Pharmaceutical Progress for Neglected Diseases: Using Non-Traditional Development Models to Overcome Market Deficiencies

by

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Program in Bioethics and Science Policy
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Michael Waitzkin

Thesis submitted in partial fulfillment of the requirements for the degree of Master of Arts in the Program in Bioethics and Science Policy in the Graduate School of Duke University

2015
ABSTRACT

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Abstract

Technological advancements and developments in public and private sector medical research capacities have ushered an era of novel therapies and hopes against illness and disease at an unprecedented rate. However, not all diseases have fared similarly in this era of progress. Neglected diseases, those that afflict large numbers of the impoverished, continue to impart significant morbidity, mortality, and economic damage, largely unchecked, due to persistent deficiencies in treatment options. Inadequacies in pharmaceutical development comprise a major component of the problem, due to exorbitant costs associated with the drug approval process, combined with financial inequalities of the target clientele. Despite this market failure, in certain cases, drugs have in fact been developed and approved for use against neglected diseases. However, given the unique economic circumstances, such developments have often been funded, supported, and catalyzed through nontraditional means. The innovation and development policy mechanisms that yielded such progress against difficult odds can serve as models upon which to build and promote future pharmaceutical development for neglected diseases, if these mechanisms are explicitly characterized and common trends associated with successful drug production are identified. This thesis performs exactly such an analysis, by identifying relevant instances of approvals of drugs for neglected diseases, exploring their development
histories, characterizing such histories into broad categories, and evaluating those broad categories against one another. In an examination of eighteen such approvals that occurred between 1989 and 2014, this thesis finds that six broad categories of development incentive policies were employed: (1) product development partnerships, (2) private pharmaceutical industry development, (3) corporate philanthropy, (4) military development, (5) priority review voucher issuance, and (6) intellectual property transfer. Of these policies, the product development partnership mechanism accounted for the most drug approvals, across a diverse array of diseases and jurisdictions, which suggests a particular robustness of this policy mechanism. As such, this thesis will contend that this particular policy mechanism theoretically, as well as empirically, represents the most propitious policy option for future endeavors to reduce the societally detrimental effects of the persistence of neglected diseases.
Contents

Abstract ................................................................................................................................. iv

List of Tables ......................................................................................................................... x

List of Figures ........................................................................................................................ xi

Acknowledgements ................................................................................................................ xii

Introduction ............................................................................................................................ 1

1. Rudiments of a Public Health Deficiency ........................................................................ 3
   1.1 Market Failure: Insufficient Research and Development ......................................... 3
   1.2 Public Health and Economic Impact of Neglected Diseases ..................................... 5

2. Identification of Neglected Diseases and Relevant Drug Approvals .............................. 8
   2.1 Defining Neglected Diseases for Identification ......................................................... 8
   2.2 Relevant Drug Approvals Associated with Neglected Diseases ............................... 10
       2.2.1 Timeframe and Type of Approvals .............................................................. 11
       2.2.2 Approvals from the U.S. Food and Drug Administration (FDA) .................... 12
       2.2.3 Approvals from the E.U. European Medicines Agency (EMA) ....................... 13
       2.2.4 Approvals from Other Regulatory Agencies .................................................. 14

3. Characterization of Development Histories into Incentive Mechanisms and Policy
   Approaches ......................................................................................................................... 15
   3.1 Exploration of Incentive Policy Options .................................................................... 16
   3.2 Potential Incentive Mechanisms .............................................................................. 19
   3.3 Actual Incentive Mechanisms .................................................................................. 22
   3.4 Characterizations of Approved Products .................................................................... 23
3.5 Individual Histories

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5.1 Product Development Partnerships</td>
<td>25</td>
</tr>
<tr>
<td>3.5.1.1 Artemether &amp; Lumefantrine (Coartem) for Malaria</td>
<td>26</td>
</tr>
<tr>
<td>3.5.1.2 Artemotil (Arteceft) for Malaria</td>
<td>28</td>
</tr>
<tr>
<td>3.5.1.3 Pyronaridine &amp; Artesunate (Pyramax) for Malaria</td>
<td>29</td>
</tr>
<tr>
<td>3.5.1.4 Artesunate (Artesun) for Malaria</td>
<td>30</td>
</tr>
<tr>
<td>3.5.1.5 Dihydroartemisinin &amp; Piperaquine (Eurartesim) for Malaria</td>
<td>31</td>
</tr>
<tr>
<td>3.5.1.6 Benznidazole (pediatric) for Chagas Disease</td>
<td>32</td>
</tr>
<tr>
<td>3.5.1.7 Miltefosine (Impavido) for Leishmaniasis</td>
<td>33</td>
</tr>
<tr>
<td>3.5.2 Private Pharmaceutical Industry Development</td>
<td>35</td>
</tr>
<tr>
<td>3.5.2.1 Rifabutin (Mycobutin) for Tuberculosis</td>
<td>35</td>
</tr>
<tr>
<td>3.5.2.2 Rifapentine (Priftin) for Tuberculosis</td>
<td>36</td>
</tr>
<tr>
<td>3.5.2.3 Moxifloxacin (Avelox) for Tuberculosis</td>
<td>36</td>
</tr>
<tr>
<td>3.5.2.4 Delamanid (Deltyba) for Tuberculosis</td>
<td>37</td>
</tr>
<tr>
<td>3.5.3 Corporate Philanthropy</td>
<td>38</td>
</tr>
<tr>
<td>3.5.3.1 Ivermectin (Stromectol/ Mectizan) for Onchocerciasis</td>
<td>38</td>
</tr>
<tr>
<td>3.5.3.2 Atovaquone &amp; Proguanil (Malarone) for Malaria</td>
<td>40</td>
</tr>
<tr>
<td>3.5.3.3 Nitazoxanide (Alinia) for Cryptosporidiosis</td>
<td>40</td>
</tr>
<tr>
<td>3.5.4 Military/ Wartime Development</td>
<td>41</td>
</tr>
<tr>
<td>3.5.4.1 Mefloquine (Lariam) for Malaria</td>
<td>42</td>
</tr>
<tr>
<td>3.5.4.2 Halofantrine (Halfan) for Malaria</td>
<td>43</td>
</tr>
<tr>
<td>3.5.5 Priority Review Voucher Issuance</td>
<td>44</td>
</tr>
</tbody>
</table>

vii
3.5.5.1 Bedaquiline (Sirturo) for Tuberculosis .................................................44

3.5.6 Intellectual Property/ Data Transfer.................................................................45

3.5.6.1 Para-Aminosalicylic Acid (Granupas) for Tuberculosis ..............................45

4. Merits and Deficiencies of Neglected Disease Pharmaceutical Development Incentive
   Mechanisms ........................................................................................................47

4.1 Development Incentive Mechanisms of Recent Approvals ............................47

4.1.1 Product Development Partnerships ...............................................................49

4.1.1.1 Medicines for Malaria Venture (MMV) ......................................................50

4.1.1.2 Drugs for Neglected Diseases Initiative (DNDi) .......................................52

4.1.2 Private Pharmaceutical Industry Development .............................................56

4.1.3 Corporate Philanthropy ..................................................................................57

4.1.4 Military/ Wartime Development .................................................................58

4.1.5 Priority Review Voucher Issuance ...............................................................59

4.1.6 Intellectual Property/ Data Transfer .............................................................61

4.2 Differential Capabilities of Development Incentive Mechanisms ....................61

5. Efficacy of the Product Development Partnership Model: Underlying Factors ....64

5.1 NGO-Mediated Partnerships ............................................................................64

5.2 Dynamics of the Product Development Partnership Mechanism ..................66

5.2.1 An Infrastructure of Collaboration ...............................................................66

5.2.2 Partner Organizations for Each Stage of the Development Pipeline ..............69

5.2.3 Advantages in Ethics and Political Optics .....................................................72

5.2.4 Limitations ....................................................................................................74
List of Tables

Table 1: Neglected Diseases by Infectious Agent.................................................................10
Table 2: FDA Approvals for Neglected Disease Indications..............................................12
Table 3: EMA Approvals for Neglected Disease Indications ............................................13
Table 4: Approvals from Agencies Other Than the FDA or EMA ..................................14
Table 5: CEWG Incentive Mechanism Categories.........................................................20
Table 6: Development Incentive Mechanisms and Abbreviations of Reference..............23
Table 7: Primary Incentive Mechanisms for Product Development.................................24
List of Figures

Figure 1: Proportions of Development Incentive Mechanisms Amongst Approvals........48

Figure 2: Schematic of Possible Organizational Contributions (Financial or Operational) Across the Drug Development Pipeline in PDP Collaborations ..............................................71
Acknowledgements

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**Introduction**

Neglected diseases represent a significant and enduring contemporary global public health deficiency. These diseases, typically defined as those that disproportionately impact the poor in economically less developed settings, have been estimated to collectively contribute to approximately thirty five thousand deaths per day globally [1]. In addition to mortality, morbidity is a major result as well [2]. Overall, it is estimated that upwards of one billion people, across 149 countries worldwide, are subject to the effects of these diseases, which inflict billions of dollars of economic damage internationally [3].

Despite the significant and negative public health impact, a market deficiency exists with regard to the development of novel therapeutic options [1]. This is due to a combination of factors. The stringent and costly clinical trial requirements associated with drug development, along with inauspicious prospects for pharmaceutical firms to profit from products designed for the poor, create barriers to pharmaceutical development in this context.

However, despite these inherent barriers, pharmaceutical products have indeed been produced and approved, in some cases, for neglected diseases. This means that these products were developed fully, from the initial pre-clinical and laboratory studies to the final phase III human clinical trials, ultimately gaining regulatory approval and the concomitant market availability. As such, these cases represent instances in which bleak odds were overcome and health prospects of affected patients were improved.
Despite these drug approvals, more progress remains to be made, as many diseases continue to lack treatment options, and large numbers of patients continue to experience morbidity and mortality as a result. Fortunately, the past instances of drug approvals for neglected diseases suggest that future developments and approvals are realistic possibilities. The key to ensuring that such possibilities become realities will be to examine exactly what scientific and health policy mechanisms allowed for market deficiencies to be overcome and products to be developed in the past instances of approvals.

This thesis performs exactly such an analysis. Recent instances of approvals of drugs for neglected diseases are identified. Subsequently, the histories that underpinned the drug development process in each case are elucidated. Once these histories are illustrated, development incentive policy mechanisms that were at play before and during the development process are identified and characterized into broad categories of development incentive policy mechanisms. Finally, these broad categories of incentive mechanisms are assessed, theoretically and practically, with regard to their potentials for success in future applications. Thus, potentially auspicious policy mechanisms can be identified and recommended for application against the many neglected disease therapeutic needs that persist.
1. Rudiments of a Public Health Deficiency

1.1 Market Failure: Insufficient Research and Development

The general structure and chronology of the pipeline of research and development that ultimately leads to the approval, production, and distribution of new drugs is lengthy and complex. Initial stages involve basic laboratory research that identifies new, potentially useful, compounds that may eventually be developed into medicines. Subsequent stages involve multiple stages of trials, first in non-human animals, then in humans, of candidate compounds. If such trials demonstrate sufficient efficacy and safety of novel compounds, then these compounds may ultimately be approved by regulatory agencies, produced by pharmaceutical companies, and marketed to patients as drugs. This process typically takes several years and can cost upwards of 800 million U.S. dollars per new drug, according to a 2003 study published in the *Journal of Health Economics* [4].

The development incentive mechanism of patent protection can assist to overcome the barriers created by high investment requirements regarding time and funding by providing market exclusivity to the pharmaceutical developer and allowing it to receive a financial return on investment from the patients to whom the newly developed drug is distributed. However, in cases of neglected diseases, where the majority of patients belong to significantly impoverished populations of developing countries, there is little purchasing power from the patient cohort to render market exclusivity useful to pharmaceutical companies. As Bernard Pecoul, the Executive
Director of the not-for-profit public health organization Drugs for Neglected Diseases Initiative, writes in a *PLoS Medicine* article, “the basic mechanics of the market-driven system are failing to help these populations,” suggesting a market failure in this context [5].

Indeed, this market failure is demonstrated in the proportions of drug approvals in recent decades. A 2002 study published in *The Lancet* found that, of the 1,393 novel drugs approved and marketed between 1975 and 1999, merely 16 of them, or approximately one percent, were for diseases that could be considered neglected, despite the fact that these diseases account for approximately ten percent of the global disease burden [6]. This deficiency in development persists in spite of significant medical need, as many neglected diseases continue to lack treatment options, and, amongst the treatment options that do exist, many are antiquated drugs that are prohibitively costly, induce difficulties with regard to clinical administration, and are poorly tolerated by patients [5].

However, scientific knowledge regarding potential new options for treatments does exist. For example, an appreciable amount of laboratory research on the biology of trypanosome and leishmania parasites, which cause neglected diseases such as human African trypanosomiasis and leishmaniasis, respectively, has been published [7]. The novel information from this research could be utilized to initiate pharmaceutical development with regard to these diseases, but, despite these scientific advances, archaic, and often poorly tolerated or ineffective, treatments continue to be employed against these diseases, due to a dearth of novel pharmaceutical development. As a
result, developmental neglect allows poor prospects and prognoses to persist for affected patients. Alternative and innovative policy mechanisms, other than traditional methods such as patent protection, are acutely needed to spur novel development from the pharmaceutical sector in this context.

1.2 Public Health and Economic Impact of Neglected Diseases

The neglected diseases, collectively, represent the most commonly occurring infections in the world and contribute to the exacerbation and perpetuation of the conditions of poverty [8]. The World Health Organization estimates that the collective impact of these illnesses is experienced across 149 countries and by upwards of one billion people internationally [3]. This impact takes the forms of both mortality and morbidity. Measurements of disability-adjusted life-years, or DALYs, account for both outcomes by accounting for the total years of healthy life lost due to illness. For the seventeen neglected tropical diseases (NTDs) recognized by the World Health Organization (WHO), malaria, and tuberculosis, it has been estimated that DALYs amount to 56.6 million, 46.5 million, and 34.7 million, respectively, resulting in a total amount of approximately 138 million DALYs annually. Additionally, it is estimated that there are approximately 530,000 fatalities, globally, from neglected tropical diseases annually [9]. Prevalence of individual instances of neglected diseases can exceed 800 million cases, with a total of approximately 1.4 billion people affected. Most of these instances occur in the developing world, exacerbating the conditions and difficulties of poverty.
In addition to a considerable global direct health impact, neglected diseases also produce a significant economic impact. Neglected diseases impose economic costs upon afflicted populations in direct as well as indirect ways. In the direct sense, these diseases prompt healthcare expenditures related to treatment and prevention. In an indirect, more pernicious sense, neglected diseases inflict morbidity and mortality that prevents affected people from working and being economically productive, resulting in harm both at the individual and societal levels.

It is difficult to accurately assess the holistic economic impact of neglected diseases, given the many variables involved. However, estimates of productivity loss due to individual instances of neglected diseases highlight the economic urgency of the issue. For example, Chagas disease, a neglected disease caused by a protozoan parasite that is particularly prevalent in Latin America, is estimated to cause approximately 752,000 lost working days due to mortality and roughly 1.2 billion U.S. dollars in lost productivity amongst seven surveyed Latin American countries. Additionally, lymphatic filariasis, a neglected disease caused by helminth infection, is estimated to cost 1.3 billion U.S. dollars annually in lost productivity across endemic countries. Furthermore, cysticercosis, a neglected disease resulting from helminth infection, is estimated to impose direct costs of 15.27 million U.S. dollars, 28.3 million U.S. dollars, and 16.6 million U.S. dollars in the endemic regions of India, Honduras, and the Eastern Cape Province of South Africa, respectively [10].

Since these diseases tend to flourish in societies subject to impoverishment and underdeveloped economies at the outset, they exacerbate the conditions and difficulties
of poverty. The incidence of neglected diseases reduces prospects for public health and economic development in these settings. As a result, the innovation of solutions, particularly pharmaceutical products, to address such diseases and reduce their collective impact, is a pressing imperative in the context of global economic and public health development.
2. Identification of Neglected Diseases and Relevant Drug Approvals

The first step in the analysis of this thesis is the identification of relevant neglected diseases to explore. Once a sample frame of such diseases is established, new approvals with indications related to these diseases can be enumerated. Creation of this sample frame of diseases is actually not a straightforward task, as there is not a universal consensus with regard to which diseases are considered neglected and which diseases are not [11].

To be clear, the type of neglected diseases being explored by this thesis is that that involves illnesses of poverty, as opposed to ‘orphan diseases’ or rare diseases that have exceedingly low prevalence, but do not necessarily disproportionately affect the poor [1]. One of the main public health issues of neglected diseases is that they do indeed affect such large numbers of people. The other issue is the market deficiency associated with an impoverished clientele.

2.1 Defining Neglected Diseases for Identification

The World Health Organization (WHO) has previously defined neglected diseases that “persist exclusively in the poorest and most marginalized communities, and have been largely eliminated elsewhere...” [11]. The organization currently lists seventeen diseases, representing a variety of medical etiologies, as being neglected [3]. This list is fairly comprehensive, encompassing bacterial, viral, protozoan, and helminth infections. However, this list is not exhaustive and does not include certain diseases that
fit the aforementioned characterization of neglected disease. Namely, the diseases of tuberculosis, malaria, and cryptosporidiosis/ giardiasis are excluded. However, this thesis will consider these three diseases, along with those enumerated by the WHO, as part of its working definition of neglected diseases.

The reason for consideration of tuberculosis is that its epidemiology fits that of a neglected disease. As recently as 2011, tuberculosis caused 1.7 million deaths worldwide and produced roughly 9 million new cases per year [12]. Additionally, most mortality from tuberculosis occurs in developing countries [13]. Despite the availability of current treatments, therapeutic deficiencies exist due to the often high costs and toxicities of treatment, along with the evolution of drug resistance by the bacterial strains involved [12]. As such, given the high prevalence and mortality and persistent deficiencies in treatment, tuberculosis will be interpreted as a neglected disease in this thesis.

Malaria, similarly to tuberculosis, is disproportionately prevalent amongst developing countries [14]. In addition, as is the case with tuberculosis, malaria infections have demonstrated the evolution of drug resistance, often rendering existing therapies ineffective or obsolete [15]. As a result, new developments in therapies are needed, and malaria will be considered a neglected disease for the purposes of this thesis.

Cryptosporidiosis and giardiasis are protozoan infections of the gastrointestinal tract. Like malaria and tuberculosis, these infections disproportionately afflict the developing world and have a scarcity of available treatment options [16]. As such, these conditions will be addressed as neglected ones, and they will be referenced together, due to the similarity in medical pathology involved.
The combination of diseases listed by the WHO as being neglected, with tuberculosis, malaria, and cryptosporidiosis/giardiasis, results in a total of twenty diseases for consideration. These illnesses are medically diverse, resulting from either bacterial, viral, protozoan, or helminthic infections. A list of all twenty neglected diseases considered is presented in Table 1 below.

### Table 1: Neglected Diseases by Infectious Agent

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Protozoa</th>
<th>Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Buruli ulcer</td>
<td>• Dengue/chikungunya</td>
<td>• Chagas disease</td>
<td>• Dracunculiasis</td>
</tr>
<tr>
<td>• Yaws</td>
<td>• Rabies</td>
<td>• Sleeping sickness</td>
<td>• Echinococcosis</td>
</tr>
<tr>
<td>• Trachoma</td>
<td></td>
<td>• Leishmaniasis</td>
<td>• Foodborne trematodiases</td>
</tr>
<tr>
<td>• Leprosy (Hansen disease)</td>
<td></td>
<td>• Malaria</td>
<td>• Lymphatic filariasis</td>
</tr>
<tr>
<td>• Tuberculosis</td>
<td></td>
<td>• Cryptosporidiosis/Giardias</td>
<td>• Onchocerciasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Schistosomiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Soil-transmitted helminthiases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Taeniasis/Cysticercosis</td>
</tr>
</tbody>
</table>

#### 2.2 Relevant Drug Approvals Associated with Neglected Diseases

In recent decades, pharmaceutical development has been pursued, by various actors, toward treatments for some of the diseases listed in the previous section. In some cases, these pursuits yielded drug approvals. These approvals were granted primarily by the Food and Drug Administration (FDA) of the United States and the European Medicines Agency (EMA) of the European Union, but other agencies associated with other jurisdictions granted a few of the relevant approvals as well.
2.2.1 Timeframe and Type of Approvals

The timeframe of approvals examined by this thesis spans from 1992 to the present. The initial year of 1992 was selected due to the introduction, at the FDA, of a regulatory review process that largely established the current review climate. Specifically, it was in that year that the process of “accelerated approval,” in which surrogate endpoints of clinical studies could be submitted for analysis, instead of overall clinical benefits [17]. This development altered the climate of regulation with regard to drug approval, in that pharmaceutical products could be approved based on observed improvements in biomarkers indicative of disease progression, as opposed to end outcomes such as mortality. As a result, drugs for serious diseases could receive approval more rapidly and easily than before, establishing a new regulatory standard and climate that endures to the present.

As such, any drugs that received approval from 1992 onward, with indications that involve one of the diseases listed in Section 2.1, were included in the scope of this analysis, with one exception. The drug mefloquine, with the trade name Lariam, received FDA approval in 1989. However, mefloquine was developed simultaneously with another drug, halofantrine (Halfan), in the same development program at the Walter Reed Army Institute of Research (WRAIR) [18]. Halofantrine received approval in 1992. In order to highlight the common development histories involved, both halofantrine and mefloquine are included in the scope of examination of this thesis, despite the fact that the approval of mefloquine occurred shortly before 1992.
With regard to the pharmaceutical products themselves, this thesis focuses on the developments and approvals of new chemical entities, as opposed to developments and approvals of biologic products, such as vaccines. This is due to the different natures of development of chemical entities versus biologic entities. As the majority of pharmaceutical development with regard to neglected diseases has involved new chemical entities, a focus is maintained on that type of approval. In addition, approvals of new combinations of existing approved drugs are not included in the scope of analysis, unless at least one of the compounds in the combination had not been previously approved for use by itself.

2.2.2 Approvals from the U.S. Food and Drug Administration (FDA)

A search of approval records from the FDA reveals drug approvals with indications associated with the neglected diseases identified in Section 2.1 spanning from 1989 to 2014 [19]. The disease indications associated with these approvals are malaria, tuberculosis, onchocerciasis, leishmaniasis, and cryptosporidiosis. The total of eleven approvals identified in accordance with the parameters outlined in Section 2.1.1 are presented in Table 2 below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Mefloquine (Lariam)</td>
<td>Malaria</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>1992</td>
<td>Halofantrine (Halfan)</td>
<td>Malaria</td>
<td>Roche</td>
</tr>
<tr>
<td>1992</td>
<td>Rifabutin (Mycobutin)</td>
<td>Tuberculosis</td>
<td>Pharmacia &amp; Upjohn</td>
</tr>
<tr>
<td>1996</td>
<td>Ivermectin (Stromectol)</td>
<td>Onchocerciasis</td>
<td>Merck</td>
</tr>
<tr>
<td>Year</td>
<td>Drug</td>
<td>Indication</td>
<td>Recipient</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------</td>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1998</td>
<td>Rifapentine (Priftin)</td>
<td>Tuberculosis</td>
<td>Sanofi Aventis</td>
</tr>
<tr>
<td>1999</td>
<td>Moxifloxacin (Avelox)</td>
<td>Tuberculosis</td>
<td>Bayer</td>
</tr>
<tr>
<td>2000</td>
<td>Atovaquone &amp; Proguanil (Malarone)</td>
<td>Malaria</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>2004</td>
<td>Nitazoxanide (Alinia)</td>
<td>Cryptosporidiosis</td>
<td>Romark Laboratories</td>
</tr>
<tr>
<td>2009</td>
<td>Artemether &amp; Lumefantrine (Coartem)</td>
<td>Malaria</td>
<td>Novartis</td>
</tr>
<tr>
<td>2012</td>
<td>Bedaquiline (Sirturo)</td>
<td>Tuberculosis</td>
<td>Janssen</td>
</tr>
<tr>
<td>2014</td>
<td>Miltefosine (Impavido)</td>
<td>Leishmaniasis</td>
<td>Knight Therapeutics</td>
</tr>
</tbody>
</table>

2.2.3 Approvals from the E.U. European Medicines Agency (EMA)

A search of approval records from the EMA yields drug approvals with neglected disease associations spanning from 2011 to 2014 [20]. The disease indications associated with these approvals are malaria and tuberculosis. One approved drug, bedaquiline, was granted approval by both the FDA and EMA. The total of five approvals, including that of bedaquiline, are presented in Table 3 below.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Dihydroartemisinin &amp; Piperaquine (Eurartesim)</td>
<td>Malaria</td>
<td>Sigma Tau</td>
</tr>
<tr>
<td>2012</td>
<td>Pyronaridine &amp; Artesunate (Pyramax)</td>
<td>Malaria</td>
<td>Shin Poong</td>
</tr>
<tr>
<td>2014</td>
<td>Bedaquiline (Sirturo)</td>
<td>Tuberculosis</td>
<td>Janssen</td>
</tr>
<tr>
<td>2014</td>
<td>Delamanid (Deltyba)</td>
<td>Tuberculosis</td>
<td>Otsuka</td>
</tr>
<tr>
<td>2014</td>
<td>Para-Aminosalicylic Acid (Granupas)</td>
<td>Tuberculosis</td>
<td>Lucane</td>
</tr>
</tbody>
</table>

Table 3: EMA Approvals for Neglected Disease Indications
2.2.4 Approvals from Other Regulatory Agencies

Three approvals were identified from the period of 1992 to the present for drugs for neglected diseases that were not approved by the FDA or EMA but were approved by other agencies. The approving agencies were the Medicines Evaluation Board of the Netherlands [2], the government of Brazil [21], and the World Health Organization (WHO) [22]. The former two organizations granted standard marketing approvals within their jurisdictions, whereas the WHO issue a “pre-qualification,” fostering international use of the recipient drug using donor funds. The approved drugs are presented in Table 4 below.

Table 4: Approvals from Agencies Other Than the FDA or EMA

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Indication</th>
<th>Recipient</th>
<th>Approving Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Artemotil (Artecef)</td>
<td>Malaria</td>
<td>Artecef</td>
<td>Medicines Evaluation Board (Netherlands)</td>
</tr>
<tr>
<td>2010</td>
<td>Artesunate (Artesun)</td>
<td>Malaria</td>
<td>Guilin</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>2011</td>
<td>Benznidazole (pediatric)</td>
<td>Chagas disease</td>
<td>LAFEPE/ DNDi</td>
<td>Brazil</td>
</tr>
</tbody>
</table>

The instances of drug approvals in the previous chapter represent examples of developmental successes against difficult economic odds presented by the deficient nature of the market for neglected diseases. These difficulties are reflected in the marginal numbers of drug approvals for such diseases, which accounted for one [6] to two [2] percent of total drug approvals from 1975 to 1999, depending upon the analytical methodology. Despite total development costs that may range from five hundred million U.S. dollars to over one billion U.S. dollars [23], the research and development of these pharmaceutical products were executed from start to finish, from initial stages such as lead identification, pre-clinical laboratory and animal studies, to three phases of human clinical trials. After demonstrating convincing efficacy and safety, these products were approved by various regulatory agencies around the world, including the Food and Drug Administration (FDA) in the U.S., the European Medicines Authority (EMA) in the European Union, and other national regulatory bodies.

The eighteen approvals identified in the previous chapter pertain to a variety of diseases and were granted to a diverse array of applicants. The diseases included widely recognized ailments, such as malaria, as well as less known infections, such as leishmaniasis. The recipients of commercial marketing approval ranged from large pharmaceutical companies, such as GlaxoSmithKline of the U.K., to relatively young and small start-up companies, such as Romark Laboratories of the U.S.
The significance of each approval can be found in the development history that led to the approval. Analysis of these histories provides insights into exactly how difficult economic and financial odds were overcome to produce approved products that are available to the public, as opposed to trial products that are available only to patients participating in trials, or investigational products made available in a limited manner under regulatory compassionate use or other exemptions. Such an analysis of developmental histories will yield an understanding of the mechanisms that led to successful approval.

Examination of the histories of research and development, with regard to funding and organizational participation, will allow for characterization of the policy approaches that underpinned the catalysis of successful approval. Such characterizations, on an individual level, can reveal trends or commonalities of policy approaches at the collective level. Thus, collectively, these development histories can inform future approaches toward the development of drugs for neglected diseases.

3.1 Exploration of Incentive Policy Options

In 2008, the sixty-first annual meeting of the World Health Assembly (WHA), the supreme governing body of the World Health Organization (WHO), produced a resolution, titled WHA61.21, which directed the Director-General of the WHO "to establish urgently a results-oriented and time-limited expert working group to examine current financing of research and development, as well as proposals for new and innovative sources of funding to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing
countries in relation to Type I diseases, and open to consideration of proposals from Member States...” [24]. In this context of the WHO, Type I diseases are those that have significant incidence in “both rich and poor countries,” Type II diseases are those that have significant incidence in poor countries and some incidence in rich countries, and Type III diseases are those that primarily affect poor or developing countries [25]. Thus, WHA61.21 refers largely to neglected diseases, as defined by this thesis.

In response to resolution WHA61.21, the WHO established the Expert Working Group (EWG) to examine and evaluate proposals for incentivizing pharmaceutical research and development for neglected diseases. The EWG produced a report in 2010 that cited a need to further examination of the proposals that it received, prompting the sixty-third WHA to issue resolution WHA63.28. This resolution calls for the “establishment of a consultative expert working group on research and development: financing and coordination,” in recognition of a need to “explore and... promote a range of incentive schemes for research and development including... de-linkage of the costs of research and development and the price of health products, for example through the award of prizes, with the objective of addressing diseases which disproportionately affect developing countries.” In other words, the resolution directed the establishment of a committee to explore and identify means of stimulating pharmaceutical research and development to reduce the global public health impact of neglected diseases.

Subsequently, the Consultative Expert Working Group, or CEWG, was established in 2011, by the WHO, with a mandate to assess such means.
The final report of the Consultative Expert Working Group (CEWG) of the World Health Organization, which was released in April of 2012, evaluated submissions of proposals of stimulation of research and development for overcoming market deficiencies related to neglected diseases. The committee ultimately grouped the proposals into broad categories that can be interpreted as various incentive mechanisms. Incentive mechanisms were judged either favorably or unfavorably with regard to their potential for success in stimulating research and development [24].

The categorical groupings offered by the report capture the current global environment of potential incentive policy mechanisms fairly well, as proposals were received, worldwide, from a wide array of stakeholders from academia, industry, and the public sector. Thus, this chapter will characterize the developmental histories of drugs for neglected diseases approved from 1992 to 2014 by mapping them onto the policy approach categories identified in the report. This mapping process was ultimately effective in that actual development histories did indeed map onto the categories offered by the CEWG report fairly well.

However, there was one notable exception. The CEWG report did not explicitly identify the policy concept of product development partnerships (PDPs), which represent a type of public-private partnership (PPP) [26], as a development incentive policy mechanism, despite the fact that many organizations with the primary goal of fostering such partnerships have developed in recent years. Examples of such organization include the Drugs for Neglected Diseases Initiative (DNDi), the Medicines for Malaria Venture (MMV), and the Global Alliance for Tuberculosis Drug
Development (GATB) [27]. This development mechanism, which can be characterized as one in which public and philanthropic funding and resources are channeled to a diverse array of public and private entities for the purpose of coordinated research and development of a particular pharmaceutical product or set of products, does indeed underlie many of the recent successes in drug development, and was therefore explicitly considered, in this thesis, as a potential incentive policy mechanism, in addition to the ones offered by the final report of the CEWG.

3.2 Potential Incentive Mechanisms

The incentive mechanisms that were identified through proposal groupings in the CEWG final report were assessed by the CEWG as either meeting their criteria (for potential to effectively stimulate research and development) “less well,” “best,” or as having “other merits” but not necessarily catalyzing research and development. The total of fifteen policy approaches are reviewed in Table 5 below.
### Table 5: CEWG Incentive Mechanism Categories

<table>
<thead>
<tr>
<th>“Best” Met Criteria</th>
<th>Did Not Meet Criteria/ Had “Other Merits”</th>
<th>Met Criteria “Less Well”</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Global framework on research and development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Open approaches to research and development and innovation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pooled funds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Direct grants to companies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Milestone prizes/ end prizes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patent pools</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Regulatory harmonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Removal of data exclusivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tax breaks for companies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Orphan drug legislation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Green intellectual property</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Priority review voucher</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Transferrable intellectual property rights</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Health Impact Fund</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Procurement agreements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The product development partnership (PDP) mechanism, which does not explicitly appear in this list, indeed has some of its tenets captured in some of the categories that are listed. Specifically, “Open approaches to research and development and innovation” is a characteristic of PDPs, as such partnerships require collaborative data sharing and intellectual property agreements. Additionally, the concept of “pooled funds” applies to PDPs, as the non-profit organizations, such as MMV, DNDi, or GATB, essentially function to pool available funds for specific diseases and causes to which such organizations are devoted. In addition, “removal of data exclusivity” and “transferrable intellectual property rights” are processes which also may apply to PDP strategies as well.
Despite the fact that many tenets of the PDP model are captured within the list of mechanisms enumerated by the CEWG, the PDP model warrants separate consideration as a distinct policy mechanism, as the individual tenets, by themselves, cannot account for the PDP process as a whole. As such, this thesis will consider the implementation of public-private product development partnerships as a separate and distinct category for the purpose of characterization of development mechanisms.

Another development model that will be considered, for characterization purposes, by this thesis, is simply the one of private investment and development within a pharmaceutical company, as would be the case for drug development for non-neglected diseases for which effective markets exist. This is due to a finding that some drugs for neglected diseases were in fact developed according to a traditional model of private development within pharmaceutical firms. One subcategory of this model that was found amongst the approved drugs is that of corporate philanthropy, in which a private firm within the pharmaceutical industry developed, to completion, a drug for use primarily with neglected diseases, with the express intention of marketing such drugs in a financially accessible manner to improve public health.

A final development model that was encountered in the analysis of approved drugs was a fairly unique one of military, or wartime, development. This mechanism arose in contexts of international armed conflict where military personnel were exposed to certain disease threats and therapeutic solutions were funded and developed for the benefit of such personnel, with incidental societal benefit added by the fact that civilians also benefitted from such developments due to the subsequent availability of new drugs.
These various models result in a total of nineteen possible mechanisms through which drug development and approval may have taken place: the fifteen categories enumerated by the CEWG report, along with the product development partnership model, traditional private development by pharmaceutical firms, corporate philanthropy, and military or wartime development.

3.3 Actual Incentive Mechanisms

Examination of the histories of the eighteen approved drugs included within the scope of this thesis revealed that, of the nineteen possible paradigms of development stimulation, in reality, six were primarily involved in catalyzing and stimulating drug development. Although more mechanisms may have been inherent in the complex processes that led to drug approval for the eighteen candidates in question, analysis of the most salient or relevant factors in each case revealed six major mechanisms at play. These six mechanisms were: (1) military/wartime development, (2) private pharmaceutical industry development, (3) corporate philanthropy, (4) product development partnerships, (5) intellectual property/data transfer, and (6) priority review vouchers. These mechanisms are presented, along with the abbreviations with which this thesis may refer to such mechanisms, in Table 6 below.
Table 6: Development Incentive Mechanisms and Abbreviations of Reference

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Military/ wartime development</td>
<td>MIL</td>
</tr>
<tr>
<td>Private pharmaceutical industry development</td>
<td>PVT</td>
</tr>
<tr>
<td>Corporate philanthropy</td>
<td>PHL</td>
</tr>
<tr>
<td>Product development partnerships</td>
<td>PDP</td>
</tr>
<tr>
<td>Intellectual property/ data transfer</td>
<td>IPT</td>
</tr>
<tr>
<td>Priority review voucher issuance</td>
<td>PRV</td>
</tr>
</tbody>
</table>

3.4 Characterizations of Approved Products

Developmental histories of approved products were analyzed through the examination of regulatory approval documents, company documents (such as annual reports), press releases, scientific literature, and other documents that included information regarding sources of funding and operational mechanisms leading to the development of each product in question. A determination was made as to which development mechanism most accurately describes the process that led to development and approval of the subject of analysis. The single mechanism that best described the development process on a holistic level was selected as the development mechanism. If mechanisms other than the primary mechanism were involved in the stimulation of development activity as well, then such mechanisms will be mentioned along with the details of development histories in subsequent sections of this thesis. The determinations
regarding primary development incentive mechanisms for each approved drug are presented in Table 4.3 below.

**Table 7: Primary Incentive Mechanisms for Product Development**

<table>
<thead>
<tr>
<th>Approval Year</th>
<th>Drug Product</th>
<th>Primary Indication</th>
<th>Primary Development Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Mefloquine (Lariam)</td>
<td>Malaria</td>
<td>MIL</td>
</tr>
<tr>
<td>1992</td>
<td>Halofantrine (Halfan)</td>
<td>Malaria</td>
<td>MIL</td>
</tr>
<tr>
<td>1992</td>
<td>Rifabutin (Mycobutin)</td>
<td>Tuberculosis</td>
<td>PVT</td>
</tr>
<tr>
<td>1996</td>
<td>Ivermectin (Stromectol)</td>
<td>Helminths</td>
<td>PHL</td>
</tr>
<tr>
<td>1998</td>
<td>Rifapentene (Priftin)</td>
<td>Tuberculosis</td>
<td>PVT</td>
</tr>
<tr>
<td>1999</td>
<td>Artemether &amp; Lumefantrine (Coartem)</td>
<td>Malaria</td>
<td>PDP</td>
</tr>
<tr>
<td>1999</td>
<td>Moxifloxacin (Avelox)</td>
<td>Tuberculosis</td>
<td>PVT</td>
</tr>
<tr>
<td>2000</td>
<td>Atovaquone &amp; Proguanil (Malarone)</td>
<td>Malaria</td>
<td>PHL</td>
</tr>
<tr>
<td>2000</td>
<td>Artemotil (Arteceft)</td>
<td>Malaria</td>
<td>PDP</td>
</tr>
<tr>
<td>2002</td>
<td>Nitazoxanide (Alinia)</td>
<td>Cryptosporidiosis</td>
<td>PHL</td>
</tr>
<tr>
<td>2010</td>
<td>Artesunate (Artesun)</td>
<td>Malaria</td>
<td>PDP</td>
</tr>
<tr>
<td>2011</td>
<td>Dihydroartemisinin &amp; Piperaquine (Eurartesim)</td>
<td>Malaria</td>
<td>PDP</td>
</tr>
<tr>
<td>2011</td>
<td>Benznidazole (pediatric)</td>
<td>Chagas Disease</td>
<td>PDP</td>
</tr>
<tr>
<td>2012</td>
<td>Pyronaridine &amp; Artesunate (Pyramax)</td>
<td>Malaria</td>
<td>PDP</td>
</tr>
<tr>
<td>Year</td>
<td>Product Name</td>
<td>Indication</td>
<td>Development Method</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------</td>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>2012</td>
<td>Bedaquiline (Sirturo)</td>
<td>Tuberculosis</td>
<td>PRV</td>
</tr>
<tr>
<td>2014</td>
<td>Miltefosine (Impavido)</td>
<td>Leishmaniasis</td>
<td>PDP</td>
</tr>
<tr>
<td>2014</td>
<td>Delamanid (Deltyba)</td>
<td>Tuberculosis</td>
<td>PVT</td>
</tr>
<tr>
<td>2014</td>
<td>Para-Aminosalicylic Acid</td>
<td>Tuberculosis</td>
<td>IPT</td>
</tr>
</tbody>
</table>

3.5 Individual Histories

This section will highlight details of developmental histories of individual approved products that yielded the determinations of primary development mechanisms. Histories were compiled using data regarding each approval obtained from regulatory agency documents, company documents, press releases, academic literature, along with other sources. Approved products will be grouped according to the primary development method.

3.5.1 Product Development Partnerships

Seven, or roughly thirty-nine percent, representing a plurality, of the approved drug products, were assessed as having development stimulated primarily by a public-private product development partnership (PDP) mechanism. This means that development occurred largely as a result of coordinated collaboration of resources, funding, and activities by a combination of public and private entities (with the private entity usually being a pharmaceutical company) for the specific purpose of development of a pharmaceutical product. These products were, in chronological order of approval, artemether & lumefantrine (Coartem), artemotil (Artecef), miltefosine (Impavido),
artesunate (Artesun), dihydroartemisinin & piperaquine (Eurartesim), benznidazole (pediatric), and pyronaridine & artesunate (Pyramax), which were approved in 1999, 2000, 2002, 2010, 2011, 2011, and 2012, respectively.

3.5.1.1 Artemether & Lumefantrine (Coartem) for Malaria

The first of these products, artemether & lumefantrine (Coartem), first received approval for distribution in Kenya in 1999 [2] and subsequently received FDA approval in 2009 [19]. Approval by the FDA was given to pharmaceutical company Novartis for this “new molecular entity” (NME) under NDA application number 022268. There are two forms of Coartem currently available, both of which were developed as a result of some form of public-private product development partnership. The first form of Coartem was that of standard oral tablets developed by Novartis. The development endeavor was supported by a partnership agreement between the government of China and Novartis, in which, starting in 1994, clinical trials of the artemether and lumefantrine combination were co-administered by the Beijing Academy of Military Medical Sciences and Novartis, the first such development program of its kind in China. The collaboration resulted in roughly twenty clinical trials, involving over 3,500 patients, that ultimately led to the approval of the original format of Coartem [28]. The subsequent version of Coartem took the form of dispersible tablets, which employed the same active ingredients artemether and lumefantrine, as the original form of Coartem, but came in a physical manifestation that was better suited for pediatric use, expanding the size of the patient population that stands to benefit from the product. The dispersible form was developed, and trials were supported, as a result of a partnership between
Novartis, the manufacturer of the original version of Coartem, and the Medicine for Malaria Venture (MMV), a non-profit organization dedicated to alleviating the public health impact of malaria through fostering research and development, particularly through the product development partnership (PDP) model [29]. Under the partnership format of MMV and Novartis, Novartis provided the final manufacturing capacities for the dispersible product, whereas MMV financially supported the research and trial activities leading to approval. MMV, in turn, received funding from a variety of governmental as well as private non-profit organizations, including the Gates Foundation, Irish Aid, the U.K. Department for International Development (DFID), the U.S. Agency for International Development (USAID), the U.S. National Institutes of Health (NIH), and the Rockefeller Foundation.

The cases of Coartem (both the original oral format and the subsequent dispersible oral format) represent instances in which public-private product development collaboration resulted in the removal of barriers to development. Novartis provided manufacturing capacities and expertise, and in turn, MMV collected funds from a variety of public and non-profit sources to support the costly developmental phases of clinical trials. As a result, Novartis subsequently supplied more than 215 million units of Coartem treatments without collecting profits, making the final product more accessible to the populations most in need [30]. It should be noted that Novartis received a priority review voucher (PRV) for this drug upon receipt of approval from the Food and Drug Administration [31]. Although such vouchers, in some cases, can provide an incentive mechanism for developers, in this case, the concomitant award of
the voucher along with approval did not likely provide significant impetus compared to that provided by the collaborative development agreements that Novartis undertook with the Beijing Academy of Military Medical Sciences and with the Medicines for Malaria Venture during product development. Thus, the overall primary development incentive mechanism for Coartem can more appropriately be described as the formation of a product development partnership and not the award of a priority review voucher.

3.5.1.2 Artemotil (Artecef) for Malaria

Artemotil (Artecef), developed by the eponymous Dutch firm Artecef B.V., was granted regulatory approval by the Medicines Evaluations Board of the Netherlands in 2000, under marketing authorization number RVG 24881, for the treatment of malaria [32]. Although final approval took place in the Netherlands, the origins of the development of artemotil as a malaria drug can be traced to the United States, where activity of artemotil against malaria was discovered against animal models at the Walter Reed Army Institute of Research (WRAIR) [33]. Subsequently, the compound was co-developed by WRAIR and Artecef B.V., in an arrangement where WRAIR performed clinical trials and Artecef provided manufacturing capabilities. Thus, coordinated collaboration between the public agency WRAIR and the private firm Artecef utilized the unique strengths, specialties, and resources of each entity. Ultimately, this public-private product development partnership yielded successful approval of a novel pharmaceutical product for a neglected disease.
3.5.1.3 Pyronaridine & Artesunate (Pyramax) for Malaria

Regulatory approval of the combination of pyronaridine and artesunate (Pyramax) was granted by the European Medicines Agency (EMA), although not in the standard format for marketing approval within the European Union. The EMA offers an alternative evaluation process for pharmaceutical products that are not intended for use within the European Union (statutorily established by Article 58 of EC Regulation No. 76/2004), in which an applicant submits data similar to that which would be submitted for a standard drug evaluation and issues either a positive or negative opinion [34]. In the case of Pyramax, the EMA granted a positive opinion, recommending use, to Shin Poong Pharmaceutical Co., Ltd., of Korea, in 2012, under Procedure No. EMEA/H/W/002319, for the indication of malaria [35].

The development of Pyramax that yielded the positive EMA opinion occurred as a result of a collaborative product development partnership agreement between Shin Poong, a private pharmaceutical company and EMA opinion applicant, and the Medicines for Malaria Venture (MMV), a private non-profit organization dedicated to the employment of the product development partnership mechanism to develop pharmaceutical products for use toward malaria. The partnership was initiated with Shin Poong by MMV when it acquired the Pyramax development project from the Special Programme for Research and Training in Tropical Diseases (TDR) of the WHO in 2002 [36]. MMV acquired the project at the pre-clinical trial stage, and subsequently, upon adoption of the project, provided expertise and funding toward trial activities.
while Shin Poong provided manufacturing capacities, similarly to other public-private product development partnerships undertaken by MMV.

3.5.1.4 *Artesunate (Artesun) for Malaria*

Although the compound artesunate is not, in itself, a novel recent development, its injectable format, marketed as Artesun, is. In addition, the approval that Artesun received did not originate from a national regulatory authority, but from the World Health Organization (WHO), in the form of a “prequalification.” Nonetheless, receipt of this status from the WHO removes barriers from the use of philanthropic funds to distribute this compound for use in affected patients [22]. This “prequalification” approval status was awarded by the WHO to the pharmaceutical manufacturer Guilin in 2010, as a result of an instance of coordinated product development collaboration between Guilin and the non-profit organization Medicines for Malaria Venture (MMV).

As part of this partnership, Guilin developed the product in association with expertise and funding provided by MMV. MMV is, in turn, funded by donations from a variety of public and private entities from across the world, including government agencies such as the U.S. Agency for International Development (USAID) and the U.K. Department for International Development (DFID), private non-profit entities such as the Gates Foundation, as well as philanthropic arms of private sector companies such as ExxonMobil [37]. Thus, MMV served as a coordination apparatus of resources and funding with public and private origins and forwarded such funding to a pharmaceutical company appropriately equipped to develop a drug in this context, leading to a novel product for the treatment of malaria. Indeed, subsequently to
approval, multiple studies demonstrated a superior efficacy of injectable artesunate in improving malaria outcomes compared to that of quinine, another standard treatment [38].

3.5.1.5 Dihydroartemisinin & Piperaquine (Eurartesim) for Malaria

Approval for the combination of dihydroartemisinin and piperaquine, marketed as Eurartesim, was granted by the European Medicines Agency (EMA) to Italian pharmaceutical company Sigma Tau Industrie Farmaceutiche Riunite S.p.A (Sigma Tau), for the indication of malaria, in 2011, under the ‘Agency Product Number’ EMEA/H/C/001199 [39]. Support for the development and approval of Eurartesim was provided to Sigma Tau, in large part, by Medicines for Malaria Venture (MMV). This collaborative product development partnership was initiated by a 2004 partnership agreement between Sigma Tau, MMV, Chinese pharmaceutical company Holleykin, and Oxford University [40].

Under the collaborative agreement, Holleykin provided expertise resulting from prior experience with production of the dihydroartemisinin and piperaquine combination. MMV, in turn, provided expertise regarding international regulatory standards and processes. Scientists from Oxford University were able to provide expertise regarding the performance of clinical trials in malaria-endemic settings, and Sigma Tau provided manufacturing capacity. This agreement culminated in a series of three phase I trials conducted in France and Australia, two phase II trials conducted in Burkina Faso and Thailand, and two phase III trials conducted in Asia (Thailand, India, and Laos) and Africa (Burkina Faso, Kenya, Uganda, Mozambique, and Zambia).
The phase III trials demonstrated an efficacy of Eurartesim that was comparable to that of other available malaria therapies involving artemether and lumefantrine as well as artesunate and mefloquine. Ultimate approval by a stringent regulatory authority, the EMA, in 2011, demonstrated the overall success achieved through the product development partnership agreement between public and private entities that took place in 2004.

3.5.1.6 Benznidazole (pediatric) for Chagas Disease

A novel pediatric formulation of the compound benznidazole was approved in Brazil by the National Health Surveillance Agency (ANVISA) in 2011 for the treatment of Chagas disease (otherwise known as American trypanosomiasis). Approval went to the Pernambuco State Pharmaceutical Laboratory (LAFEPE), a public Brazilian pharmaceutical company operated by the State of Pernambuco and the only producer of benznidazole internationally [41]. Development of the new pediatric formulation was conducted by LAFEPE in collaboration with the Drugs for Neglected Diseases Initiative (DNDi), a private non-profit organization dedicated toward the development of pharmaceuticals for neglected tropical diseases. Under the collaborative product development agreement, which was initiated in 2008, DNDi provided technical expertise regarding the use of benznidazole against Chagas disease [42] and secured funding for development activities from a variety of public and private sources, including the U.K. Department for International Development (DFID), the U.S. Agency for International Development (USAID), Medecines Sans Frontieres (MSF/ Doctors Without Borders), various Swiss private foundations, and individual donors [43].
Ultimately, the arrangement between a public manufacturer and a private non-profit organization led to approval of the new dosage form. One notable distinction in this case is that the ultimate pharmaceutical manufacturer is a public sector institution, whereas in most other cases of PDP collaboration, the pharmaceutical supplier is a private entity. Nonetheless, the dynamics of collaboration between DNDi and LAFEPE functioned largely similarly to other partnerships, in that DNDi assisted in the collection of development funds and LAFEPE provided manufacturing capacity, culminating in final product approval three years subsequently to the initiation of the agreement.

3.5.1.7 Miltefosine (Impavido) for Leishmaniasis

Two instances of approval have occurred with regard to miltefosine. The first and original instance was granted to German pharmaceutical company ASTA Medica/Zentaris by the government of India, in 2002, for the treatment of leishmaniasis [44]. Subsequently, in 2014, Canadian firm Knight Therapeutics was granted approved by the FDA to market miltefosine for the same indication [45]. The original development activity leading to the first approval was catalyzed by a product development partnership model of research and development.

The initial research that led to the identification of miltefosine as a promising drug candidate against leishmaniasis was an academic study conducted by S.L. Croft and colleagues at the London School of Hygiene and Tropical Medicine that identified the biological activity of miltefosine against the *Leishmania donovani* organism that causes leishmaniasis [46]. This initial academic impetus spurred a 1995 agreement between the German pharmaceutical company ASTA Medica/Zentaris and the Special Programme
for Research and Training in Tropical Diseases (TDR) of the World Health Organization (WHO) to develop miltefosine into a treatment for visceral leishmaniasis [44].

This agreement ultimately proved to be productive, as it led to the completion of phase I, II, and III human clinical trials, in India, demonstrating sufficient safety and efficacy of the novel compound against visceral leishmaniasis, such that ASTA Medica/Zentaris was ultimately granted marketing approval, in India, for miltefosine in 2002. Given that visceral leishmaniasis was particularly prevalent in India, the product development partnership between ASTA Medica/Zentaris and TDR helped to ensure that trials were conducted and that subsequent distribution was executed in a locality that exhibited a significant public health need for a neglected disease. The participation of TDR, which took the form of a task force consisting of medical scientists with relevant expertise, provided the resources and expertise necessary to catalyze the pharmaceutical development of a compound, initially identified in an academic study not directly tied to any pharmaceutical company or drug development agendas, by a private pharmaceutical firm.

As such, the primary catalytic mechanism for the development of miltefosine was a PDP model of collaboration. It should be noted that Knight Therapeutics was awarded a priority review voucher by the Food and Drug Administration upon receipt of drug approval [45]. However, given the circumstances in which the initial and original round of development of miltefosine did not involve any priority review voucher, such a voucher program cannot be characterized as a primary driver of development in this case.
3.5.2 Private Pharmaceutical Industry Development

Four, or roughly twenty-two percent, of the examined approved drugs were assessed as having been developed primarily as a result of private pharmaceutical industry development. This means that development activities were executed primarily using the funds, resources, and expertise of the pharmaceutical company that ultimately secured approval for the pharmaceutical product, with marginal to no infusion of resources from external public or private organizations. These products are, in chronological order of approval, rifabutin (Mycobutin), rifapentine (Priftin), moxifloxacin (Avelox), and delamanid (Deltyba), which were approved in 1992, 1998, 1999, and 2014, respectively.

3.5.2.1 Rifabutin (Mycobutin) for Tuberculosis

Approval for rifabutin (Mycobutin) was granted to pharmaceutical company Adria Laboratories by the U.S. Food and Drug Administration (FDA) in 1992, initially for the indication of preventing mycobacterium avium complex (MAC) infection in AIDS patients [47]. However, despite the primary impetus for development, it was also found that the compound exhibited activity against and could serve a treatment for active tuberculosis [48]. Thus, this approval yielded the commercialization of a novel therapeutic option against tuberculosis.

Development of Mycobutin was undertaken primarily by Adria Laboratories with its own internal resources and funding, and clinical trials were conducted, by Adria in association with local physicians, in the United States and Canada [49]. The impetus for Adria for this development endeavor was not actually provided by a goal of treating
tuberculosis, but approval of the ultimate product resulted in increased options for patients affected by the disease. Thus, the private pharmaceutical development and subsequent approval of Mycobutin provides an example of a case where private industrial investment and development for non-neglected diseases can produce incidental benefits for those afflicted by neglected diseases.

3.5.2 Rifapentine (Priftin) for Tuberculosis

Approval for rifapentine (Priftin) was given in 1998 to pharmaceutical company Hoechst AG (now a part of Sanofi Aventis) by the U.S. Food and Drug Administration (FDA) for the indication of tuberculosis [50]. The application, NDA 021024, was processed by the FDA as one regarding a “priority review drug” as well as an “orphan drug,” given that the indication was for a neglected disease. Development of the compound subsequent performance of clinical studies were primarily undertaken by Hoechst, with the aim of receiving marketing approval from the FDA, which was ultimately granted [51]. As a result, the primary catalyst of drug approval in this case was the initiative taken by Hoechst AG, yielding an instance of neglected disease drug development spurred from within the pharmaceutical industry.

3.5.2.3 Moxifloxacin (Avelox) for Tuberculosis

Approval for moxifloxacin (Avelox) was granted by the U.S. Food and Drug Administration (FDA) to pharmaceutical company Bayer Healthcare in 1999 for the indication of various bacterial infections (to ultimately include tuberculosis) under NDA application number 021085 [51]. Development and clinical trial activities for moxifloxacin were primarily undertaken by Bayer Healthcare, with the aim of
commercialization to treat a variety of bacterial infections, including sinusitis, complications related to chronic bronchitis, and community-acquired pneumonia [52]. This prospect of multiple uses of the compound, against both non-neglected and neglected, likely increased the commercial impetus for development in this case, with the incidental benefit that a new therapeutic option against tuberculosis was subsequently gained [53].

3.5.2.4 Delamanid (Deltyba) for Tuberculosis

Approval for delamanid (Deltyba) was granted to Otsuka Novel Products GmbH, a branch of the Japanese pharmaceutical company Otsuka Pharmaceutical Co., Ltd., in 2014, by the European Medicines Agency (EMA), for the indication of tuberculosis, under EMA agency product number EMEA/H/C/002552 [54]. Development and clinical trial activities for delamanid were performed and supported primarily by Otsuka, with the intent of receiving approval for the indication of tuberculosis [54]. In this case, development of a drug for tuberculosis was consistent with the corporate history and philosophy of the developer, as Otsuka has exhibited a historical commitment to investing in pharmaceutical solutions for tuberculosis and is “currently the largest funder of TB drug development worldwide” [55]. In this case, development was spurred from within the pharmaceutical industry, but from a relatively small pharmaceutical firm with a historical and philosophical proclivity toward production of drugs for a neglected disease.
3.5.3 Corporate Philanthropy

Three, or roughly seventeen percent of the approved drugs assessed, received approval primarily as a result of corporate philanthropic initiatives. This development mechanism is similar to that of the previous subsection, private pharmaceutical industry development, in that development activities, from pre-clinical laboratory work to human clinical trials, were primarily financially and operationally supported by a private pharmaceutical company. The distinction in these cases, however, is that the companies in question developed these products with the explicit aim of philanthropy. This means that drug development for neglected diseases was intentionally initiated with the aim of charitable activity in the form of distribution of such products to needy populations. Indications of such a primary aim may be given through explicit statements in company reports or press releases, or may be demonstrated through charitable activities such as the establishment of donation programs subsequently to product approval. The approved products in this category, are, in order of approval, ivermectin (Stromectol/Mectizan), atovaquone & proguanil (Malarone), and Nitazoxanide (Alinia), which were approved in 1996, 2000, and 2002, respectively.

3.5.3.1 Ivermectin (Stromectol/ Mectizan) for Onchocerciasis

Approval for ivermectin (Stromectol) was given by the U.S. Food and Drug Administration (FDA) to pharmaceutical company Merck & Co. in 1996, under NDA application number 050742, for the indications of strongyloidiasis and onchocerciasis [56]. Both of these diseases involve infection from nematode parasites, and one, onchocerciasis, is recognized as a neglected tropical disease (in the hem ninth category of
infections). The origin of development of ivermectin as an anti-parasitic agent for human use can be traced to the Merck Sharp & Dohme Research Laboratories (MSDRL) in New Jersey, where, in 1975, the family of compounds, avermectins, which included ivermectin, were obtained from microbial cultures, obtained by MSDRL from the Kitsato Institute in Japan, demonstrated anti-helminthic activity in murine studies [57]. Merck subsequently pursued further development by conducting human trials, beginning in 1981, in Senegal. Subsequently, further trials were conducted by Merck, in association with the World Health Organization (WHO), in Ghana, Guatemala, Cote d’Ivoire, Liberia, Mali, Senegal, and Togo, demonstrating efficacy and safety of ivermectin and ultimately receiving approval from France in 1987 and from the United States in 1996 [58].

The fact that the primary indications of the product are for neglected parasitic diseases suggests a philanthropic impetus on the part of Merck in pursuing the development of this drug. This suggestion is further bolstered by the fact that members of the Merck staff involved with the ivermectin project, including William Campbell, Ralph Hirschmann, Mohammad Aziz, Ken Brown, and Roy Vagelos, worked to ensure that, subsequently to approval, the new drug was distributed, by Merck, in global donation programs to affected patients internationally, ensuring access by poor communities [59]. Indeed, Merck has maintained an ivermectin donation program, known as the Mectizan donation program (in which ivermectin is distributed under the trade name Mectizan), through which more than 2 billion treatments have been donated to over 250 million patients of onchocerciasis (otherwise known as river blindness), as
well as, since 1998, patients of lymphatic filariasis, in disease endemic areas [60], indicating a corporate philanthropic aim as a primary driver of development in this case.

3.5.3.2 Atovaquone & Proguanil (Malarone) for Malaria

Approval for atovaquone and proguanil hydrochloride (Malarone) was granted by the U.S. Food and Drug Administration (FDA) to the pharmaceutical company Glaxo Wellcome Inc. (now GlaxoSmithKline) in 2000 for the indication of Plasmodium falciparum malaria [61]. Development of the drug had been performed by Glaxo Wellcome with the intent of treating malaria [62]. Given that malaria is a neglected disease affecting primarily poor populations, this development activity suggests that the aim of Glaxo Wellcome in pursuing this project was one of philanthropy. This suggestion is further bolstered by the initiation of the Malarone Donation Programme, which was announced by the company in 1996 as an initiative to donate up to one million doses of Malarone annually. The program was implemented in a pilot phase in Uganda in 1999, and subsequently in Kenya in the same year [62]. The development and subsequent donation of Malarone demonstrates a corporate gesture of philanthropy that resulted in an increase in approved therapeutic options for malaria.

3.5.3.3 Nitazoxanide (Alinia) for Cryptosporidiosis

Approval for nitazoxanide (Alinia) was granted by the U.S. Food and Drug Administration (FDA) to American pharmaceutical firm Romark Laboratories, L.C. in 2002 for the indication of diarrheal protozoan parasitic infections cryptosporidiosis and giardiasis, caused by the protozoan species Cryptosporidium parvum and Giardia lamblia, respectively [63]. The origins of the development of nitazoxanide can be traced to
studies, in the 1980s, of the compound at the Pasteur Institute, by scientist Jean Francois Rossignol [64]. The development rapidly transformed from academic study to pharmaceutical industrial development, when, upon observing the biological activity of nitazoxanide against tapeworms, Rossignol, along with private investor Marc Ayers [65], co-founded Romark Laboratories, L.C., with the aim of developing nitazoxanide into a treatment for cryptosporidium infection.

Subsequent development and clinical trials of nitazoxandie were indeed conducted by Romark, ultimately culminating in marketing approval in 2002. Given the scenario that this private pharmaceutical firm was established with the explicit goal of producing improved treatment options for cryptosporidium diarrheal disease, the origins and founding of the firm, by Rossignol and Ayers, may be characterized as a philanthropic or charitable pursuit within the private pharmaceutical industry. Their subsequent investment of resources and operations can thus be characterized as corporate philanthropy occurring within private industry. In this case, fortunately for patients of cryptosporidiosis and giardiasis, such philanthropic efforts were ultimately successful in producing a marketed product, demonstrating the potential of corporate philanthropy in this regard.

3.5.4 Military/ Wartime Development

Two, or roughly eleven percent of the approved pharmaceutical products assessed, were developed, in large part, due to support from military organizations, spurred by military or wartime needs. This means that the provision of financial and/or operational resources and expertise by military organizations yielded ultimate approval
of the drug products in question. The approved products in this category are, in chronological order of approval, mefloquine hydrochloride (Lariam) and halofantrine hydrochloride (Halfan), which were approved in 1989 and 1992, respectively.

3.5.4.1 Mefloquine (Lariam) for Malaria

Approval for mefloquine hydrochloride (Lariam) was granted by the U.S. Food and Drug Administration (FDA) to pharmaceutical company Roche Laboratories Inc. in 1989 for the indication of malaria, under NDA application number 019591 [19]. The origin of the development of mefloquine can be traced to the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR) of the U.S. Army, which conducted a malaria drug discovery program that was initiated in 1963 [18].

Pre-clinical laboratory activities of the program resulted in the identification of mefloquine as a compound with promising anti-malarial activity. Subsequent to identification of the compound, WRAIR performed phase I and phase II human clinical trials and provided the trial data, free of charge, to the pharmaceutical firm Hoffmann-La Roche, so that the firm could pursue the final stages of development. Hoffmann-La Roche did indeed complete the development of the drug and was ultimately successful in receiving marketing approval from the FDA. In this case, the WRAIR was responsible for both pre-clinical and a significant proportion of the clinical development, and actively sought a pharmaceutical partner for the final stages of development. As such, WRAIR can be characterized as the primary catalyst for the development of mefloquine. The catalyst for the interest of WRAIR in developing anti-malarial pharmaceuticals can be traced to the wartime difficulties encountered by the U.S. military during the
Vietnam War, in which as much as one percent of troops were dying as a result of malaria infection per day [18]. As a result, the development of mefloquine, on a holistic level, can be characterized as one that resulted from difficulties encountered in a military context; such development ultimately resulted in improved malaria therapeutic options for military personnel and civilians alike.

3.5.4.2 Halofantrine (Halfan) for Malaria

Approval for halofantrine hydrochloride (Halfan) was granted by the U.S. Food and Drug Administration (FDA) to pharmaceutical company Smith Kline Beecham (now GlaxoSmithKline) in 1992 for the indication of malaria, under NDA application number 020250 [19]. The origins of the development of halofantrine can, like those of mefloquine, be traced to the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR), of the U.S. Army, and its malaria drug discovery program that was established in 1963 [18].

The program conducted pre-clinical studies involving laboratory screening of compounds for anti-malarial activity. Halofantrine, similarly to mefloquine, was identified as possessing anti-malarial activity as part of this screening activity. Subsequently, WRAIR performed phase I and II trials, demonstrating human use potential, and proceeded to provide the results of such trials, free of charge, to pharmaceutical company Smith Kline Beecham, so that it could proceed to develop the compound through the final stages of drug development. Indeed Smith Kline Beecham completed development of halofantrine and ultimately received marketing approval for the drug. Similarly to the case of mefloquine, a major impetus for the development of
this compound was provided by WRAIR and its military context and objectives.

Therefore, the development of halofantrine can be characterized as being spurred by military activities. Regardless of the development impetus, the ultimate drug approval improves treatment options for military members and civilians alike.

### 3.5.5 Priority Review Voucher Issuance

One, or roughly six percent of the approved pharmaceutical products assessed, resulted in the approval applicant receiving a priority review voucher (PRV) from the U.S. Food and Drug Administration (FDA), as part of a federal statutory program to incentivize drug development for neglected diseases. Given that a PRV was sought and obtained, it can be characterized as having incentivized, in part, the development of the drug in question. The approved product in this category is bedaquiline (Sirturo), which was approved in 2012.

#### 3.5.5.1 Bedaquiline (Sirturo) for Tuberculosis

Approval for bedaquiline (Sirturo) was granted by the U.S. Food and Drug Administration (FDA) to pharmaceutical company Janssen Research and Development, LLC, in 2012, for the indication of tuberculosis (specifically, multi-drug-resistant tuberculosis), under NDA application number 204384 [66]. Initial pre-clinical identification of the anti-microbial activity of the relevant compound was conducted by the scientific staff of Johnson and Johnson Pharmaceutical Research and Development (Johnson and Johnson is the parent company of Janssen Pharmaceuticals) [67]. Subsequently, the company conducted clinical trials up to the second phase, at which
point the company applied for and was awarded FDA approval, on an accelerated schedule, due to the priority status of tuberculosis [68].

As part of the approval, Janssen received priority review voucher PRV 204384, allowing the company to request expedited priority review of a non-priority drug candidate in the future [66]. It can be argued that there were two incentive mechanisms involved in the approval of bedaquiline, with one being the accelerated approval based on a surrogate endpoint with regard to clinical trial outcomes, and the other being the issuance of the PRV to the applicant. However, in essence, the PRV is more truly an incentive mechanism for drug development, in the form of a “pull” mechanism. The primary purpose of accelerated approval based on a surrogate endpoint is to allow for earlier marketing of a needed drug for a neglected, orphan, or otherwise priority disease. Thus, the incentive mechanism in this case may be primarily assessed as being that of the PRV.

3.5.6 Intellectual Property/ Data Transfer

One, or roughly six percent, of the approved pharmaceutical products assessed, received approval in a process that primarily involved the transfer of intellectual property or data from one organization to another. The approved product in this category is para-aminosalicylic acid (Granupas), which received approval in 2014.

3.5.6.1 Para-Aminosalicylic Acid (Granupas) for Tuberculosis

Approval for para-aminosalicylic acid (Granupas) was granted by the European Medicines Agency (EMA) to French pharmaceutical company Lucane Pharma in 2014 for the indication of tuberculosis under agency product number EMEA/H/C/002709 [69].
Para-aminosalicylic acid actually had previously been developed before Lucane obtained EMA approval to market the product in the European Union, as Jacobus Pharmaceutical Company had already been marketing the compound in the United States as “Paser” [19]. However, the compound had not previously been approved for use in the European Union, despite a need for tuberculosis treatment options. Lucane Pharma enabled Europeans to access the para-aminosalicylic acid compound by obtaining a license, from Jacobus, to distribute the same compound in Europe [70]. Although, in this case, the development process itself was not spurred by the transfer of intellectual property rights, an agreement related to the transfer of intellectual property enabled Lucane Pharma to subsequently obtain marketing approval in the European Union, allowing for the distribution of the compound in new geographic areas and for the drug to provide increased treatment options regarding tuberculosis to populations that previously did not have such access.
4. Merits and Deficiencies of Neglected Disease Pharmaceutical Development Incentive Mechanisms

The previous chapter enumerated examples and cases of regulatory approvals of pharmaceutical products from recent years. The noteworthy aspect of these cases is that development was pursued to completion, as opposed to mere initiation of development. As such, given the fact that these products were approved for neglected diseases subject to market deficiencies, their development mechanisms produce insights into effective methodologies for stimulation of drug development in cases where there is a deficiency in market impetus. Although regulatory approval, alone, does not guarantee a public health impact, as, subsequently to approval, effective implementation and distribution mechanisms are necessary components of public health policy, such approval is the first major milestone in the process that yields public health benefit from pharmaceutical development.

4.1 Development Incentive Mechanisms of Recent Approvals

The recent pharmaceutical approvals assessed resulted from a variety of development incentive or stimulus mechanisms that were applied toward a variety of diseases by numerous organizations. Analysis of these approvals, however, reveals certain commonalities and trends amongst these individual cases. Namely, multiple cases of development were driven by the same incentive mechanism. Of these, the most commonly encountered is that of the product development partnership (PDP), followed by those of private pharmaceutical development (PVT), corporate philanthropy (PHL),
military development (MIL), priority review voucher (PRV) issuance, and intellectual property/data transfer (IPT), in decreasing order with regard to number of associated regulatory approvals. The proportions of primary development mechanisms attributable to each instance of regulatory approval are presented in Figure 1 below.

![Proportions of Approvals](chart.png)

**Figure 1: Proportions of Development Incentive Mechanisms Amongst Approvals**

Given that the actual development histories of each approved compound were complex, resulting from the intricate nature of the drug development and approval processes, it may have indeed been the case that multiple incentive mechanisms were at
play in a given case of development. However, the assessments in the previous chapter weighed these multiple factors and qualitatively determined the primary stimulating factor in each case of development, and formed an overall, holistic characterization, in the form of a development incentive mechanism, accordingly. The resultant six categories of development mechanisms represent policy different policy approaches, each with its own merits and deficiencies, as highlighted by the case histories.

4.1.1 Product Development Partnerships

The product development partnership (PDP) model of development incentive mechanism was the most well represented model in the approval sample assessed, as shown in Figure 1 above. The PDP model resulted in drug development toward novel therapeutic options for malaria, leishmaniasis, and Chagas disease, representing three, or half, of the six total diseases addressed by these recent approvals. The approvals, ranging from 1999 to 2014, were granted by a diverse array of regulatory authorities, including that of Kenya, the U.S. Food and Drug Administration (FDA), the Medicines Evaluation Board (MEB) of the Netherlands, that of India, the World Health Organization (through its “prequalification” procedure), that of Brazil, and the European Medicines Agency (EMA) of the European Union.

Developments resulting from the PDP incentive model thus represent an international reach and effectiveness. Given the large time span of regulatory approvals, these developments are also indicative of an enduring model. As half of the total number of diseases that were targeted by the recently approved products were
addressed with the PDP model, public-private product development partnerships may be the most effective of the currently proposed development incentive mechanisms.

The product development partnership model implementations encountered from the analysis of recent approvals can be divided into two broad categories. The first is one in which coordination of the public-private product development partnership was provided by an non-profit non-governmental organization dedicated to producing therapeutic solutions for a particular disease. The other is one in which a product development partnership was created by a direct agreement between a pharmaceutical manufacturer and a public (governmental or intergovernmental) entity, on an ad hoc basis, without mediation from a disease-specific non-profit organization. With regard to the former category, the disease-specific non-profit organizations involved were the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi).

4.1.1.1 Medicines for Malaria Venture (MMV)

The Medicines for Malaria Venture (MMV) was established, as a non-profit organization, in 1999 in Switzerland, with a mission “to reduce the burden of malaria in disease endemic countries by discovering, developing, and delivering new, effective and affordable antimalarial drugs.” Initial funding was provided by the governments of Switzerland and the Netherlands, the Department for International Development (DFID) of the United Kingdom, the Rockefeller Foundation, and the World Bank [71]. The impetus for establishment was provided by a deficient development pipeline for malaria
drugs, combined with mortalities attributable to malaria ranging from one to two million people per year [72].

This deficiency of development, according to Christopher C. Hentschel, a former chief executive officer of MMV, results from a “market mechanism” that often fails to cater to “global diseases of the poor, such as malaria” [73]. MMV obtains funds, mostly from public sources [74], and channels them to different public and private organizations with capacities to provide development activities in distinct parts of the drug development value chain, “from basic drug discovery to late-stage development” [75].

The resultant collaboration has yielded “the world’s largest malaria research and development portfolio,” which includes four, or approximately twenty-two percent, of the total drug approvals assessed by this thesis [75]. In addition to these approved products, MMV is currently supporting a malaria development pipeline of seventeen projects, each representing potential new drug products in various stages of development, ranging from pre-clinical and translational studies to human clinical trials preceding regulatory approval [76]. Of these projects, eight are in the pre-clinical and translational stages and nine are in various stages of human clinical trials, representing realistic possibilities of yet novel products for malaria therapy.

Such possibilities are supported by the fact that the annual financial income obtained by MMV has grown fairly steadily and consistently since its founding, with an income in 2000 of approximately 7.6 millions U.S. Dollars (USD) to an income in 2014 of approximately 79.2 million USD [77]. Additionally, expenditures in 2014 totaled
approximately 67.2 million USD, representing an operational surplus of approximately 12 million USD. New pledges received in 2014 totaled 43.1 million USD, with funds to be received through 2018.

In addition to stable finances, MMV has maintained a robust array of operational partnerships with a range of pharmaceutical companies for product development. These include large multi-national companies, such as Novartis, as well as smaller firms, such as Shin Poong and Guilin. The combination of these factors bodes well for the future of MMV and its product development objectives for malaria. As such, the founding and subsequent operations of MMV may serve as a model for future approaches to address neglected diseases. The model of MMV, of course, is one of dedication to a single disease. Another possible approach by PDP-fostering non-profit organizations is one of dedication to a group of diseases, as opposed to that toward a single disease. An example of such a non-profit organization is the Drugs for Neglected Diseases Initiative (DNDi).

4.1.1.2 Drugs for Neglected Diseases Initiative (DNDi)

The Drugs for Neglected Diseases Initiative, or DNDi, was responsible for one, or approximately six percent, of the product approvals assessed by this thesis. The origin of this non-profit organization can be traced to 1999, when the non-profit public health organization Medecines Sans Frontieres (MSF) created a working group to identify approaches to innovate new drugs for neglected diseases, many of which were encountered by MSF staff in the field. This working group recommended the
establishment of a new dedicated initiative, the Drugs for Neglected Diseases Initiative (DNDi).

This proposal for a new initiative was indeed realized in 2003, when resources were combined from the contributions of seven public health related institutions from around the world: (1) the Indian Council of Medical Research, (2) the Institut Pasteur (of France), (3) the Kenya Medical Research Institute, (4) Medecines Sans Frontieres (MSF), (5) the Ministry of Health (of Malaysia), (6) the Oswaldo Cruz Foundation/ Fiocruz (of Brazil), and (7) the Special Programme for Research and Training in Tropical Diseases (TDR) of the WHO (with a status as a “permanent observer”) [78]. DNDi was subsequently incorporated as a non-profit organization in Geneva, Switzerland, in 2003.

The organizational mission of DNDi was established as one “to develop new drugs, or new formulations of existing drugs, for patients suffering from the most neglected communicable diseases” [79]. Thus the disease portfolio of this organization, unlike that of MMV, was left open-ended. DNDi ultimately developed objectives to develop treatments for leishmaniasis, sleeping sickness (otherwise known as human African trypanosomiasis), Chagas disease (otherwise known as American trypanosomiasis), malaria, pediatric HIV, and various helminth (parasitic worm) infections. All of these diseases, with the exception of HIV, were assessed by this thesis as being neglected diseases. This expanded portfolio, compared to that of MMV, yields benefits as well as difficulties for the PDP-fostering organization in question.

The benefit is that the organization has a greater potential to impact public health, with regard to neglected diseases, on a holistic level, due to activities that seek
developments for multiple diseases, as opposed to a single disease. As a result, a greater number of patients can be positively impacted as a result of developments, and, additionally, the organization may be eligible for more sources of funding, resources, and partnerships, on account of having a more diverse research and development portfolio resulting from broader institutional objectives. On the other hand, the drawback is that having a more diverse portfolio allows for less focus, expertise and specialization, at the institutional level, and may require the organization to have to draw upon more resources to support a broader range of activities, resulting in greater organizational costs and less overall efficiency in achieving objectives.

The achievements and outcomes of DNDi can be compared to those of MMV in order to elucidate how well each organization has fared relative to each other, given different breadths of portfolios. Some factors that may help to facilitate such a comparison include that of organizational age; both MMV and DNDi are fairly young organizations, having been established in 1999 and 2003, respectively. Additionally, both organizations are incorporated as not-for-profit organizations in Geneva, Switzerland, and are thus subject to the same legal requirements and environment in the country of incorporation.

DNDi, in contrast to MMV, has produced one approved product compared to four. However, it is important to note that DNDi operations did yield certain approved products that were not included in the product sample of this thesis. These excluded products were combinations of existing approved compounds and were thus excluded from the scope of analysis, on account of the fact that the development leading to such
approvals did not require certain stages of the development process, such as pre-clinical and laboratory development. More information regarding the types of approvals that were excluded from this assessment, and the associated rationales, can be found in Chapter 2.

If excluded approvals are taken into account, then DNDi produced five total approvals, a comparable amount to that of MMV. However, the majority of such approvals, in the case of DNDi, were new combinations of existing drugs, in which it was not necessary to traverse the entire research and development process, as it would be the case for development of new chemical entities. Regarding financial strength, the total income garnered by DNDi in 2014 was approximately 41.7 million USD (compared to 79.2 million for MMV), and total expenditures by DNDi were 41.5 million USD (compared to 67.2 million USD for MMV). This resulted in an operating surplus of approximately 180,000 USD (compared to 12 million USD for MMV) [80].

Thus, MMV was able to recruit more funding from many of the same donors from which DNDi benefitted, including the Bill and Melinda Gates Foundation of the U.S. and the Department for International Development of the U.K. Both expenditures and the operating surplus for MMV were significantly greater than those of DNDi, demonstrating greater financial strength and stability. Regarding development pipelines, DNDi currently is involved with ten different projects involving the development of new chemical entities (NCEs), whereas MMV is involved with fourteen of such projects [81]. As a result, the differential progress, between the organizations, with regard to approvals, finances, and development pipelines, suggests that the
approach of one may be more effective than that of the other. In this case, the primary
difference, in terms of organizational mission, between MMV and DNDi is that MMV
pursues development for a single disease, whereas DNDi pursues development with
regard to a multitude of diseases. Although there may be other factors at play (and
should be examined as part of further study), one reason for the greater progress of
MMV may be its narrow institutional focus, allowing for greater concentration of
resources toward a specific context and greater efficiency in the process.

4.1.2 Private Pharmaceutical Industry Development

The private pharmaceutical industry development (PVT) model, responsible for
two of the eighteen drug approvals addressed, is unique amongst those assessed by this
thesis on the account that it is not actually an incentive policy. Rather, approved
products developed as a result of the PVT model achieved development through a
traditional drug development process primarily involving the resources and activities of
a private pharmaceutical firm, similarly to the drug development process pertaining to
non-neglected diseases. The pharmaceutical firms involved were relatively small firms
such as Adria Laboratories and Otsuka Pharmaceutical Co., as well as larger companies
such as Hoescht AG (now a part of Sanofi Aventis) and Bayer Healthcare.

The likely impetuses for such private development are varied. In some cases,
such as that of Otsuka and the development of delamanid (Deltyba) for tuberculosis,
there was a small firm committed to certain diseases, including neglected ones. In other
cases, such as that of the approval of rifabutin (Mycobutin) for tuberculosis,
development within the firm was actually spurred by an objective to treat a different
disease, which, in this case, was mycobacterium avium complex (MAC) infection secondary to AIDS. The subsequent identification of utility toward a neglected disease was an incidental benefit.

Although the adoption of a development agenda addressing a neglected disease by a pharmaceutical firm can be a potent force with regard to novel drug approval, whether or not such adoption occurs in the first place can be an unpredictable and unreliable process. For instance, a product being developed for a non-neglected disease may, subsequent to initial approval for the initial indication, be found to be effective against a neglected disease. However, the nature of such occurrences is stochastic and cannot be relied upon by communities affected by neglected diseases for future development. As a result, although developments toward neglected diseases arising from within the private pharmaceutical industry are welcome instances of progress, this model, by itself, cannot sufficiently fulfill the needs and agendas of those who are aiming to actively engage in producing developments for neglected diseases.

4.1.3 Corporate Philanthropy

The corporate philanthropy (PHL) model was responsible for three of the eighteen drug approvals assessed. In terms of mechanics, this model is similar to that of private pharmaceutical industry development (PVT) model. This is due to the fact that the process of development, from start to finish, was primarily financially and operationally supported by a private pharmaceutical firm. The distinction from the PVT model is that, in the PHL model, the private firm undertook the development with the explicit intent of addressing neglected diseases. This intent may have been manifested in
numerous ways. One way would be for the firm to explicitly state such a commitment to neglected disease treatment in annual reports or other company documents or official statements. Another way would be to, subsequently to product approval, establish a drug donation program in which poor and affected populations would receive the new drug free of charge, as was the case with ivermectin (Stromectol/ Mectizan for onchocerciasis) and Merck and Co.

Similarly to the PVT model, the PHL model can be a potent force for drug development for neglected diseases. Pharmaceutical firms may allocate certain proportions of resources and funds to devote to this purpose due to potential benefits, such as positive publicity, that the firm may resultantly receive. Any such developments do indeed represent progress for causes related to neglected diseases, but, similarly to the case of the PVT model, cannot be relied upon, by itself, by communities affected by neglected diseases. This is due to the unpredictable and stochastic nature of what diseases will or will not be the subject of philanthropic activity on the part of pharmaceutical firms.

4.1.4 Military/ Wartime Development

The military/ wartime (MIL) development mechanism was responsible for two of the eighteen approvals assessed, both of which pertained to malaria. In both cases, a medical need, regarding a neglected disease, was encountered by combat troops in the commission of activities of the U.S. Army. As a result, the Walter Reed Army Institute of Research (WRAIR) supported, not only financially but operationally as well, drug development addressing malaria. The approvals that resulted would be beneficial not
only for combat troops, but for civilians as well. Given that military budgets and resources tend to be significant in terms of magnitude, attention, by military organizations, toward neglected disease can be a promising development for affected communities and military personnel alike. However, the needs of military forces and organizations are not always in line with those of the civilian populations affected by neglected diseases. Although such civilian communities may enjoy incidental benefits when needs do align, such alignment is not necessarily predictable or stable, as military needs may change as a result of political and other forces. As a result, although military developments can yield progress for public health needs related to neglected diseases, they cannot be relied upon for this purpose.

4.1.5 Priority Review Voucher Issuance

The issuance of a priority review voucher (PRV) by a regulatory agency was determined to play a relevant role with one of the eighteen drug approvals assessed. With regard to the dynamics of incentive mechanisms, the PRV model is unique amongst those addressed by this thesis in that it represents the only “pull” mechanism in the group. The other models, whether PDP collaboration, military development, etc., functioned through a “push” mechanism, in that resources were typically allocated toward the purpose of research and development before the commencement of such operations. For example, in the PDP model, an organization such as MMV may solicit funds from donors and subsequently distribute those funds to a pharmaceutical firm, in order to “push” the firm to commence development of products for neglected diseases.
PRVs, in contrast, were (legislatively) designed as a “pull” mechanism. Under the PRV model, which is administered by the U.S. Food and Drug Administration (FDA), the FDA does not “push” firms to develop products for neglected diseases by issuing grants or funds. Rather, the PRV is awarded to a firm that successfully develops a drug for a neglected disease, so that that firm can receive priority review and expedited approval of another, unrelated drug designed to treat a non-neglected disease. As a result, the firm is likely to reap greater profits from the other drug, on account of having that drug on the market for a greater period of time. The expectation of the PRV program is that such an end result will entice, or “pull” the firm to pursue drug development for neglected diseases.

Although this mechanism may work in theory, there is an inherent deficiency in pull mechanisms. The deficiency is that, from the perspective of the drug developer (such as a pharmaceutical firm), there is an inherent risk in attempting to avail this incentive. As the award of a PRV is contingent upon successful development of a drug, a firm would have to invest significant funds and resources in pursuing such a development, without any certainty that the end reward will be reaped. This is due to the risky nature of drug development, in which hundreds of millions of dollars and several years may be spent, and an ineffective drug product may be yielded, resulting in significant sunk costs and time and an unattractive prospect for a pharmaceutical firm. Thus, the effectiveness of PRVs in stimulating development is theoretically questionable. Furthermore, in practice, it has not often been availed, as it has been used a total of seven times since the program was first launched in 2007 [31], resulting in a utilization
rate of less than once per year from the industry. As such, the PRV may play a role in stimulating certain instances of development, but the overall effectiveness of this fairly new program is unclear as of yet.

4.1.6 Intellectual Property/ Data Transfer

There was once instance of intellectual property/ data transfer (IPT) encountered amongst the approvals assessed. In this case, the granting of a license, from the original firm to a new firm, to produce and market a drug for a neglected disease, enabled its use in a new geographic location. In this scenario, the transfer of intellectual property rights yielded a new approval (in a new geographic area) but did not necessarily catalyze the development that preceded the approval, as did the other models. Although this approval was beneficial for residents of the new geographic area, it did not represent pharmaceutical innovation. However, the transfer of intellectual property can, in other contexts, yield innovation in development. In the context of open approaches to development, where data generated by one firm is made freely available for use by other firms, may lead to greater efficiency through increased synergy and decreased redundancy in the development process, at a global level. As such, policies to promote transfer of intellectual property, at organizational, national, and international levels can support the catalysis of drug development for neglected diseases.

4.2 Differential Capabilities of Development Incentive Mechanisms

There are a variety of policy mechanisms that allowed for market deficiencies to be overcome and drugs for neglected diseases to be developed to completion and
approval. However, inherent in the diversity of these mechanisms are differentials in merits and deficiencies of such approaches. As governments, non-profit organizations, foundations, and private donors weigh options for philanthropic contributions toward solutions for neglected diseases, not only will amounts of contributions be a relevant factor in the returns generated, so will the development mechanisms to which such funds are applied.

Examination of recent approvals for drugs for neglected diseases reveals that, both in theory and in practice, some methods may be more effective than others in yielding drug approvals. Of the development mechanisms characterized, the one best represented amongst the sample is that of the product development partnership (PDP) model. Under this model, development agreements between public, private, for-profit, and not-for-profit entities enable different organizations to apply distinct strengths and capacities collaboratively toward a unified project of developing one specific drug for one specific disease. In most of the cases analyzed, such partnerships were facilitated by a non-profit organization dedicated to forming such collaborations.

The specific organizations in this case were the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi), although numerous other organizations of the same type are currently in operation as well. Both MMV and DNDi were successful in recruiting funds, developing pipelines, and producing approvals. However, each has a different overall approach, MMV focuses on projects for one disease, malaria, whereas DNDi focuses on projects for a variety of neglected diseases.
Despite the progress made by MMV, DNDi, and similar public-private product development partnership organizations, there remains a significant need for further therapeutic developments for neglected diseases. As various funders, from different sectors, aim to address these needs through contributions, it may be most effective to invest in public-private product development partnerships, like MMV and DNDi, that have established collaborative connections between relevant entities in the public and private sectors. In addition, as the current array of public-private product development partnerships cannot sufficiently address the overall global need for therapeutic developments, more of such organizations could provide needed developments in areas currently not addressed. As the recognition of global public health needs led to the establishment of MMV and DNDi by relevant organizations, it is conceivable that similar organizations can be similarly established in the future, providing more philanthropic investment opportunities in a model that leverages the strengths of different sectors to overcome market deficiencies and produce improved prospects for global public health.
5. Efficacy of the Product Development Partnership Model: Underlying Factors

5.1 NGO-Mediated Partnerships

Six out of seven, or roughly an eighty-six percent majority, of the approval instances characterized as being stimulated primarily by the product development partnership model of development occurred as a result of the action of dedicated non-profit non-governmental organizations (NGOs). In the approvals assessed, the particular organizations involved were the Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi), both of which are public health oriented NGOs. Both are distinctly dedicated to the development of pharmaceutical products through the coordination of partnerships between public and private entities, and both have been successful in pursuing development to completion and approval.

MMV and DNDi, however, are not the only examples of NGOs operationally structured around a model of public-private product development partnership. Other similar organizations exist, and, like the aforementioned two, are relatively nascent organizations. For example, the Global Alliance for Tuberculosis Drug Development (GATB) was established in New York in 2000. GATB recruits funding from governmental and philanthropic sources and channels it to partner entities with the goal of developing novel candidate drugs for tuberculosis. To date, GATB has amassed a portfolio that includes nine potential novel drug candidates [82].

Another example of a relevant NGO is that of the Institute for OneWorld Health (IOWH), which was established in San Francisco in 2000 [27] and received funding from
private sources including the Gates Foundation. Since 2011, IOWH has been affiliated with another public health organization, PATH, formerly called the Program for Appropriate Technology in Health [83]. IOWH, and, more broadly, PATH, are similar to DNDi, in that these organizations do not focus on a specific disease, instead promoting development for a variety of neglected infectious diseases.

What is common amongst the NGOs exemplifying the product development partnership model of pharmaceutical development for neglected diseases is that all operate independently of governments or private industry, but establish ties between these sectors by serving as central coordinators with regard to specific development efforts. Additionally, each entity can claim significant progress, in the form of approved pharmaceutical products, or, at the least, candidate products at various stages of the development pipeline. These relatively successful outcomes, associated with relatively young and small organizations, suggest a particular efficiency and efficacy associated with the operational dynamics employed within the overall public-private product development partnership structure employed by these organizations. These unique and relatively novel dynamics warrant further examination and analysis, as they represent promising models of compensation for the deficiencies of traditional market-oriented models of pharmaceutical development in the public health context. Such consideration can elucidate the particular factors and qualities that these dynamics possess that make them especially effective.
5.2 Dynamics of the Product Development Partnership Mechanism

The root challenge in pharmaceutical development for neglected diseases, and, indeed, any diseases, is the significant investments of time and funds that are inherently required, given the rigorous and lengthy scientific and regulatory processes that underlie drug development. These high investment requirements can produce barriers to the establishment of development efforts, unless market dynamics, in traditional instances of non-neglected diseases, can provide a sufficient impetus. As market dynamics cannot provide the driving force behind pharmaceutical development for neglected diseases, the impetus for developmental activity must originate elsewhere.

5.2.1 An Infrastructure of Collaboration

The significant investment requirements associated with pharmaceutical development for neglected diseases represent high risks, which create barriers to entry into developmental activities. If these risks could be spread and shared amongst multiple entities, as opposed to being borne by a single entity, such as a for-profit private sector pharmaceutical company, the barrier to entry can be lowered for each individual participating entity. This is the point at which collaboration plays a role.

Instead of one pharmaceutical company pursuing research and development activities with the goal of producing a new drug, there are multiple organizations, including pharmaceutical companies, non-profit organizations, and government entities, pursuing the same goal of developing a new drug. As a result, the desired output remains the same, the total input requirements regarding required investments of time
and funds remain the same, but the proportion of the total investment to be borne by each participating entity changes. In this alternative model, each participating entity bears significantly less of an investment burden, and therefore less risk, lowering the barriers to entry for each participating partner and increasing the likelihood of the adoption of the drug development project in question.

Although coordinated collaboration, as described, can lower barriers to entry, another significant issue and challenge for pharmaceutical development is that of failure rates and endurance. The pipeline of drug development requires multiple stages, and it is well documented that high attrition rates prevent most drug candidates from ever being marketed or distributed to consumers and patients. For example, although estimates vary, the overall success rate of drug candidates in the clinical development process has been described as being around 11 percent, suggesting that roughly 89 percent, a vast majority of drug candidates, never attain regulatory approval, despite reaching the clinical development stage [84]. Additionally, most attrition within the clinical development stages occurs in later stages of the clinical trial process, namely, phase II and phase III trials, which happen to be amongst the costliest stages of clinical development.

As such, for any collaboration to be ultimately successful in yielding a novel drug, endurance of research and development efforts is requisite. This is where the role of the central NGO, dedicated toward the goal of product development, is particularly important. Collaboration can be established in an ad hoc manner, directly between governmental or philanthropic funders and private pharmaceutical companies, the
initial barriers to entry of pharmaceutical development can be overcome, and projects can be initiated. However, given the generally high attrition rates associated with pharmaceutical development in later stages, there has to be a mechanism to ensure that projects that are initiated do not ultimately fail to produce any useful results or outcomes.

This mechanism is provided by the NGO dedicated to fostering product development partnerships. For development projects that are catalyzed by these NGOs, collaboration is not established between funders and developers on a transient or ad hoc basis; rather, an infrastructure of collaboration is created and maintained by the dedicated NGO. As demonstrated by Medicines for Malaria Venture (MMV) and the Drugs for Neglected Diseases Initiative (DNDi), dedicated NGOs recruit various partners with differential funding and operational capacities, initiate collaborations between them, but continue to play roles as central managers of the projects that were initiated. This locus of management provides stability to the overall project, and promotes long-term commitment to the development endeavor by the constituent partners.

These NGOs can recruit partners based on the differential and unique strengths that each can offer to the overall project and establish diverse and qualified product development teams to pursue drug development projects [27]. As time and activities progress, the NGO at the center of the project can serve in oversight and assessment roles to ensure that budgets, timelines, and milestones are met by individual partners, promoting the success of the overall project. Thus, the inherent challenge of attrition
associated with pharmaceutical development can be addressed, and its likelihood reduced, by an enduring accountability and coordination mechanism created by the collaboration infrastructure established by the dedicated NGO in the implementation of a product development partnership.

5.2.2 Partner Organizations for Each Stage of the Development Pipeline

Each point of the innovation chain associated with pharmaceutical development yields distinct challenges, and the NGO-mediated public-private product development partnership mechanism offers a robust means to address them. As mentioned in the previous section, dedicated NGOs can unite different partners with unique strengths that are relevant to various points in the pharmaceutical development process. Examples of such partners include large pharmaceutical companies ("big pharma"), small pharmaceutical and biotech firms, academic organizations, and contract research organizations (CROs) [27].

Dedicated NGOs can recruit funding from sources such as government entities, philanthropic foundations, and private donors and channel them toward operational partners such as pharmaceutical companies, academic labs, and contract research organizations. Indeed, government entities such as the United States Agency for International Development (U.S.A.I.D.) and the Department for International Development (D.F.I.D.), of the United Kingdom have frequently and substantially contributed toward the efforts of NGOs such as MMV and DNDi. Additionally, private
foundations, such as the Gates Foundation, have been frequent and significant contributors as well.

Once initial funding is secured, the dedicated NGO can recruit operational partners. In the pre-clinical and laboratory stages of drug development, academic labs can be recruited to identify compounds of interest. If and when such compounds are identified, pharmaceutical companies or contract research organizations can be recruited to conduct the various stages of clinical trials. As dedicated NGOs tend to have significant knowledge of target populations and local conditions, they can advise the company conducting clinical trials on the execution of trials in the target localities. If and when clinical trials demonstrate sufficient safety and efficacy of the candidate compound, a large pharmaceutical company can be recruited to apply for regulatory approval and prepare for subsequent manufacturing and distribution, as large pharmaceutical companies tend to have particular expertise in such matters. An example schematic of the types of organizations that can be recruited, as constituents of product development partnerships, for financial or operational support in various stages of the pharmaceutical development pipeline is presented in Figure 2 below.
In summary, dedicated NGOs using the public-private product development partnership model can solicit funds for a specific purpose and subsequently recruit and unite operational partners with differential strengths to pursue development activities. Barriers to entry are overcome by the distribution of investments and risks across these partners, as each entity participates in a separate stage. Moreover, each constituent partner contributes to the stage of development that is most in line with its own operational strengths, increasing the overall efficiency of the development process and reducing the likelihood of attrition at any given developmental stage.
5.2.3 Advantages in Ethics and Political Optics

In addition to increasing the efficiency of the development pipeline by recruiting and uniting partners with differential strengths, dedicated NGOs using the public-private partnership model may also increase the likelihood and improve the political optics of the initial solicitation of funds. Given that these NGOs serve in an intermediary role between funders and operational partners, they obviate the need for funders to contribute directly to the operational partners. The result is that potential conflicts of interest can be reduced or avoided.

For example, an NGO such as MMV may solicit funds from government entities such as D.F.I.D. and subsequently distribute it to private for-profit pharmaceutical companies for development activities. Without the NGO serving in the intermediary role, the funds would proceed directly from the government entity to the private-sector pharmaceutical company. Although such an arrangement can be a fruitful one, it may also give rise to potential conflicts of interest. For example, the allocation of funds from a particular government agency to a specific company may raise concerns regarding the relationship between the two entities. For example, it may be the case that the director of the government agency in question has a financial stake in the private sector recipient of funds. This situation may raise ethical concerns regarding conflicts of interest in fund distribution. Moreover, it may actually hinder pharmaceutical progress if the perception or presence of such conflicts of interest prevents the allocation of funds at the outset.

If funds originating at the government agency are channeled through a non-profit intermediary, the direct conflict of interest is removed, and the political optics of
such a financial transfer are improved. Thus, the way is paved for funds to be solicited and allocated. In this context, the dedicated NGO can serve as an impartial intermediary that promotes the legitimacy, whether perceived or actual, of the initial financial transactions.

In addition to addressing substantive ethical issues relating to conflicts of interest, dedicated NGOs can improve the public relations aspects of the funding of pharmaceutical research. This improvement applies to both funders and pharmaceutical developers. Funders can benefit from the reduced ethical concerns and superior political optics of contributing funds to a non-profit intermediary, and the ultimate recipients of funds benefit from the public image manifested by a partnership with a public health related non-profit organization with the ultimate philanthropic goal of the development of drugs to improve aspects of public health. Such a relationship can be appealing to private sector pharmaceutical companies as it can provide public relations and advertising value for the company.

In summary, dedicated NGOs, in utilizing the product development partnership model of development, can reduce both perceived and actual ethical issues associated with the allocation of public funds toward private entities. The resultant improvement in optics can promote and ease the process of solicitation of funds, increasing the likelihood that sufficient funds will be acquired. Thus, the product development partnership model can stimulate the allocation of funds toward the purpose of pharmaceutical development for neglected diseases.
5.2.4 Limitations

Despite its virtues, the product development partnership model of development is not without its limitations. Although organizations such as MMV and DNDi have successfully employed the model to produce novel pharmaceutical products for neglected diseases, they have encountered setbacks as well. However, analysis of the hindrances faced by these organizations will suggest, that, on the whole, the virtues of the model outweigh its associated obstacles.

One limitation is with regard to the recruitment of funding. There are circumstances in which it is difficult for the dedicated NGO to recruit funds for a particular drug development project. For example, Julia Tuttle, a Research Associate with the Global Health Innovations Alliance at Duke University, reports that, based on experience with the Drugs for Neglected Diseases Initiative (DNDi) in South America, some governments may prefer to sponsor projects specific to their own countries, and, as a result, projects involving regional international collaboration may be stymied [85]. However, these NGOs are positioned to recruit funds from a variety of sources, and may be able to overcome funding deficiencies in one area by channeling funds from other areas and sources.

Another issue related to funding is the degree to which the funder, as opposed to the dedicated NGO, exerts control over selection and operation of projects. For example, Catherine Hennings, the Director of Commercialization and Corporate Partnerships of the Vaccine Development Global Program at PATH, reports that the Gates Foundation is a major funder of projects pursued by PATH. As such, the developers of projects within
PATH may design projects around existing funding opportunities that exist at the Gates Foundation, providing an external funder organization some de facto control over project development [86]. This dynamic can have a number of impacts, many of which are not necessarily detrimental to the overall goal of pharmaceutical development for neglected diseases. Although one impact may be that the NGO dedicated to projects related to neglected diseases will have to yield to the interests of external organizations that are not similarly dedicated, it may also result in an increase in the NGO’s prospects of receiving funds in general and thereby bolster the overall financial strength of the organization.

In contrast, in some cases, such external control by funders is actively avoided by the dedicated NGO. For example, Mariana Abdalla, a former Chagas Disease Program Coordinator and Communications Assistant for DNDi, reports that her former organization had a policy in which not more than 25 percent of overall operational funds could be recruited from a single funder, thereby reducing the chance of external funders exerting de facto control over the internal operations of DNDi [87]. This policy can have a number of effects, and chief among them is that of the maintenance of a relative degree of operational independence from funders, allowing the dedicated NGO to maintain its own operational focus and internal control over project selection and dynamics. However, one drawback may be a reduced prospect of receiving funds from major funders, resulting in lower total operational income.

The effect of the differential approaches to funding adopted by different dedicated NGOs, such as PATH and DNDi, is that the overall landscape of product
development partnership oriented NGOs is a diverse one. Each organization has a unique history and philosophy that has given rise to distinct operational policies. As these organizations are relatively young, the long-term efficacies of many of these policies are yet to be demonstrated. However, the mere presence of diversity in policy within the industry of these NGOs can ensure its holistic robustness, as, with time, the most effective policies can be identified and organizations can evolve to incorporate such policies. Moreover, at present, NGOs, such as MMV, DNDi, and PATH, which utilize the public-private partnership model, have demonstrated an ability to overcome current limitations and produce promising outcomes in terms of pharmaceutical development and, ultimately, regulatory approval and distribution of products for neglected diseases.
6. Product Development Partnerships for Innovation: Conclusions, Further Study, and Broader Applications

Scientific and technological advances have significantly ameliorated health prospects related to many illnesses, greatly improving prognoses for patients of many ailments. However, often exempt from these advances are the roughly billion patients, worldwide, who suffer from neglected diseases. These diseases are particularly pernicious from a public health standpoint, as, despite the significant proportion of the world’s population that is subject to these debilitating and often fatal conditions, there is a dearth of medical treatment options to address their incidence and reduce their impact. As the cohort of patients subject to these diseases is largely impoverished, there is a paucity of purchasing power amongst them. Resultantly, the traditional market-oriented mechanism of pharmaceutical development, in which sales revenues are expected to retroactively subsidize research and development endeavors, is not appropriately suited to serving this population.

Despite the market inadequacy, there have been instances of successful drug development for neglected diseases. Although a variety of mechanisms yielded these instances, the most common amongst them, per the assessment of this thesis, is that of the product development partnership (PDP) model of incentivizing innovation. As such, it is the primary contention of this thesis that such a model is currently the most auspicious option for the development of pharmaceutical products to counter the incidence and impact of neglected diseases.
This assertion is based both on empirical analysis of the histories of recent drug approvals related to neglected diseases, as well as on a theoretical analysis of the operational dynamics that underpin collaborations formed around the public-private product development partnership model. In theory, these collaborations promote development of pharmaceutical products, despite a deficit in market impetus, by reducing the risk to each constituent development partner by distributing the costs of investment across multiple entities. Thus, the barriers to entry for each participating entity are lowered, and the prospect of initiation of a development project is improved. In addition, the central non-governmental non-profit organizations (NGOs) involved in catalyzing the public-private product development partnership may be more able to solicit funds from government sources than are private pharmaceutical companies, due to ethical and public relations issues. Finally, these NGOs can reduce the risk of developmental attrition by uniting partners with differential capabilities and strengths suited to each stage of the development process.

The aforementioned theoretical claims can be explored empirically by assessing the behaviors and tendencies of the organizations and entities that constitute public-private product development partnerships. For example, the financial investments made by the participating entities within a product development partnership-based pharmaceutical development project can be compared to the investments made by pharmaceutical companies in traditional market-based private industry development. It may be found that, due to the leveraging of differential strengths of distinct entities as part of a product development partnership, the overall development costs are actually
typically lower than the overall development costs associated with the traditional
market-based development model, suggesting an improved efficiency of development
from a collaborative model.

Another example of further study would be to assess and compare the ethics,
political optics, and legal issues of direct financial contributions from government
agencies to private pharmaceutical companies, versus those of financial contributions
that are distributed through an intermediary NGO. Public opinion can be gauged with
regard to perceptions on the direct funding of pharmaceutical companies by
government agencies versus funding via non-profit intermediaries. Legal and political
issues with regard to each can be assessed and compared in various jurisdictions. Such
study can empirically bolster the theory that the use of intermediary NGOs in the public
funding of private pharmaceutical company activities can reduce ethical issues and
barriers to development in this context.

The instances of pharmaceutical product approvals explored by this thesis have
collectively demonstrated the effectiveness of the product development partnership
model of research and development in contexts of market deficiency. This mechanism of
incentive policy succeeded in promoting innovation against unfavorable odds. What is
promising about this innovation model is that it may be applied in a variety of contexts
and not just that of pharmaceutical development.

The product development partnership model involves recruiting and uniting
multiple organizations and entities with different strengths to reduce the risks of
investing in innovation for each constituent. As such, it can lower barriers to entry for
innovators and developers in a multitude of fields in which market deficiencies exist. Therefore, further exploration of the applicability of this innovation mechanism in other aspects of public health, such as those of sanitation or potable water, or in fields outside of public health, such as that of agriculture, would be worthwhile endeavors.

Although many aspects of the use of product development partnerships to catalyze development in contexts of insufficient market impetus remain to be studied, the available data and insights from recent years of pharmaceutical approvals suggest that this may be a particularly promising mechanism. As neglected diseases, as well as other health, economic, and infrastructure issues, continue to exacerbate the conditions of poverty in the contexts of developing and emerging markets, innovative policies are needed to produce solutions that can counter their persistence. The collaborative product development partnership model, despite its relative infancy and limitations, represents such an innovative policy. Its exploration and adoption, by non-profit organizations, government agencies, academic organizations, funders, and the private sector, may serve to demonstrate that market deficiencies are not intractable, and that innovative and worthwhile developments can be achieved in spite of ostensibly inauspicious economic prospects.
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87
