standards set forth in the Helsinki Declaration. Cf 21 C.F.R. § 312.120(a), (c) (2002) (indicating need for safety of clinical trial and accuracy of data that is not submitted as part of an investigational new drug application). The Helsinki Declaration which enunciates standards for the protection of human rights during the course of medical research. §312.120(c)(4). The conduct of pharmaceutical companies in the developing world since the mid 1990's suggests that placing conditions on the acceptance of foreign clinical data was a warranted precaution. See Joe Stephens, Where Profits and Lives Hang in Balance, WASH. POST, Dec. 17, 2000, at A01. Stephens's article is one of several published as a part of a series called "The Body Hunters" in the Washington Post. See also Karen DeYoung and Deborah Nelson, Latin America Is Ripe For Trials, and Fraud, WASH. POST, Dec. 21, 2000, at A01. The series sounded an alarm regarding the practices of pharmaceutical companies in developing countries. Id.

Cf. Gathii, supra note 152, at 342-43 (noting stringency of FDA requirements for acceptance of foreign clinical data).


See infra Part II.A; notes 61-65 (discussing applicability of orphan designation for diseases of poverty).

See Milne, Kaitin & Ronchi, supra note 4, at 5 (describing "availability of technical and administrative assistance ... provided directly by the [FDA]").

See Gathii, supra note 152, at 132 (noting increased efficiency of clinical trials as a result of
One way to complement the incentives available under the ODA would be to modify the Federal Food, Drug and Cosmetic Act to allow for export based on approval by a WHO-supported program, or reputable public-private partnerships. This change would eliminate the need to undertake a costly pre-export review in the U.S. The Federal Food Drug and Cosmetic Act allows for export of pharmaceuticals from the U.S. prior to receipt of FDA marketing approval in narrow circumstances. Generally, drugs that have not received FDA marketing approval may be exported from the U.S. only if they receive marketing approval from countries with advanced regulatory regimes. The purpose underlying the conditions placed on exportation is to prevent

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FDA involvement in trial design. See also Rohde, supra note 17, at 342-43 (describing FDA’s unwillingness to accept foreign clinical data).

179 See 21 U.S.C.A. § 355(a) (2007) (indicating that new drugs must receive approval from the Secretary of Health and Human Services before being introduced into interstate commerce). See also 21 U.S.C.A. § 382 (2007) (describing conditions under which pharmaceutical products may be exported from the U.S. for marketing purposes).

180 CONGRESSIONAL BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 20 (2006) (discussing cost and time to develop a new drug). According to the Congressional Budget Office study, it takes on average 11.8 years and $802 million dollars to bring a new molecular entity to market in the U.S. See also Kuszler, supra note 15, at 950 (describing phases of clinical trial undertaken pursuant to FDA approval). See also Kevin Outterson, Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets, 5 Yale J. Health Pol’y, L, & Ethics 193, 236-37 (2005) (discussing inefficiency of national drug regulation and its effect on drug access).

181 See 21 U.S.C.A. § 382 (2007) (indicating conditions under which a drug may be exported without prior FDA approval).

182 21 U.S.C.A. § 382(b) (2007). Currently drugs may be exported based on prior marketing approval in Australia, Canada, Israel, Japan, New Zealand, Switzerland, or South Africa. 21 U.S.C.A. § 382(b)(1)(A)(i) (2007). Additionally, drugs may be exported without prior FDA approval where they have been approved by “the European Union or a country in the European Economic Area… if the drug or device is marketed in that country or the drug or device is authorized for general marketing in the European Economic Area.” 21 U.S.C.A. § 382(b)(3)(A) (2007) (requiring adequate proof that the treatment is safe and that the drug is requested by the importing country). The Secretary of Health and Human Services may, by regulation, modify the list of countries whose marketing approval is sufficient to allow for export from the U.S. provided any countries added are able to ensure the safety and efficacy of the products. 21 U.S.C.A. §382(b)(1)(B) (2007). Any countries added to the list must have statutory and regulatory requirements providing for review by competent experts. 21 U.S.C.A. §382(b)(1)(B)(i) (2007). Further, the “marketing authorization system in such country or countries [must be] equivalent to the systems in the countries described in clauses (i) and (ii) of subparagraph (A).” 21 U.S.C.A. §382(b)(1)(B)(ii) (2007). In other words, the marketing authorization system should be equivalent to the enumerated list of acceptable countries (i.e., Australia, Canada, etc.). See 21 U.S.C.A.
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avoidable pharmaceutical disasters, like the Elixir Sulfanilamide and Thalidomide disasters, from occurring as a result of U.S. exports.\textsuperscript{183}

One exception to the requirement that exported drugs must receive prior marketing authorization from a country with an advanced regulatory regime is described at 21 U.S.C.A. § 382(e).\textsuperscript{184} Under this subsection, drugs designed to treat tropical disease may be exported from the U.S. provided the Secretary of Health and Human Services "finds that the drug . . . will not expose patients in such country to an unreasonable risk . . . and the probable health benefits from the use of the drug . . . outweigh the risk of injury . . . ."\textsuperscript{185}

The European Medicines Agency can provide scientific opinions for products that are intended for use outside the European Community on behalf of the WHO.\textsuperscript{186} In contrast, the text of the U.S. export statute calls for prior marketing approval inside the European Community, not simply a scientific opinion provided on behalf of another organization.\textsuperscript{187} It is not clear whether a scientific opinion for products not intended for use in the E.U. would fall short of the requirements for export of unapproved pharmaceutical products.\textsuperscript{188} Additionally, the tropical disease export exception places the burden of showing the treatment's safety on the manufacturer.\textsuperscript{189} Providing U.S. manufacturers with a clear export procedure would enhance their ability to collaborate with public-private partnerships.\textsuperscript{190}

\textsuperscript{183} See 21 U.S.C.A. §382(b)(1)(B) (2007) (indicating that if drugs are exported pursuant to marketing approval by a foreign country, the country must have statutory and regulatory provisions to ensure that approved drugs are in fact safe). Compare 21 C.F.R. § 312.110(b)(1) (2002); § 312.120(a) (2002) with 314.106(a)-(b) (2002). See also James L. Zelenay, Jr., The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration? 60 FOOD & DRUG L.J. 261, 261 (2005) (describing FDA response to the Elixir Sulfanilamide and thalidomide disasters).

\textsuperscript{184} 21 U.S.C.A. § 382(e)(1) (2007) (providing conditions under which a drug or device to treat, prevent or diagnose tropical disease may be exported in lieu of formal marketing approval).


\textsuperscript{186} See Council Regulation 726/2004, Art. 58, 2004 O.J. (L136) 3 (EC). "The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use outside the Community." Id.

\textsuperscript{187} See 21 U.S.C.A. § 382(b)(1)(A) (2007) (indicating that valid marketing approval from the European Union is necessary to allow for exportation).

\textsuperscript{188} See id.


\textsuperscript{189} Cf. Outterson, supra note 180 at 236-37 (discussing need for more efficient drug regulation). Outterson notes the inefficiency of national regulatory regimes and proposes a "reference approval system." Id. at 237. Under a reference system, "safety and efficacy testing would be
Conclusion

Recent efforts by intergovernmental organizations and public-private partnerships have brought new life to ongoing efforts aimed at generating treatments for diseases that affect millions of people in rural areas of developing countries. Organizations like DNDi have made progress in addressing long-ignored public health threats. Part of their success is attributable to their ability to stretch the value of public and private contributions as far as possible. Despite significant contributions, organizations like TDR and DNDi face severe financial constraints. While these recent efforts have shown promise, for many diseases of poverty, like Chagas disease, no safe and effective treatments currently exist.

Perhaps recognizing that private industry is more capable of converting basic research into actual treatments, many countries have passed orphan drug legislation to encourage private industry to research and develop treatments for rare conditions. By lowering financial barriers to drug development, these incentives allow manufacturers to justify investment in otherwise unprofitable markets. With modest statutory, regulatory and policy changes, they might also provide crucial support for intergovernmental organizations and public-private partnerships working to eliminate diseases of poverty.

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 referenced against approval in certain benchmark countries.  Id. This would have the affect of increasing access to medications in developing countries. Id. The reference system Outterson proposes is similar to the Federal Food Drug and Cosmetic Act proposed in section III.F of this note. Id. See also infra, section III.F.