Drug Development for Neglected Tropical Diseases: DNDi and the Product Development Partnership (PDP) Model

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Abstract

Neglected tropical diseases (NTDs), including leishmaniasis, Chagas disease, sleeping sickness, dengue fever, and schistosomiasis to name a few, are endemic in 149 countries and impact 1.4 billion people- often the most vulnerable groups in the poorest countries (WHO 2016). Unfortunately, many of these diseases have no vaccines to prevent them, nonexistent or incredibly problematic treatments, and limited resources dedicated to monitoring, controlling, and improving the situation of those who are infected. These diseases may impact millions of people, but the affected population is too poor to exert economic sway and attract investment under the current medical research and development system, and a long-standing market failure has left their needs unmet. However, since the turn of the century, the growing humanitarian concern for NTDs has prompted exploration into innovative partnership and financing mechanisms for developing health technologies for these diseases. Product development partnerships (PDPs), such as the Drugs for Neglected Disease Initiative (DNDi), have emerged to coordinate new collaborations between private industry, academia, and the public sector. Furthermore, the political landscape around NTDs is changing as exemplified by the fact that the World Health Organization (WHO) is endorsing demonstration projects to experiment with "delinkage" principles that aim to separate the innovation market from the price of products and increase affordability and access. These novel approaches to drug development are important case studies in understanding how to best address the market failure around diseases of poverty and offer insight as to what strategies effectively advance the development of innovative health technologies. The lessons learned from the activities of DNDi and other PDPs shed light on how to align the goals of global health with political and economic realities.

Introduction

The health challenges facing the world's poorest and most vulnerable populations are no longer a topic reserved for discussion among international development experts. Celebrity campaigns, television advertisements, and newsreels have helped make the suffering that happens in far corners of the world part of the conscience of everyday citizens in high-income countries. However, while the efforts of many individuals and organizations have been able to advance the global health agenda in recent decades, systemic barriers that prevent the prioritization of the world's poor in the international agenda still remain. There is a disconnect between sympathetic global concerns and the way our world's economy actually functions- a disconnect exemplified by the 35,000 people every day who die from neglected tropical diseases (Sorenson 2009). If we care equally about everyone's life, we must examine the deeply ingrained patterns of neglect in the international economy and look for innovative ways to bring those who fall on the fringes into the folds of a global system for health.

Neglected tropical diseases are an example of a problem that needs to be addressed by the representation of poor countries' concerns at the international level, and not just by humanitarian aid workers. NTDs, including leishmaniasis, Chagas disease, sleeping sickness, dengue fever, and schistosomiasis to name a few, are endemic in 149 countries. They impact over 1.4 billion people- often the most vulnerable groups in the poorest countries (WHO 2016). These diseases are devastatingly neglected in many ways: control programs lack in funding and a strong evidence-base; already weak health care systems have especially substandard technical capacity when it comes to monitoring and treating these diseases; there is insufficient collaboration and international support targeted at addressing these diseases and supporting patients who are impacted. In addition, market forces fail to incentivize research into drug

development for NTDs. This means that there are no vaccines capable of preventing these diseases, and the people who do get infected may not have treatment options available to them after diagnosis because medications have not been invented. Even when treatments do exist they are often incredibly problematic because of toxicity levels, side-effects, duration and burden of treatment, or cost.

This on-the-ground reality of insufficient NTD treatment access reached a head around the start of the 21st century. In 2001, a seminal publication reported that less than 1.1% of new drugs approved between 1974 and 1999 were for neglected diseases, despite the fact that these diseases make up 12% of the global disease burden; this disconnect was coined 'The Fatal Imbalance' (MSF). This publication highlighted the dearth of innovation in the NTD space and made the need for alternative approaches to drug development very clear. Doctors at Médecins Sans Frontières (MSF), a leading emergency medical aid organization with experience on the frontlines of healthcare delivery, grew so frustrated with the lack of medical technology available to their doctors and their inability to treat patients suffering from NTDs that, after receiving the Nobel Peace Prize in 1999, they recommended the formation of a product development partnership, the Drugs for Neglected Disease initiative (DNDi 2016). Today, DNDi represents one of several recent attempts to correct the historical disregard for diseases that affect some of the world's most marginalized people and, along with other global health groups, they have started to explore alternative business models and policy proposals to address the fundamental neglect surrounding these diseases.

This paper aims not only to describe the way in which the current global system fails to adequately address NTDs, but also to give an overview of different ideas to target this market failure. This research closely evaluates the merits and drawbacks of the product development

partnership model in addressing this unmet need, with DNDi as a case study of how innovative financing and partnership mechanisms can be deployed to advance drug development for neglected tropical diseases. In addition to a literature review regarding the basic economic and policy problems surrounding NTDs, found in *Chapter 1: Background*, the author reviewed available print and digital resources as well as conducted personal interviews with over 15 experts in the field of drug development policy and neglected diseases. The findings from these resources are summarized and analyzed in *Chapter 2* and *Chapter 3*. Ultimately, this research revealed important lessons for success, and *Chapter 4: Conclusions* provides recommendations to confront the remaining challenges that face the global health community as it continues the demanding yet essential task of drug development for NTDs.

1. Background

1.1 Economics of drug development

The world has traditionally relied on the expertise of private corporations for the production of pharmaceuticals, and there is no question that these companies are among the most powerful economic actors in global health. In the US, the industry reports over half a trillion dollars' worth of investment in research into development of new medicines since 2000, and over 500 new medicines have received marketing approval from the Food and Drug Administration (FDA) during that same time period (PhRMA 2016). The pharmaceutical market is worth US$300 billion per year and several individual companies have profit margins exceeding 30%, placing their yearly profits above US$10 billion. Importantly, six of the world's ten largest pharmaceutical companies (pharma) are based in the United States, and the other four are in Europe (WHO 2016). These companies provide everything from lifesaving drugs to cosmetic therapies to markets around the world.

In order to understand the concept of neglected tropical diseases, it is essential to understand the business model that allows these companies turn a profit. First of all, government-granted intellectual property rights (IPR) play a key role in these corporations' ability to protect their investment in research and development (R&D). The theory behind IPR holds that "public goods", or knowledge considered non-rivalrous and non-excludable will be under-produced in a decentralized market. In other words, if someone invests time and money in developing a public good there is no way to prevent others from manufacturing the same product; those competitors will not have invested in the invention of the product and are able to "free ride" on the innovator's work. Furthermore, because the competitors have invested less than the inventor of a public good, they will be able to make a profit by selling it at a lower price

than the originator, thus making the originator's product less competitive in the market. The non-rivalrous and non-excludable criteria hold true in the drug innovation market, and thus the public good phenomenon is of concern. Ultimately, without government intervention, this would produce a market failure where there is no incentive to conduct pharmaceutical R&D, even though it is essential to good health.

As with other public goods, governments have developed policies to correct this market failure; IPRs, including patents, copyright, trademarks, and others, grant a monopoly right to the owner who is then able to use this period of market exclusivity to recoup their investment costs. This provides an environment whereby investment in public goods actually makes financial sense for a business and has allowed numerous industries, including pharmaceuticals, to exist and thrive. However, as globalization has made our world more interconnected than ever, international legislative inconsistencies regarding intellectual property have become an issue. The World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO), responsible for international IP law and trade, respectively, have addressed this issue through various iterations of international law. In 1994, this culminated with the passage of the WTO Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. This mandates that all WTO member states provide patent coverage for "all fields of technology," including pharmaceuticals and other medical technologies. Although there are some temporary exceptions for least-developed countries (LDCs) in TRIPS, when taken in consideration with the "most-favored-nation" clause that guarantees national treatment of all WTO members and the various free-trade agreements that have been passed with TRIPS-Plus provisions that promote high standards for IP, it is safe to say that patent protection has become a global norm. This means that the pharmaceutical companies have the right to certain periods of monopoly for their

products in most of the world, including all high and middle-income countries (WTO 2015). For the most part, these legislative tools have corrected the market failure around pharmaceutical innovation, rendering the public goods problem irrelevant so long as IPRs are in effect. This is because, during the period of monopoly, companies do not face price competition from generic manufacturers and can set drug prices based on the market coverage they hope to achieve.

The pharmaceutical industry is considered the most research-intensive industry and studies approximate that only 1 out of 5,000-10,000 chemical compounds that enter R&D actually makes it through the different stages of testing and regulatory approval to reach the market (Scherer 2000; PhRMA 2007). Under these conditions, IPRs undoubtedly provide necessary security for the industry, but at the same time they increase the price that consumers pay for medicines. For example, a case study of pharmaceutical company Eli Lilly's antibiotic drug, Keflex, (Figure 1) shows how much patent protection is relevant to a company's ability to stay competitive:

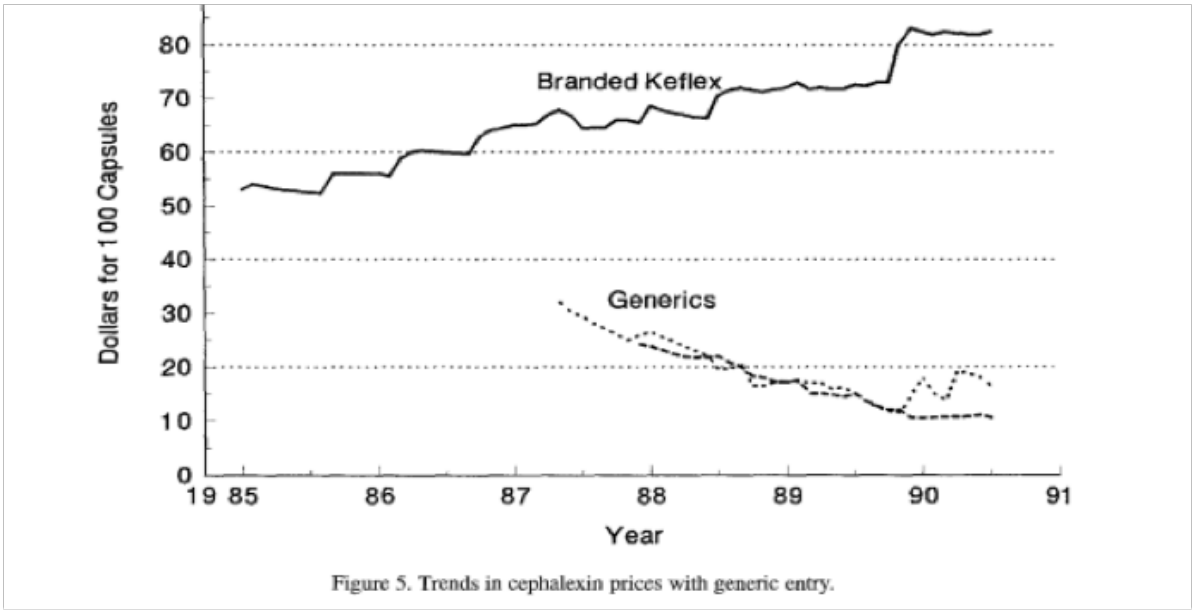


Figure 5. Trends in cephalexin prices with generic entry.

Figure 1: Scherer, F.M. "The Pharmaceutical Industry." Handbook of Health Economics. Vol 1. 268. Eds. Culyer, A.J.

This graph illustrates that before the 20 years of market exclusivity granted by a patent comes to an end, branded drugs are typically sold at prices far above the marginal cost pricing that generic competitors approach when they are allowed to enter the market. This period of time before generic entry is critical for companies looking for a return on investment to grow their company, gain capital for future reinvestment, and ultimately retain their shareholders. In fact, recent pharmaceutical lobbying has pushed an amendment to the Hatch-Waxman Act in order to ensure that the regulatory approval process does not cut into the market exclusivity period for newly approved drugs, clearly illustrating how important this monopoly is for industry (Troy 2003). After patent expiration, pricing trends often differ: sometimes generic competition brings down the brand-name price, and other times brand-loyalty, advertising, or incremental innovation will allow the company to continue charging prices that allow a high profit margin. However, it is undeniable that for whatever period IPR protection applies, it provides an important foundation for the pharmaceutical industry. Qualitative data also echoes this message: as one health economist explains, "Surveys asking researchers and development managers what factors permit them to reap the profit benefits from their innovations… consistently show the pharmaceutical industry to be one in which the greatest stress placed on patent protection" (Scherer 2000). When considering access to medicines, there is clearly a trade-off between providing market exclusivity as an incentive for companies to innovate, and public health considerations.

Pharmaceutical companies are adamant that the amount they spend on R&D and their need to continuously reinvest in future innovation justify the monopoly prices they charge before patent expiration and entry of generic competition. For example, in a document by the Pharmaceutical Research and Manufacturers of America describing their perception of the

unique contributions industry makes to society, the organization boasts that their member companies reinvest an average of 20% of their profits into more R&D (PhRMA 2016). Their own records are kept confidential, but there is no doubt that the years of effort that go into getting a new drug to market require immense investment. For example, the pharmaceutical industry cites studies such as the most recent calculations out of the Tufts Center for the Study of Drug Development, which estimates that it costs a company over US$2.5 billion to develop a new drug (Tufts 2014). However, it should also be noted that this estimate is subject to immense criticism. First of all, the number of US$2.5 billion includes the price of failed compounds and opportunity cost for drugs that are not developed, not simply out-of-pocket expenses. There is also no publicly available data from pharmaceutical companies to support this approximation nor are the details of the clinical trials which are used in the study's calculations available for corroboration. Furthermore, the Center for the Study of Drug Development receives funding from a number of pharmaceutical companies, suggesting a conflict of interest exists in the publication of these estimates (Love 2014).

In addition, the study ignores an important trend in drug discovery: reliance on publicly sponsored basic research. The NIH spends about US$30.3 billion per year mostly on upstream medical research, while drug companies have spent about US$50.2 billion per year, mostly focused on applied translational research and clinical trials (NIH 2015; Powalney 2015). This government contribution to basic research provides foundational knowledge to support the pharmaceutical industry, and industry will sometimes licenses advancements in basic science from academic and other publicly funded institutions. According to a survey of the FDA approvals between 1990 and 2007, 9.3% of drugs were developed as a result of publicly funded research. This number is even higher (19%) when you look at drugs that are considered more

useful and unique, and therefore received priority review from the FDA (WTO, WIPO and WHO 2012, 107).

Clearly, the exact cost of drug development may be debated, and the question of how the relative cost to industry compares with the cost to society is particularly vague. Unsurprisingly, this lack of transparency contributes to critiques that pricing does not reflect these investments and pharmaceutical companies are simply charging what the market will bear. Overall however, there is no question that drug development is an expensive and risky business. For obvious reasons, pharmaceutical companies tend to focus on drugs which can make the most amount of money during their patent life; the prototype of these "blockbuster drugs" is that they typically target a large, stable market, address a chronic disease or need to be taken for long periods of time, and are price inelastic because they are necessary or appealing enough that consumers are willing to pay high prices. For example, in the United States in 2011, the most lucrative drugs were for heart disease and depression. The top 20 most popular drugs accounted for about US$319.9 billion in sales (Nisen 2012). During the patent life of these highly lucrative drugs, companies are often able to recoup investment losses from unsuccessful areas of their portfolios as well earn a profit. Furthermore, PhRMA literature on approved medicines states that their member companies' ability to continue bringing innovative medicines to market depends on the commercial success of a few products (PhRMA 2016).

Although there are debates about the real cost of drug development, the contribution of public research, the actual novelty and health impact of new products, and ultimately to what extent the industry should profit from government-granted IPRs, there is no doubt that the medical technologies industry has provided society with many life changing medical technologies. Since 2000, more than 500 new pharmaceutical products have been brought to

patients in the US (PhRMA 2016). Despite the public goods nature of the products, there are tremendous financial opportunities in the pharmaceutical industry and companies have the incentive to engage in otherwise very risky investments to discover certain new drugs. The remaining dilemma is that IPRs, which are designed to correct the market failure around global public goods, have only corrected the situation under certain economic circumstances. Current policies have only done so much to correct the innovation gap: a drug that could benefit thousands is still a far less appealing investment if it impacts a poor market, as is the case with neglected tropical diseases.

1.2 NTDs: The remaining market failure

The well-documented conundrum of private sector under-supply of public goods remains a pressing problem for the 1.4 billion poor and marginalized individuals whose diseases, unlike heart disease or depression, don't make economic sense for pharmaceutical companies to develop drugs of vaccines. Even where TRIPS norms for patent protection may ensure that a drug would receive market exclusivity, the profit-generating prices that a patent would enable the companies to charge (and which would allow them their recover costs and make an income) are unaffordable to the infected patients and the health systems that care for them. This means that drugs for these diseases are priced out of reach of the majority of consumers, fail to be a priority for further investment and improvement, or are never developed at all. History has shown that IPRs alone have failed to ensure that the needs of the world's poor are attended to by the pharmaceutical industry- upon which the world has historically relied upon for production of its medicines.

This issue came to international attention around the turn of the century. As is mentioned above, the humanitarian aid organization, MSF, raised the topic during its acceptance speech for the Nobel Peace prize. The international president of the organization, Dr. James Orbinski (1999), called for international action when he remarked,

> "Some of the reasons that people die from diseases like AIDS, TB, Sleeping Sickness and other tropical diseases is that life saving essential medicines are either too expensive, are not available because they are not seen as financially viable, or because there is virtually no new research and development for priority tropical diseases. This market failure is our next challenge. The challenge however, is not ours alone. It is also for governments, International Government Institutions, the Pharmaceutical Industry and other NGOs to confront this injustice. What we as a civil society movement demand is change, not charity."

This challenge came just before the turn of the century, around the same time that the HIV/AIDS crisis in Africa was making global headlines. For context, the adult HIV prevalence rate in South Africa was near 20%, and anti-retroviral (ARV) treatment cost about US$1,000 per month in a country where average annual income was only US$2,600 (Fisher and Rigamonit 2005). When asked to lower the price, companies argued that tiered pricing would undermine their business models in the developing world and prevent them from recouping their expenses. The medicines' costs remained the same and treatment was simply impossible for the vast majority of people to afford. The economic term for this group of consumers that have demand for a product but simply cannot afford it is "deadweight loss," but the director of the access to medicines advocacy group, Knowledge Ecology International (KEI), is keen to remind the world that, when we are talking about health, deadweight loss means dead people (Reichman, 2014).

Nelson Mandela's government came under fire by the US and pharmaceutical companies when, in 2001, the government asked Indian generic manufacturer, Cipla, to make ARV drugs for the South African public at prices they could actually afford. The backlash from pharmaceutical companies and developed countries was immense, but with the support of civil

society groups that successfully argued against the logic of big pharma, the South African government successfully utilized a TRIPS-compliant compulsory license and parallel importation provisions to lower the price of ARVs to about US$113 per person per year. With generic drugs available at this cost, the country has been able to increase coverage and lower expenditure at the same time, thus slowing a mounting epidemic (UNAIDS 2013).

HIV/AIDS is an interesting example in the issue of access to medicines. On the one hand, the disease mainly affects poor people in LDCs who form a small market. On the other hand, the HIV/AIDS epidemic in the 1980's and 1990's was also a serious public health threat among certain populations in the United States. This American epidemic showed just how globalized our world had become and created widespread public fear. Economically speaking, the threat of a global epidemic poses an opportunity for profit unlike an epidemic isolated to LDCs. Under this set of circumstances, the industry may in fact develop therapeutic options (as they did with ARVs), although there is still the possibility that they might be priced out of reach of the poorer consumers. However, even if this is the case, TRIPS flexibilities, as interpreted through the lens of the Doha Declaration on TRIPS and Public Health, provide potential pathways for low-income countries to respond. As the story from South Africa shows, the industry does not welcome threats of compulsory licensing or parallel importation and there may be retaliation from developed countries. Furthermore, TRIPS-plus provisions have limited the policy space available to many governments and sometime eliminated these options, but nonetheless these mechanisms remain legal pathways for ensuring access in low-income markets.

As an interesting comparison, the recent Ebola outbreak in 2014 followed similar behavioral-economic patterns as the AIDS crisis. First of all, leading up to the epidemic there

was no attention paid to the disease nor a sufficient pipeline of health technologies under investigation and development; even highly promising vaccine candidates were halted at early stages of research or animal testing, and nobody had made the investment to get the drugs tested in humans. Again, the small number of cases isolated to minor outbreaks in rural Africa made the market unappealing. Even when the latest outbreak began and certain groups were raising red flags, critics say that the world was slow to respond to the disease until the threat reached the United States and other developed countries. The WHO declaration of a Public Health Emergency of International Concern, the threat of volunteers or travelers spreading the disease, not to mention the concerns about bioterrorism, mobilized wealthy donors and jump-started R&D for a disease that had never before seen international attention. This heightened level of interest caused a tangible impact on the drug development process; vaccines can take up to 15 years to develop, but in this case candidates were being tested in the clinics in under a year (Barnes-Weise and Santos-Rutschman 2015). The world is hoping that at least some of the clinical trials will be successful and that vaccines, therapeutics, and diagnostics will be ready for the next outbreak. However, because the epidemic waned, patient enrollment in clinical trials dropped, and of all the vaccine candidates that were pushed forward, only the Merck product has been able to obtain significant patient data. Currently this vaccine has been approved for Emergency Use with the FDA, and Merck plans to file for general use approval in 2017. Having vaccine for use in emergencies is certainly an improvement, but that does not make up for the fact that the R&D system failed to prevent 11,316 Ebola deaths this time around, or even play a role in its management (CDC 2016).

There are also concerns about the future of Ebola medical technologies: Dr. Joanne Liu, the International President of MSF, reminds the world, "Thousands of samples of human tissue,

blood and semen have been taken from patients and dead bodies and shipped to South Africa, the US and around the world. How are these samples being used? Who benefits? R&D should not just be about finding a miracle drug to defend ourselves in the US or Europe. How will it help families in affected countries?" (2015) The future deadweight loss that will result if the most needy populations cannot access whatever technologies are developed is as important an issue as the struggle to get vaccines and therapies to market in the first place.

Clearly, Ebola and AIDS are important examples to consider because they reflect the tragedy that can occur when the world fails to address a market failure around diseases of the developing world. However, as shocking as it may sound, because of the fear they created these diseases are actually better off in terms of access to medicines today when compared to many others. For comparison, only .6% (5/850) of the new therapeutic products registered between 2000 and 2011 were for NTDs, and only one of these products was actually a new chemical entity or vaccine (Pedrique 2013). This means that countless NTDs have seen no therapeutic advancement in years, or that there are absolutely no drugs available to treat them, even though they make up ten percent of the global disease burden. This ratio is vastly disproportional to the suffering these diseases cause: in 2004 the WHO estimated that these diseases account for a global deficit of about 18,325 disability-adjusted life years (DALYs)- similar to the number of DALYs lost to diabetes (Peña and Martin 2015). Furthermore, these diseases cost the world billions of dollars a year and strain the health systems of endemic countries that are already poor and underdeveloped (Sorenson 2009). As an example, an MSF briefing paper on NTDs explains that the two medications that are available for Chagas disease were developed over 35 years ago and were tested in clinical trials that weren't even targeting Chagas in the first place. The disease is deadly when left untreated, but the treatment involves painful side effects and is only 60-70%

effective in older children, adolescents, and adults. Furthermore, there are no pediatric formulations of these drugs, nor are the two drugs approved for pregnant women. There is also an absence of fixed-dosed combinations to prevent resistance- a growing problem for the few treatments that do exist for NTDs (MSF 2016). .

In the case of visceral leishmaniasis (VL), another disease that is deadly if untreated, the first line treatment has been used for over 100 years; although there was recently a new drug approved for VL, it's only used in East Africa and its effectiveness against the VL strains in Latin America has not been proven. All of the treatments currently available for VL involve injections or infusions, which means they need to be administered by trained medical professionals and sometimes require hospitalization, putting an added burden on health systems and patients. There are also drawbacks in terms of drug resistance, stability, cost, and effectiveness against different geographical strains and clinical presentations. Doctors who treat VL cases at a government referral clinic for the State of Rio de Janeiro, the Evandro Chagas National Institute for Infectious Disease, estimate that at least one hundred patients in Brazil die every year as a result of disease treatment- not the disease itself, but the medicine they receive while trying to get better. In their own experience in the capital city, where there are more resources and better medical care in general, they are able to follow-up with patients and modify their treatments so that they are less dangerous, or even deadly. However, the clinical research lags way behind their experience so there is no real evidence on the best case-management practices. Furthermore, they noted that even in a country like Brazil, diseases of poverty which only effect the most marginalized people in society are some of the last problems people choose to invest money in. While their ambulatory regularly receives funding for HIV-related projects

from industry, the NIH, and the Brazilian government, they struggle to find resources for clinical trials, equipment, and quality care when it comes to NTDs (Schubach et. al 2015, pers. comm.).

Clearly, the 'fatal imbalance' documented at the turn of the century has continued to be a significant global health challenge. Being infected with an NTD that has not been put in the international spotlight is a no-win situation that only exacerbates the poverty that often brings about these diseases in the first place. The shortcomings are numerous and vary slightly with each disease and treatment, but the dilemma is the same: doctors and their patients must endure the reality of pain, suffering, high costs, and sometimes death that is associated with these illnesses. Unfortunately, there are countless diseases for which the drug development process, pipeline, and currently available technologies are as meager as they are for Chagas and leishmaniasis. The official WHO list of neglected tropical diseases designates 17 diseases of poverty that are all communicable and tend to be geographically concentrated in tropical countries, but there are countless other diseases of similar features that are not part of the official list, and still remain a large public health issue (WHO 2016). Even though a lot of these diseases

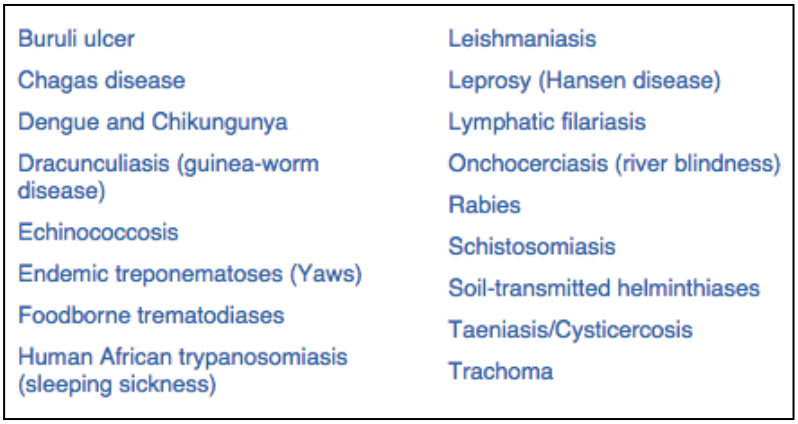


Figure 2: "Neglected Tropical Diseases." World Health Organization. 2016. <http://www.who.int/neglected_diseases/diseases/en/>

are only found in the tropics and are unlikely to spread elsewhere, the recent spread of dengue fever and Zika virus to new geographic regions, including the US, remind us that other NTDs

could also pose a pandemic threat. Also, as global warming increases the geographic scope in which tropical diseases could potentially thrive, illnesses that were previously thought to be isolated to developing countries in the tropics might reach nations where there is a sufficiently wealthy and stable market.

These are all interesting developments that should prompt further investment into developing capacity to control and treat these diseases, but regardless of the future threat to developed countries, something must be done to meet the needs of those who are currently infected. Article 25 of the United Nations Declaration of Human Rights states that, "Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services" (UN 1948). As things stand now, the standard of treatment for those infected with or at risk of getting an NTD is not adequate for health and well-being. The status quo for these diseases is particularly subpar due to the systematic institutional neglect that results from the economic climate of our world. With this in mind, the question the world needs to consider is: in the absence of a global public health emergency, can we create additional incentive structures that will result in drugs for NTDs? In the eyes of international human rights law, the lack of appropriate and effective therapeutic options for neglected tropical disease patients can be seen as an irresponsible and irreconcilable violation of basic rights that should be afforded to all humans. For the sake of the 1.4 billion people who suffer from NTDs and the billions who are threatened by these diseases in the future, international collaborations must turn their attention to addressing the 'fatal imbalance' that IPR has failed to address for the poorest of the poor.

2. Exploring Solutions

2.1 Theories of Alternative Policy Action

There are a number of experts and groups around the world that, for various ethical and other reasons, have been looking at the question of how to overcome the market failure around neglected tropical diseases. Overall, these strategies aim to reduce the risk involved with investing in areas that have historically been seen as unfavorable for business. A somewhat controversial word that has been used to describe the theory underlying the different policy proposals is "delinkage": in other words, the incentive for investing in a particular disease category needs to be independent of the price at which any developed products will be sold. In their guidelines for promoting access to medicine, the World Trade Organization, World Intellectual Property Organization, and World Health Organization have all acknowledged that,

> "In the existing patent-driven innovation ecosystem, the returns for investment in innovation are generally factored into the price of new generation products. In contrast, new and innovative finance mechanisms and initiatives aim not to finance the cost of R&D through the price of the end product, thus delinking the cost of research from the price of the product" (2012, 109).

Clearly, there is recognition at the highest levels of global health governance that the current system of innovation is failing to incentivize important investment in NTD R&D.

For this reason, it is important to consider how non-traditional models for innovation might be effective at filling this gap. Figure 2 maps a number of innovation structures according to the degree of IP exclusivity they call for and the level to which the model requires market-based incentives. All of these approaches have been explored and evaluated as routes to delinkage, to various extents.

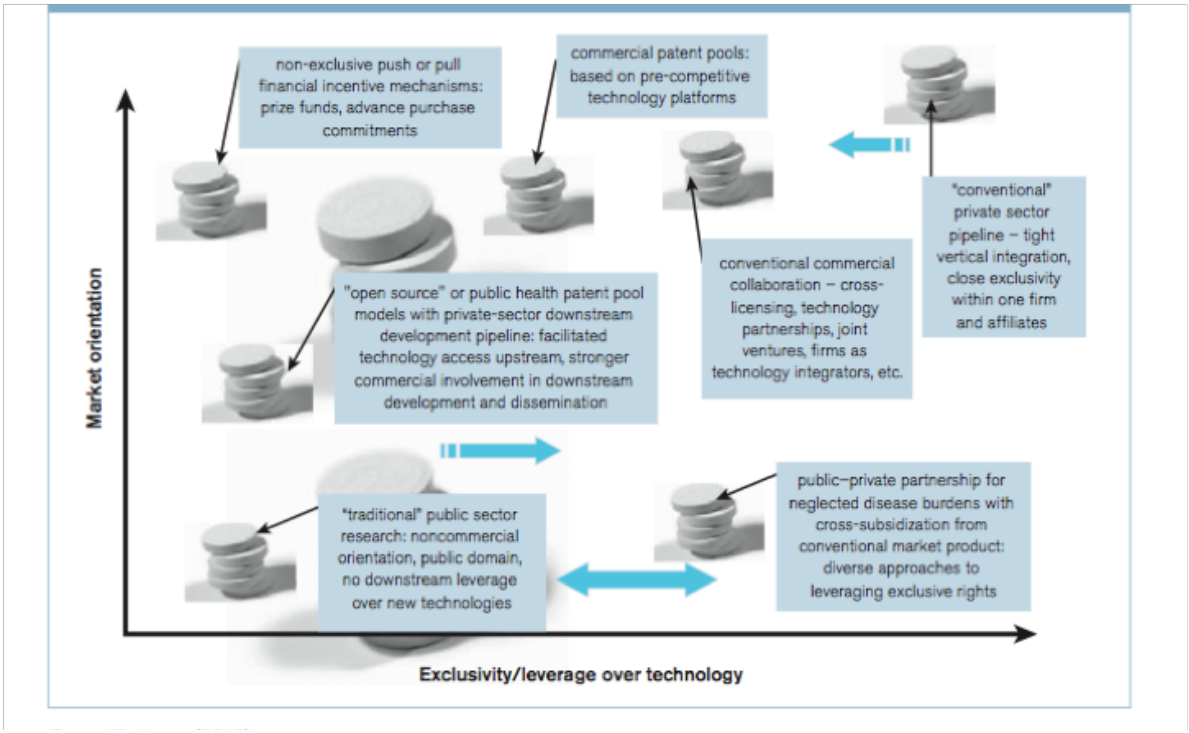


Figure 3: Taubman, Antony. "A Typology of Intellectual Property Management for Public Health Innovation and Access: Design Considerations for Policymakers." The Open AIDS Journal 4 (2010): 4–24. PMC. Web. 14 May 2015.

Starting in the top right-hand corner, this graphic begins with the option that most relies on exclusive rights to technology. As has been described, "conventional" private sector pipelines rely on IPR, are driven by the price-related market incentives provided for by patents, and for this reason, fail to deliver drugs in cases where there is a lack of reliable consumers with purchasing power. Even commercial collaborations which involve less exclusivity, including cross-licensing and joint ventures, typically follow the same pattern and have had limited success in providing for the unfavorable NTD markets.

In contrast, there are options that aim to lower the barriers to entry in the NTD space and make it more appealing for private industry to engage in, while still taking steps toward improving access for the poor. For example, suggestions have been made that companies share technology platforms that assist them in their innovation but aren't actually marketable

themselves. Rather than having every company put resources into coming up with its own pre-competitive tools, anything relevant to NTDs could be shared between corporations in order to reduce the cost of R&D while still protecting upstream advancements. The goal is that by reducing the investment required to produce a new technology, the incentive to enter the market is less contingent on the ability to charge high prices and recover costs through sales. However, with pre-competitive knowledge sharing there is no guarantee that companies will reduce their costs and reflect the reduction in their expenses or reevaluate their current emphasis on research into potential blockbusters over those for populations with less purchasing power. Clearly, this is a serious limitation to relying on the pooling of knowledge, and more holistic solution would require additional incentives or obligations for companies. In the current market environment with such limited transparency about pricing and how R&D decisions are made, it seems unlikely that pooling alone will resolve issues of patient access.

Various non-exclusive push mechanisms have also been proposed as ways to reduce R&D costs for pharma and achieve lower product prices. For example, experts in the field have discussed the idea that the government could pay for clinical trials as a way to direct research in under-explored directions (Lewis, Reichman and So 2007). Clinical trials account for a large chunk of the R&D costs pharmaceutical companies must cover in order to gain regulatory approval of a new drug and gain marketing approval. Government sponsorship of this process would therefore reduce the investment required of pharma and the costs they aim to recoup from sales of their drug, and allow healthcare providers and insurers to negotiate lower costs. Thus, although there would be costs associated with the government subsidizing these trials, they might increase industry interest in new areas and purchasers would also have leverage to negotiate reasonable prices on the back end. As an additional consideration, the treatment of clinical trials

as a public good could also eliminate the conflict of interest that exists when companies or scientists are investigating the safety and efficacy of their own drug. Recently there have been numerous instances in which evidence of adverse effects of drugs are suppressed or studies were poorly designed with the intent of moving a product forward through FDA processes despite its dubious therapeutic benefit, which suggests that an independent review process is needed.

The implementation of publicly funded clinical trials could be accomplished through a variety of ways, including the creation of an independent agency or simply by increased government oversight of the process. Added benefits would include cost-savings from building an economy of scale as well as a reduction of the inefficiency and redundancy currently present because of the privatized nature of these trials. Furthermore, because transparency around the true costs of clinical trials and R&D is practically impossible when pharmaceutical companies are responsible for the research investment, a practical implication of this new model would be that there would be a real understanding of the costs of getting a new drug approved (Reichman, 2009). Overall, the potential public health benefits of public funding for clinical trials are numerous, and along with other push mechanisms, this strategy could complement efforts to increase R&D into drugs for the poor.

Alternatively, pull mechanisms have also been proposed and aim to provide an alternative source of revenue after the product reaches the market- again, the goal of these strategies is to ensure that selling a global health product at high prices is not the only avenue available for companies to satisfy their investors. Ideas on the table include the awarding of prize funds large enough to reimburse the private investment and ensure that the public pays equally for a public good rather than placing the burden on sick individuals who pay through high costs. These inducement prizes could include cost provisions to ensure affordable market

pricing after the prize has been awarded. Prizes could be structured in a number of ways, including as milestone prizes that would reward pre-clinical achievements; this is important because it de-risks the early stages of research and creates an incentive to invest even though the outcome may or may not marketable. Prizes could also be designed to reward measurable improvements to health, as is suggested by Thomas Pogge and Aidan Hollis in the Health Impact Fund proposal. In their article entitled "making New Medicines Available", these authors posit that pharmaceutical companies could register with a Health Impact Fund and agree to at-cost pricing in exchange for a reward from the Fund based on an analysis of how well the drug actually improves health outcomes (2015). This proposal suggests that a voluntary model would be successful because rational, profit-seeking companies should opt in if the fund is big enough, but there are also other proposals for a similar system that would happen automatically. For example, 2016 presidential candidate, Bernie Sanders, introduced a bill called the Medical Innovation Prize Fund Act in 2011 which would deny the right to market exclusivity and instead provide medical technology patent holders a monetary prize paid for by the government and private insurance companies. This would allow for competitive market pricing of medicines and also reward innovators. Innovation economics and policy experts at Knowledge Ecology International (KEI) estimate that the cost savings insurers and the government would incur by paying for generic rather than brand name drugs would offset the costs of supporting the Fund (Love 2011). Overall, prize models could be structured a variety of ways, and the possibilities should all be explored for their potential contribution to delinkage.

Priority review vouchers (PRVs), given by the US FDA upon regulatory approval for a medical technology in a neglected space, are another model for delinkage that give recipients the ability to fast-track regulatory review of a more profitable drug and have a longer period of

market exclusivity. Because of the limited timeline of patent protection, avoiding bureaucratic delays in FDA approval and getting profitable drugs to market more quickly provides additional time in which companies can charge monopoly prices. This privilege theoretically recovers the costs of development for one drug through the additional sales of a different (more commercially viable) product. The United States has had this system in place for a list of 16 neglected diseases since 2007, when an amendment was made to the Prescription Drug User Fee Act. It is important to note that the PRVs can be valuable for their priority review advantage, but they are also transferrable and can be sold; in fact, Gilead just bought a voucher from Knight Therapeutics for US$125 million in 2014, and one voucher sold for US$350 million in 2015 (Carroll 2016). David Ridley and Jeff Moe, the authors of the academic paper upon which the PRV legislation was based, argue that this is encouraging evidence in favor of PRVs because there is no question that they are seen as a valuable asset by some in the pharmaceutical industry, and therefore the possibility of obtaining a voucher acts as an incentive for venture capitalists to invest in NTD research. While the incentive may not be strong enough to attract multinational pharmaceutical companies, the possibility may lure investment from companies that already have a treatment target on the shelf that had been abandoned for commercial (rather than scientific) reasons, for smaller companies and entrepreneurs, or for companies engaging in corporate social responsibility in the field (Ridley 2016).

So far, critics say that the few PRVs that have been granted rewarded drugs that were already approved in other countries or already far enough down the pipeline that they probably would have been invented anyway, and that the 6 months award time was unnecessary to create an incentive. There are also complaints from civil society that even if the incentive results in the production of new drugs for NTDs, it provides no safeguards to ensure adequate access to these

treatments. For example, Knight Therapeutics received a PRV from the USFDA for its approval of miltefosine, a drug to treat leishmaniasis in March of 2014. However, DNDi argues that there are important steps still to be taken that have been ignored by Knight, including,

> "**Disclose the actual cost** of production of the drug; **Price the drug at-cost** or with a minimal profit margin to ensure sustainable production of the drug (regardless of ordered quantities); **Maintain the registration** of the drug in all disease-endemic countries for both visceral leishmaniasis and cutaneous leishmaniasis; and **Support additional clinical studies** to optimize the use of miltefosine, including pharmacovigilance, dosing in children, use in cutaneous leishmaniasis and other complicated dermal forms of the disease, as well as co-infection with HIV" (2014).

Even though critics argue that the execution of the US's PRV scheme inadequately addresses major global health goals, considering the relative novelty of the scheme (especially taking into account the long timeline for drug development) it is hard to say exactly how it will play into long-term goals for innovation in the NTD space. Looking forward, perhaps restructuring the PRV system and requiring further commitments from voucher recipients could result in a balance that satisfies both the profit concerns inherent to industry decision-making, as well as the access concerns found among global health advocates.

In addition to monetary or non-monetary prizes, patent buyouts are an option for promoting access to medicines. The idea of buying patent privileges from a private entity and making them public is a simple idea, but how to best execute this policy is a topic of debate. One proposal describes a system in which the patent authority of a country would hold an auction for relevant patents in order to determine their market value; because the social value of NTD patents is likely to be significantly higher than the private value, the patent authority would use these offers as a baseline for calculating a buyout price, but also offer an additional markup to reflect the benefit to public good. This would mean that there is a greater incentive for pharmaceutical companies to act in this space because they are rewarded significantly more than

what the market would value for the innovation. In order to promote access, the patent authority would buy the majority of the patents and put them in the public domain. This would both enable scientists to continue additional research into the innovation and allow the innovation to be sold at competitive price. However, in order to keep the bidding fair, a small fraction of patents would be sold to the highest bidder so that auction participants would disclose their true expectations of value (Mueller-Langer 2013).

Finally, advanced purchase commitments are a type of pull mechanism that aim to encourage innovation in areas of medicine that are otherwise unappealing to drug companies by promising a sizeable purchase at a guaranteed price. Typically carried out by procurement agencies with a large demand, this removes some of the risk that a manufacturer will not be able to find a buyer. For example, Gavi, the vaccine alliance, has successfully incentivized two pneumococcal vaccines by guaranteeing a return for originator companies. They are able to ensure a 10-year supply of 200 million doses at US$3.50 per vaccine in the 51 LDCs that they serve. In addition, individual manufacturers receive a percentage of the US$1.5 billion pool at the World Bank, funded by various donor countries and the Bill and Melinda Gates Foundation, equal to the percentage of the 200 million doses that they provide (Gavi 2015). Interestingly, a similar technique has proved successful in the defense industry, but the Gavi approach is an innovative step in the world of global health. It should also be noted that Gavi also utilizes pooled procurement as a cost-reduction strategy: by purchasing large quantities of health technologies, they can negotiate wholesale prices that might not be available to individual countries with limited purchasing power.

Different “open” models for collaborative innovation are also considered an option for correcting the market failure around NTDs. The term “open source” traditionally refers to a

computer code that is available for use and modification, but the use of "open" licensing has also been used in the health technologies field. Open Source Malaria uses a truly open-source approach with everything online that allows add-on user innovation at every stage of the process. They have ongoing collaborations happening online in real time, facilitated by a website that enables user contribution and is open to anyone in the world (OSM 2016). Others take a more limited approach, such as the "open" collaboration business model of the Tres Cantos Open Lab Foundation. This Lab, sponsored by GlaxoSmithKline, (GSK) the European Commission, the Wellcome Trust, the Gates Foundation, and others, has a campus where academic researchers can perform their research and have access to GSK's facilities and industry expertise- including high-throughput screening technology. Tres Cantos has negotiated license agreements between GSK and the researching institutions on several compounds being explored for neglected tropical disease treatment purposes. The portfolios that GSK has signed over are carefully selected with the goal of increasing collaboration for global health purposes while not detracting from GSK's growth. In the 6 years since Tres Cantos' establishment in 2010, none of the research has resulted in marketed drugs. However, the Foundation's Director of External Opportunities pointed to the long timeline for drug development and said that both Tres Cantos and its partners remain optimistic that they are seeing promising results and that they will be able to find ways to carry their mission of being "open and generous" forward through the stages of product commercialization (Ballel 2015).

Another delinkage model that relies on "open" collaboration is the Medicines Patent Pool (MPP). This United Nations-backed organization aims to lower the cost of and improve medications for HIV/AIDs through voluntary licensing of relevant patents. So far they have signed agreements for twelve ARVs and one drug for an opportunistic infection. Their

agreements allow for generic production and competition of these HIV/AIDS medications in specific geographic areas (mainly LDCs) with the payment of reasonable royalties (UNITAID 2015). The result is that patent owners retain the rights to manufacture in markets where they can make a profit, but the MPP ensures that patents are shared in countries that might not have attracted industry interest because of the limited resources available to buy medicines. This has created some controversy because the majority of HIV/AIDS patients are actually found in middle-income countries, but many pharmaceutical companies have refused to allow the MPP to extend the geographic range of their agreements to include emerging economies, therefore leaving millions of poor patients without access to medicines sold at-cost. Furthermore, it should be noted that drug discovery for HIV/AIDS is not the main issue since there are cohorts of patients in developed and middle-income countries that provide a stable market. This patent pool relies on the fact that inventions have been made due to the normal functioning of industry and doesn't create an incentive for innovation as is needed with NTDs. However, within the field of HIV/AIDS therapeutics there are certain areas, including fixed-dose combination and pediatric formulations, which are greatly lacking because of the same economic factors in play with NTDs create a market failure around these products. For this reason, the MPP also aims to use its open licenses to increase innovation of what is currently available into products that address these neglected areas. The MPP recently announced their intent to expand beyond just an HIV/AIDS portfolio and into the Hepatitis C and Tuberculosis spaces, and in theory the same application could potentially be extended to NTDs.

Finally, at the least market-oriented side of this chart is public sector research. As has been noted, for years the NIH and other government agencies have contributed immense amounts of capital to medical R&D and have made a significant contribution to the health

technologies available to the public. Some of these grants support research specifically targeting NTDs with the goal of encouraging research in an under-funded area. However, Steve Ferguson, Deputy Director of Licensing and Entrepreneurship at the NIH's Office of Technology Transfer, has described the attrition that occurs between promising NIH-funded, downstream research and product development: he estimates that only one in every four or five patents that the NIH scientists believe might have therapeutic potential find outside parties that are interested in licensing them, leaving behind potentially useful compounds that are unwanted by biotech or pharma (2015). This phenomenon has been called the "valley of death," implying that the lack of funding for translational research leaves many potential stones unturned and leaves potential solutions undeveloped. When it comes to NTDs, this leaves unmet demand for health solutions, and, again, this deadweight loss represents suffering and dying patients.

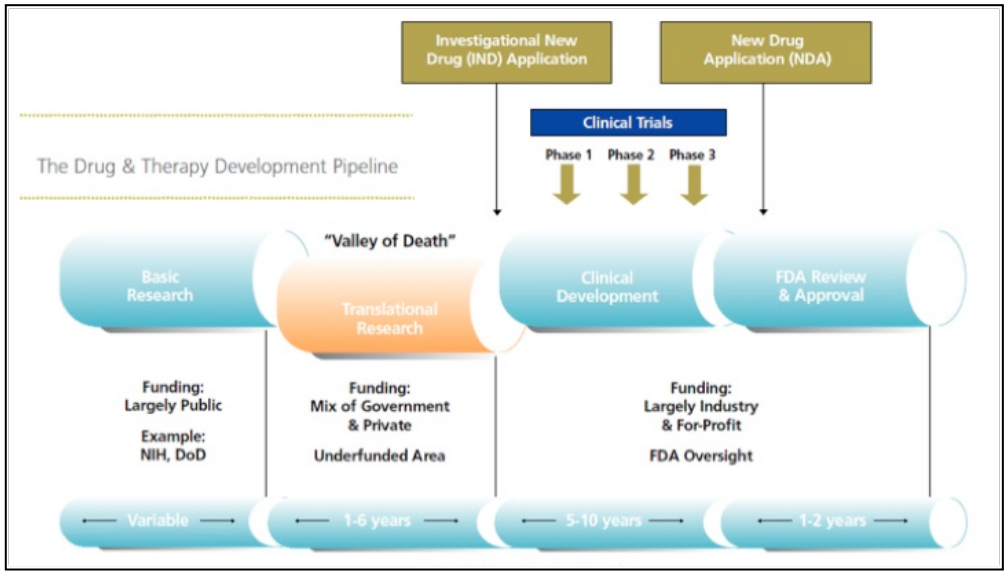


Figure 4: FasterCures. "Crossing Over the Valley of Death." Washington, DC. 2010. 5. <http://www.parkinsonsaction.org/sites/default/files/FC_PAN_VoD_12-2010.pdf>

As Figure 4 demonstrates, this stage of research is too early and too risky for industry interest, but it is beyond the expertise of academia to pursue medical applications of the

promising compounds. Clearly, although public funding decreases risk for industry, there is still a breakdown in the pipeline that can allow medical technologies, especially those targeting the poor, to remain undeveloped. R&D tax credits are also a tactic employed by the US government to try and encourage research in the field, but the same "valley of death" prevents promising basic research into NTDs from being taken forward (Rai et. al. 2008)

2.2 Public-Private Partnerships

Fortunately, since the publication of "The Fatal Imbalance," NTDs have become a growing part of global efforts to improve health. Aside from the innovative policy ideas and experiments discussed above, there has been an increase in efforts to address the unmet need for NTD drug development through unlikely alignment of public and private partners. In fact, in 2012, officials from the World Health Organization (WHO), the World Bank, the Bill and Melinda Gates Foundation (B&MGF), DNDi, several national governments, and executives from 13 major pharmaceutical companies spearheaded the London Declaration on Neglected Tropical Diseases. The Declaration recognizes the need to assist the world's poorest populations by addressing the problem of NTDs, and its 71 endorsers have committed to efforts to eliminate and eradicate these diseases according to the WHO's 2020 Roadmap on NTDs. Importantly, the London Declaration identifies that it is essential to have both the public and private sectors play a role in achieving this goal. The declaration reads,

> "No one company, organization or government can do it alone. With the right commitment, coordination and collaboration, the public and private sectors will work together to enable the more than a billion people suffering from NTDs to lead healthier and more productive lives-helping the world's poorest build self-sufficiency. As partners, with our varied skills and contributions, we commit to doing our part" (Uniting to Combat NTDs 2012).

Because of the interdisciplinary demands required when addressing the problem of NTDs, global health actors have recognized the need for a cross-sectoral approach. This trend toward public-private collaboration is a smart solution to this problem given the innovative financing and partnership opportunities they create. This type of initiative is apparent in many of the efforts aimed at improving the global situation of NTDs, such as drug donation programs, but is perhaps most innovative in the rise of the "product development partnership".

As often happens when global health concerns go unaddressed, a number of non-profit, non-governmental organizations have identified the problem and cropped up to fill the gap in NTD drug development. The different organizations have taken a variety of approaches toward strengthening the pipelines for NTDs, but they share the goal of bringing together NGOs, academia, government, and industry to achieve this goal. Moreover, the partners are able to contribute specifically during the stage of the process in which they have the most expertise; this increases the overall efficiency of the process while also ensuring there is no breakdown in the pipeline. Collectively, these public-private partnerships are typically called product-development partnerships because of their specific focus on producing health technologies as public goods. It is important to note that there are many entities that work on access to medicines issues aside from drug development and advancing innovations for NTDs. This includes pharmaceutical companies that engage in donation or global access programs, as well as organizations such the Medicines Patent Pool. However, the aim of this paper is to focus on how PDP models offer solutions to correct the market failure around innovation for NTDs. While other questions of access are incredibly important, they are beyond the scope of analysis in this research.

The image below is a visualization of the variety of organizations that have been working toward the specific purpose of product development for global health. It demonstrates

Figure 5: Wiley, Ryan. "Product Development Partnerships." Shift Health. Presented at the Product Development Bootcamp, 2015, 14:39:41 UTC. <http://www.slideshare.net/shifthealth/product-development-partnerships>

the increasingly diverse range of PDPs that have emerged in recent years in response to pressing market failures. PDPs are a relatively new phenomenon in the global health world, especially when considering the lengthy timeline of drug development. For this reason, it is difficult to determine exactly how successful their investments have been, and how they compare to traditional development models. However, emerging evidence from the work of these organizations is promising; a recent analysis showed that 7 out of the 18 drug approvals for new chemical entities (NCEs) targeting neglected diseases since 1989 have been the result of the work of PDPs. This means that PDPs account for 39% of drug development for neglected diseases, as compared to 22% from private companies, 17% from philanthropic endeavors, and even smaller percentages as a result of military, priority review vouchers, and IP transfer (Rahman 2015). Furthermore, it is important to note that the study that these numbers come

from includes tuberculosis and malaria as neglected diseases, even though there is increasing demand for treatments of these diseases in high-income countries and they are not on the official WHO list. If the results are limited to NCEs for diseases on the WHO list of NTDs only, then there have been two approvals in the past several decades, both of which resulted from the work of PDPs. When viewed from the perspective of the UDHR's human right to health, another important point is that the drug development resulting from PDPs resulted in drug registrations and approvals from a diverse range of regulatory authorities across countries' income levels. Drugs that resulted from other development models were largely limited to registration within the U.S. or Europe, suggesting that the long-term issues of access, and not just innovation success, are also a factor for consideration when evaluating development models. Overall, this suggests that PDPs are more effective than other approaches at stimulating R&D in disregarded disease areas.

The important question then becomes: how exactly to PDPs add value to the process? In response to this, Rob Lin, the Vice President of Finance at the Infectious Disease Research Institute, outlined the main advantages of the PDP model: they allow donors to pool funding with others to achieve a greater impact; they spread funding throughout the pipeline of development with the goal of both short- and long-term outcomes; and they provide expertise and arbitration to carefully select what projects to invest in (Topal 2014). Of course, besides the contribution PDPs provide in the R&D process, the role that these organizations play in securing funding and attention for their causes cannot be underestimated: without their oversight, leadership, and conductive role, the different partnerships they negotiate might never have been formed. It should also be noted that, the ethics and political acceptability of PDPs are an important aspect of these organizations' success. For example, the NGO status that PDPs carry helps mitigate the

potential conflict of interest arising from direct government and private sector partnerships and carries public relations value for supporters (Rahman 2015). Furthermore, there are several other incentives (especially for private companies) to work with NGOs for product development. As Dr. Bill Foege, a leader of the global smallpox eradication campaign and winner of the Presidential Medal of Freedom, describes, there is a public relations benefit, an internal employee satisfaction advantage, and a tax write-off to be had for any contributions (2016). Clearly, PDPs make engagement with global health product development a more plausible option for all types of partners, and aim to streamline the process of collaboration once partnerships have been established.

Although most PDPs serve a similar purpose, there are a wide range of visions and missions between the organizations. For instance, many PDPs distinguish themselves based on a specific disease focus: the Medicines for Malaria Venture targets malaria; the Global Alliance for TB focuses on TB; the International Partnership for Microbicides focuses on preventative use of ARVs against HIV. Other organizations target specific products, as demonstrated by Foundation for Innovative New Diagnostics (FIND). When it comes to NTDs, the Drugs for Neglected Disease Initiative (DNDi) has played an important role in producing new products and strengthening the pipeline of therapeutic research for Chagas, leishmaniasis, schistosomiasis, sleeping sickness, and filarial disease, among others. As has been noted, this paper is specifically interested in the methods that DNDi employs to advance their NTD agenda. There is no other PDP specifically focused on R&D to improve treatments for the WHO's list of NTDs, so DNDi is the first experiment into applying alternative drug development models in this space. For this reason, it is essential to understand how this organization compares to other PDPs and understand what successes and challenges can be attributed to their model.

There are a variety of business plans and structures that differentiate PDPs. Some PDPs have spun off of the work of pharmaceutical companies while others are essentially branches of government that have adapted to the essential need for research partnerships. For the most part, however, PDPs are non-profit organizations that act as a project management expert and channel funding through different partners. DNDi falls under this traditional description of a PDP, which some have called the "middle-man" or "conductor" role. In other words, these organizations seek to create a system for drug development that parallels the traditional system of the pharmaceutical industry, but do so through non-governmental and non-profit channels. As the image below illustrates, the range of needs throughout the process of drug development requires a complex array of partnerships, and PDPs can contribute to the process by acting as the lead coordinators.

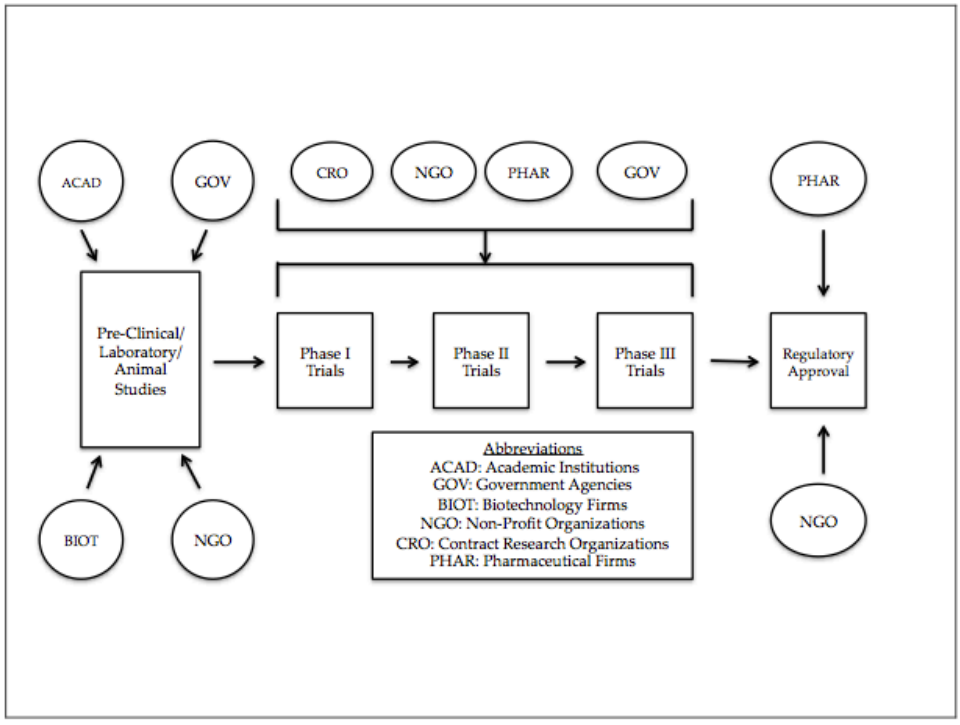


Figure 6: Rahman, Samir. "Schematic of Possible Organizational Contributions (Financial or Operational) Across the Drug Development Pipeline in PDP Collaborations." Pharmaceutical

Progress for Neglected Tropical Diseases: Using Non-Traditional Development Models to Overcome Market Deficiencies. 2015. Unpublished master's thesis, Duke University.

To date, PDPs that work in this way have repurposed or produced several new health technologies, and there are many lessons to be learned from their successes. However, as the landscape of PDPs grows and differentiates, it is important to look at the reasons for their successes as well as the challenges that still stand in their way. The chart in **Appendix 1** outlines the organizations that, like DNDi, are not driven by government or corporations but are distinct global health organizations, and specifically act as conductors for the overall research process. This means that the organizations which act as research hubs, payers/purchasers for products, or commercial ventures are excluded from further analysis, as their work is distinct from DNDi and will not be used for comparison's sake. A brief outline of the mission, expenditure, partnerships, and strategies of the PDPs that are relevant to further analysis of DNDi can be found in the chart.

For the most part, all of the organizations are still relatively siloed operations facing similar scientific barriers that pharma face, in addition to facing their own unique challenges such as fundraising and lack of political will. In particular, this paper has already shown that there is an immense need for those who are working in the NTD space to identify ways to expand the pipeline, shorten the timeline, and increase the success rates for research. Since DNDi is the primary organization focused on NTD drug development, it is important to look at this organization as a case study for what is, and is not, effective at promoting innovation for NTDs. Chapter 3 will look specifically at the strategies employed by DNDi, and Chapter 4 will offer suggestions to promote further success of the organization.

3. Case Study: DNDi

3.1 Organizational Overview

The Drugs for Neglected Disease Initiative (DNDi) is an important product development partnership to study when it comes to considering how the neglected tropical disease space can potentially benefit from the innovative partnering and financing mechanisms of this specialized class of non-profit. DNDi was established in 2003 by seven founding partner organizations: the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France's Pasteur Institute, Médecins sans Frontières (MSF), and the UNDP / World Bank / WHO's Special Programme for Research and Training in Tropical Diseases (TDR). These organizations had all witnessed the devastating effect of the 'fatal imbalance' throughout their operations. For instance, doctors in MSF field operations were regularly confronted with patients who were dying from neglected diseases, and yet as medical professionals they had no therapeutic options available to provide them with treatment. This reality was a devastating affront to the missions of these organizations, and they saw the immediate need for an alternative model for drug development that was driven by public health needs, rather than market forces. As a result, they formed the Drugs for Neglected Disease Working Group. After researching the landscape of drug development, the working group identified that existing models would have limited impact on NTD drug development. Instead, the group recommended the formation of a needs-driven network for NTD drug development that extended beyond traditional public-private partnership and would address the current market and public policy failure in this space (DNDi 2016).

The concept for DNDi was created as a result of the Working Group, and in 2003 the organization was officially chartered. The organization was designed to be a paradigmatic shift

away from traditional drug development models that would result in new drugs for the most neglected diseases. In working to deliver these new treatments, DNDi has adhered to strong philosophies about the best way to do their work. The preliminary proposal from MSF to establish DNDi outline their vision for the new organization as follows:

> "To improve the quality of life and the health of people suffering from *neglected diseases* by using an *alternative model* to develop drugs for these diseases and by ensuring *equitable access* to new and field-relevant health tools. In this *not-for-profit* model, driven by the public sector, a variety of players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven R&D. They also build *public responsibility and leadership* in addressing the *needs of these patients*" (2002; italics added).

This statement captures a sentiment that was echoed to the author of this paper by many DNDi employees. There is a strong commitment to this vision within the organization, along with a feeling of responsibility that comes from a firm belief that the DNDi model is the best hope for patients with NTDs. The determination and resoluteness of the organization is certainly admirable, but these principles are meant to guide the everyday work of the organization and lead to material improvements. This chapter seeks to outline the operations of DNDi and better understand the work that is, or is not, radically improving NTD drug development.

3.2 Therapeutic Advancements

To date, DNDi has delivered six new treatments and cultivated a promising pipeline of drugs in development. This progress is in-line with the two-pronged approach they developed in 2011, which aimed to deliver short-term optimization of existing drugs, as well as the development of entirely new chemical entities during a longer time horizon. In terms of meeting urgent needs, these approvals show that DNDi has been able to address one of the major failures of traditional pharmaceutical development- the lack of exploration into improving existing treatments.

First of all, ASAQ and ASMQ, which are both new fixed-dose combination therapies for malaria, were successfully approved in 2007 and 2008, respectively. These treatments both involve simple regimens, are registered in a wide variety of countries, and are not patented so they are sold at very competitive prices. ASAQ resulted from a partnership with the pharmaceutical company Sanofi-Aventis, whereas ASMQ resulted from partnership with the FACT Consortium. DNDi facilitated this consortium, whose key partners included: Instituto de Tecnologia em Fármacos of Farmanguinhos/Fiocruz, Mahidol University, Université Victor Segalen Bordeaux 2 (TROPIVAL), University of Oxford, University Sains Malaysia, the Shoklo Malaria Research Unit, the Mae Sot Clinic, MSF, and Cipla Ltd. For both therapies, technology transfer to African manufacturers has enabled local production of the products. Just this year, DNDi transferred the intellectual property for both ASAQ and ASMQ to MMV in order to promote further research patient access.

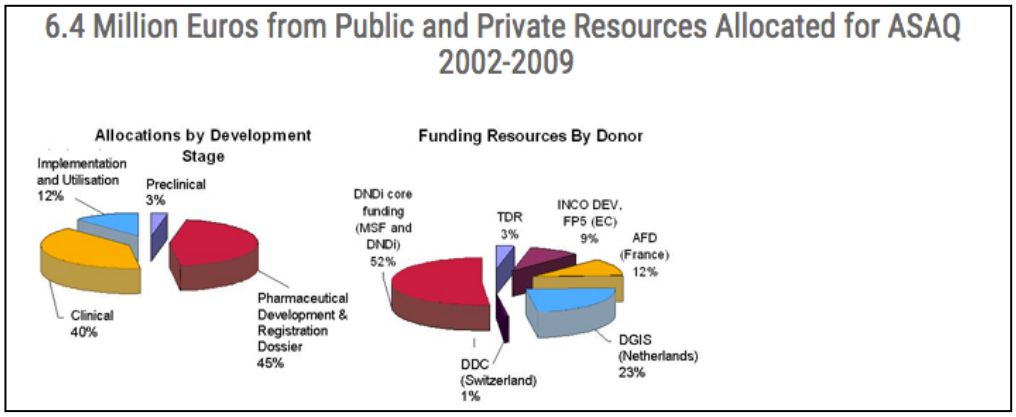


Figure 7: "ASAQ Project Overview- Funding." DNDi. 2016. <http://www.dndi.org/treatments/asaq/partnership-overview-2/funding/>

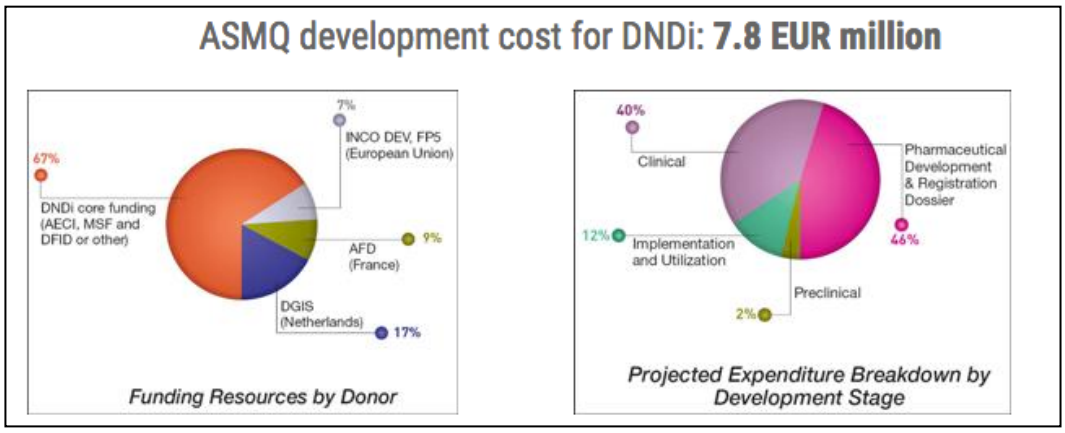


Figure 8: "ASMQ Project Overview- Funding." DNDi. 2016. <http://www.dndi.org/treatments/asmq/partnership-overview/public-funding/>

Thirdly, DNDi's research with partner Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), a state lab in Brazil, resulted in the first pediatric formulation, dosage, and regimen of benznidazole to treat Chagas disease. This medication is simple and reliable for administration to children, and is also unpatented and affordable. LAFEPE has committed to manufacture the medication, and registration and delivery of this formulation has taken off due to collaboration with multiple partners assisting in the scale-up of the innovation.

In addition, NECT is a huge therapeutic advancement for treatment of sleeping sickness (HAT) because it is safer, simpler, and more easily administered than previous options- all of which were discovered 25 years ago or more, and were very outdated. The previous treatment option was malarsoprol, which is arsenic-based and highly toxic- causing pain, and among 5% of patients, even death. (Unfortunately, there are certain strains of HAT for which malarsoprol is still the first-line treatment, indicating plenty of need for further advancement of treatment options.) These improvements were largely made possible and tested in collaboration with MSF, Epicentre, Swiss TPH, and the national HAT control program of the Democratic Republic of Congo. Now considered the first-line treatment and registered on the WHO's list of Essential

Medicines, NECT is available for free through the WHO in all endemic countries. This large-scale access is possible thanks to donation programs by Sanofi and Bayer.

DNDi's fifth product approval is the leishmaniasis treatment SSG&PM- a combination therapy that cuts the necessary time of treatment nearly in half. This therapy was the result of partnerships with the national control programs of Kenya, Ethiopia, Sudan, and Uganda, as well as MSF and the WHO. Through collaboration with DNDi and the Leishmaniasis East Africa Platform (one of DNDi's regional clinical trial platforms) these South-South and North-South partnerships have resulted in enormous cost savings. Now, LEAP is facilitating recommendation and implementation of SSG&PM programs in the region.

Finally, new VL treatment regimens have been tested and approved in India and Bangladesh, and with the evidence from DNDi's clinical trials, progress is being made toward adopting these changes into national policy. This is an important shift from the previously recommended monotherapy, which poses risks for the development of resistance. Many partners from both India and Bangladesh have participated in this process and the large-scale clinical trials and pharmacovigilance studies. This progress was made possible with funding from several parties, including the B&MGF, DFID, MSF, AECID, and SDC.

3.3 Pipeline Progress

In addition to the therapies the DNDi has delivered to market, the organization's R&D pipeline holds hope for future success. The portfolio includes 13 new chemical entities, which would represent innovative improvements in treatment options for NTD patients and could fundamentally change what a diagnosis with these diseases means for patients and health systems. An overview of DNDi's projects as of 2014 can be seen below, but it should be noted

that this graphic does not include recent additions to the organization's portfolio, including Phase III development of a combination therapy for HCV as well as a Phase III NCE for mycetoma.

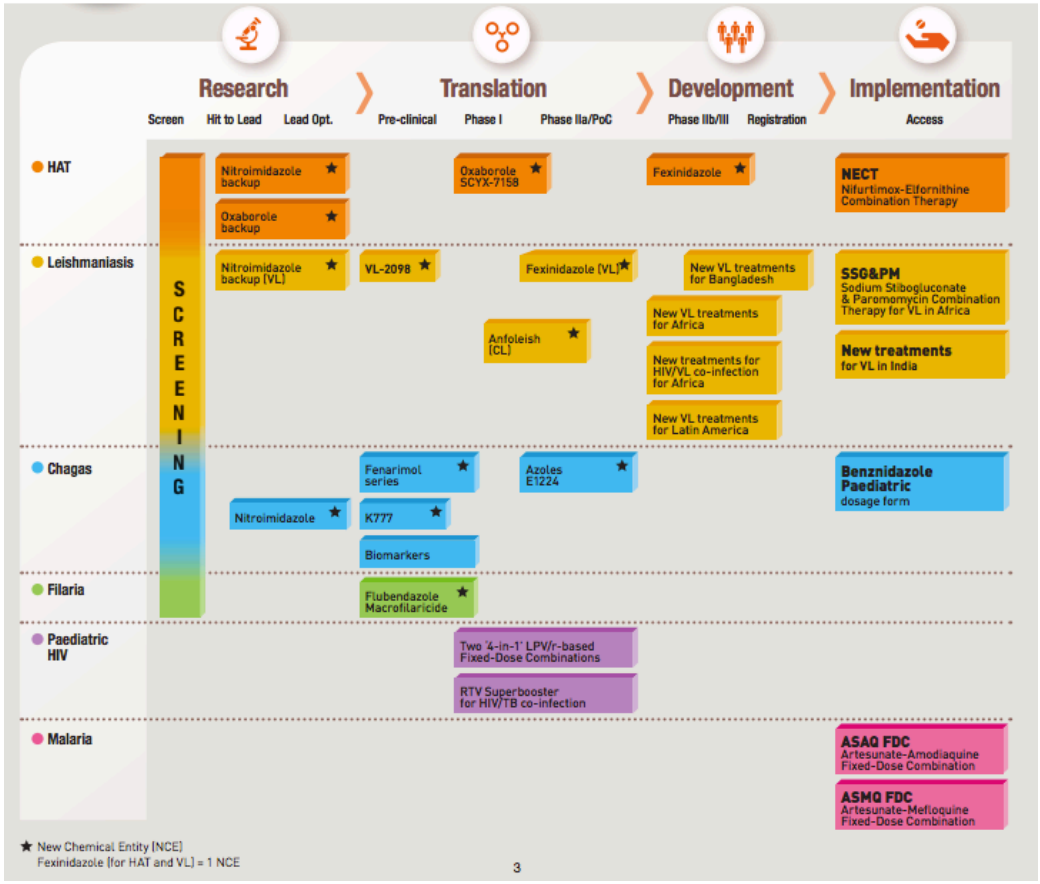


Figure 9: "R&D Portfolio: Patient Needs-Driven Collaborative R&D Model for Neglected Diseases." DNDi. 2013. <http://www.dndi.org/wp-content/uploads/2009/03/DNDi_Portfolio2013.pdf>

DNDi's portfolio of potential new treatments for sleeping sickness (HAT) contains a promising array of projects; particularly noteworthy is the fact that these projects represent NCEs that would revolutionize HAT treatment if they reach the market. This includes fexinidazole, a molecule whose potential was discovered from abandoned pharmacological literature, which is now in development with Sanofi. As the image above shows, fexinidazole is being tested for activity in several other disease areas, as well. SCYX-7158 is another molecule with indications for HAT that emerged from an optimization program of a compound library made available by

Anacor Pharmaceuticals. Other lead optimizations efforts are also being pursued for two additional hits from the Anacor library. In addition to these projects, DNDi is supporting advancement of a sleeping sickness treatment under development by the Novartis Institute for Tropical Disease.

In terms of visceral leishmaniasis (VL), there are several treatment regimens being tested for utility for specific disease contexts; these clinical trials will be essential in coming up with therapies that meet the needs of specific patient groups (such as those co-infected with VL and HIV/AIDS). There are also several NCEs being investigated for indications against leishmaniasis, including the oxaborole compounds from the Anacor library. In addition, there is a new class of drug (aminopyrazoles) under development for treatment of VL. This project originally came from Pfizer, and now funding from the Global Health Innovative Technology Fund is allowing DNDi to work with Takeda to select an optimized lead for further development. One additional NCE for leishmaniasis, DNDi-0690, came into DNDi's portfolio through a partnership with another PDP- the TB Alliance.

The DNDi portfolio also includes investigation into improved cutaneous leishmaniasis (CL) treatments. Creating combination therapies for CL is one of the organization's goals, as is coming up with a topical formulation (Anfoleish). Finally, CpG-D35 is a preclinical candidate that demonstrated efficacy in animal models undertaken by the US-FDA. The FDA gave the project to DNDi to continue, and now it has received WHO support for continued development in collaboration with the FDA and the University of Osaka.

For both leishmaniasis and Chagas, massive screening of compound libraries has been an ongoing effort. This has been a particular focus given the progress being made by several NCEs in the pipeline for HAT, and the relative dearth of similarly promising candidates for the other

two kinetoplastid diseases. The University of Dundee has played an essential role in making this possible through their development of a high-throughput screening assay for VL. Of the collections that have been screened, libraries from Sanofi, Takeda, Eisai, Merck, and AbbVie have yielded some hits, and several series from GlaxoSmith-Kline's collection have progressed through hit-to-lead programs.

For onchocerciasis and lymphatic filariasis, two diseases cause my worms, or helminths, DNDi has taken an innovative approach and started to explore the potential to repurpose existing drugs. There is a large focus on screening "repurposing libraries" because, as opposed to other diseases for which high-throughput screening is possible, a more focused approach is needed for identifying activity against filarial diseases (parasitic diseases specifically caused by roundworms). DNDi has negotiated for access to libraries with antihelmenthic properties, largely from animal health companies. By screening compounds that are known to be active against other illnesses, and testing them for activity against NTDs, DNDi is ensuring that patients are not missing out on potentially easy and efficient solutions. The compounds that they are screening have all undergone clinical trials and been proven safe for either animal or human use, but have likely never been tested for effectiveness against NTDs (Bilbe 2015).

3.4 Current Operations

DNDi's operations are diverse and span the timeline of drug development. Considering the vast array of projects that the organization is involved in, it has been called a 'conductor of a virtual orchestra'; in other words, it plays a key role in ensuring that research for NTDs successfully advances from lab science to pills for patients (DNDi 2014). Each stage of this process, from hit identification to regulatory approval, requires a specific set of skills and expertise. DNDi is largely responsible for identifying partners who can contribute to these

different stages of R&D, and coordinating the collaborative efforts needed to achieve success. An outline of DNDi's current ongoing projects demonstrates how the organization has made strategic efforts to incentivize engagement from a multitude of partners that each have expertise in the different activities necessary in R&D the process. **Appendix 2** contains a visual summary of these activities and demonstrates how, when viewed as a whole, DNDi has effectively fashioned a business model to facilitate the achievement of their objectives.

3.4.1 Target Product Profiles

Prior to beginning any portfolio work, DNDi begins to tackle a new disease area by defining the ideal R&D outcome. Starting the drug development process with this step ensures that the key DNDi pillar of patient-centeredness plays a role in all of DNDi's work. Specifically, the identification of high-priority needs and ideal target product profiles relies largely on input from clinicians, the WHO, researchers, endemic countries, and disease control programs. Furthermore, DNDi has two patient representatives that serve on the board of the organization, who also provide invaluable insight during this process. It should be noted that MSF, one of DNDi's founding partners that works directly with patients and within low-income country health system settings, is another particularly valuable asset during this process. The field experience that MSF brings to the table allows DNDi to identify patient needs and understand the reality of what would be required for effective health care delivery. At a side-event during the last WHA meeting Dr. Manica Balesegaram, the Executive Director of the MSF Access Campaign, pointed to this as one of the organization's key contributions to the R&D process. He stated that developing a TPP ensures that R&D is well-adapted to the setting in need; these profiles are not merely aspirational, but actually reflect complex decisions and how to best deploy resources (2015). Some essential topics that are considered during the process of

building a target product profile include questions such as indications, population of concern, clinical efficacy, safety and tolerability, stability, route of administration, dosing frequency and treatment duration, and cost (DNDi 2013).

By planning ahead and developing target product profiles for every new R&D goal, DNDi ensures that each patient population is considered throughout the drug development pipeline and helps to best serve these groups in the long-run. The WHO is a key partner at this stage because they are largely involved in ensuring drug access once a product is developed; if the WHO prequalifies a medications and puts it on the EML, there are less likely to be barriers for patients who need the treatment in the future. Therefore, like many other PDPs, DNDi has learned to make sure the WHO approves of the overall vision for what characteristics any new medicines should have. Once settled upon, the TPPs factor into the decision-making process for how projects are selected, progressed, and managed; in this way, the ultimately serve as true-North for the organization and direct its work to meet patient needs.

3.4.2 Clinical trial platforms

In its first decade of existence, DNDi has developed broad experience and expertise in the realm of clinical investigation. In the 2013 annual report the organization reported that it has conducted 25 clinical studies so far, reaching over 33,000 patients. The focus on clinical trials was largely the result of an organizational push for delivering short-term results and having an immediate impact on the NTD treatment landscape. This means that, while growing a strong pipeline takes time, there was some "low-hanging fruit" that DNDi took as an opportunity for relieving some, though not all, of the challenges facing NTD patients. As the earlier discussion of therapeutic advancements demonstrates, a lot of the organization's successful projects were already at the later stages of development when DNDi involvement began. It is unsurprising that

future discoveries stalled at this point because obtaining sufficient clinical evidence for drug approval is one of the most expensive stages of R&D. This means that even relatively straightforward drug combinations, which can increase efficacy of medications, shorten the time and reduce the cost of treatment, and minimize the risk of developing resistance, often remain uninvestigated.

Although this shortcoming provided an avenue for DNDi to make a tangible difference in the matter of just a few years, DNDi also has the long-term in mind when it comes to clinical trials. This can be seen in the organization's commitment to building capacity for NTD clinical research, especially in endemic countries. In addition to its own clinical trial sites, DNDi has assisted in setting up three regional disease-specific clinical trial platforms. The Leishmaniasis East Africa Platform (LEAP), the HAT Platform, and the Chagas Clinical Trial platform, in Africa, Africa, and Latin America respectively, each now serve as essential partners in DNDi's work. This approach is crucial because, in addition to the fact that clinical investigation is generally one of the most expensive stages of drug development, it is also particularly challenging in the context of NTDs. First of all, one of the many neglected areas of the NTD health technology landscape is in diagnostics, so it is often difficult or painful to diagnose patients for inclusion in the studies while in the field. Furthermore, the settings where NTD patients are found, and therefore where trials can be performed, often face challenges of infrastructure and personnel training, which act as barriers to attaining the rigorous standards required by most regulatory agencies. By building up the networks and capabilities in countries where there are actually patients who need the innovations DNDi and others are working on, these regional platforms increase the likelihood that new advancement will actually be tested,

registered, incorporated into policy recommendations, and ultimately accessed by the patients who need what is being produced.

An additional capacity building initiative that DNDi has taken on, distinct from the clinical trial platforms but similar in principle, is the creation of a network of cutaneous leishmaniasis experts across Latin America. The program, redeLEISH, enables information sharing and collaboration between 70 network members from 38 different institutions. Online web forums enable communication between the group members, and a project to build future clinical capacity maps possible research centers and institute Good Clinical Practice trainings.

3.4.3 Developing Drug Screens

In 2013, DNDi emphasized the need to shift its focus from large-scale trials of later-phase drugs to more of the early-stage testing; after the new sleeping sickness treatment and several combination therapies, the focus has especially been on discovering new chemical entities for Chagas and VL. 2013 marked an important step toward this goal. In collaboration with the University of Dundee, DNDi developed a drug screen that will allow compound libraries over 1 million compounds in size to be screened against relevant parasites. This very high throughput screening capacity plays a key role in increasing the efficiency of drug discovery and helping DNDi reach its goal of developing a strong pipeline of hits and leads in these disease areas.

In addition to the University of Dundee collaboration, DNDi recently signed an agreement with the Institut Pasteur Korea to allow DNDi use of their visual-based high throughput screening technology. This will also assist in drug discovery for VL and Chagas. DNDi has also published training manuals that offer comprehensive and user-friendly

instructions for using NTD assays and enable others who may be interested in conducting quality screens of their own.

3.4.4 Drug Discovery

Overall, DNDi uses a "virtual model" for drug screening, which means it does not have any of its own research facilities or directly engage with research. Instead, their role involves managing the projects and outsourcing actual research activities to capable partners. The organization identifies the most promising research opportunities, brings the projects on board, develops a plan for moving forward, contacts the partners it wants to involve at each step of development, and manages the project's advancement.

Initially, one of the biggest challenges facing DNDi was accessing compounds to screen for activity against NTDs. Fortunately, several companies, including Sanofi, AbbVie, MSD, Pfizer, AstraZeneca, and Bristol-Meyers Squibb just to name a few, have donated their libraries for screening against DNDi's kinetoplastid assays. Furthermore, GlaxoSmithKline has screened its library of over 1,800,000 compounds for VL and Chagas and has negotiated agreements to share the results of these screens and further explore optimization with DNDi. By combining the compound resources and development capabilities of industry partners with DNDi expertise specific to NTDs, drug discovery efforts have yielded some exciting results (DNDi, 2013).

The NTD Drug Discovery Booster is a unique initiative started by DNDi in 2013 that theoretically reduces the time needed to explore libraries and identify hit series for Chagas and leishmaniasis. So far, four pharmaceutical companies- Eisai, Shionogi, Takeda Pharmaceutical, and AstraZeneca- have agreed to participate in an iterative search process whereby the companies continuously examine their matches against each other in order to refine their results and build upon promising series. The aim of this multilateral consortium is to take advantage of

the immense compound libraries that large pharmaceutical companies have accumulated, use the capacity of these companies to speed up drug discovery, and also save a lot of time and work on the part of DNDi. The partners who have joined the consortium all signed contracts upfront agreeing to share precompetitive structural and functional information with DNDi. Furthermore, the group will share recognition for any successful outcomes, and have agreed not to patent any findings so that drugs might continue to get developed. The participation of the three Japanese companies in this effort is sponsored by the Global Health Innovative Technology Fund, a public-private partnership involving the Japanese government that funds scientific research and development for global health needs (DNDi, 2016).

In addition to engaging Japan in these efforts, DNDI is increasingly involving endemic countries in the identification of hits and leads. Lead Optimization Latin America (LOLA) as in example of a DNDi initiative to build upon R&D potential at two universities in Brazil. The project is "virtual" in that it involves international collaboration efforts, including donation of compound libraries and expert advice from pharmaceutical companies that support the group. LOLA is a precedent-setting example of how endemic countries can be part of the solution for the NTD challenges they face.

One additional project that DNDi has been a partner for is the MMV Pathogen Box. This effort is an expansion of the MMV Malaria Box model, which allowed anyone in the world to gain access to molecules for screening against malaria assays. In this case, the Pathogen Box contains over 400 drug-like molecules that have shown activity against a list of particular pathogens, including several NTDs. DNDi has advised MMV about which compounds are most promising for the type of kinetoplastid that they specialize in, and therefore which compounds would be useful to include in the Box. Now, on the Pathogen Box website researchers can

request a free delivery of the box, in return for agreeing to publicly share the results of their research within two years (2016).

3.4.5 Demonstration Project

One example of this holistic approach to drug development can be seen in DNDi's engagement with the WHO "demonstration projects". The WHO has a long history of participation with NTDs and has even been involved in health innovation. In 1974, the organization established the Tropical Disease Research Program (TDR) as a drug development research group. They dedicated their own resources toward research on diseases of poverty, but their work was greatly slowed down when funding ran out. For a long time after that, the WHO focused its neglected tropical disease efforts on the epidemiology of diseases and normative leadership. In terms of drug development, the TDR continued to function (and still does today), and has seen some success in getting drugs to market. However, stakeholders agree that the WHO stepped into more of an advisory role on this topic. For example, PDPs will present their target product profiles to the WHO in order to get country advice and expertise, and ensure that the products they develop will be appropriate for WHO prequalification and the Essential Medicines List (Spangenberg 2015, pers. comm.).

However, at the 2003 World Health Assembly, member states impacted by NTDs and other market failures in the healthcare sector called upon the WHO to examine the financing and coordination of medical R&D and brought policy discussions of this issue to the table. The Commission of Intellectual Property Rights, Innovation, and Public Health (CIPIH) was established to explore the intersection of IP and access, and in 2006 it was followed by the Intergovernmental Working Group on Public Health, Innovation, and Intellectual Property (IGWG). Following IGWG came a push for the WHO to move beyond examination of the

current R&D system and to look for innovative sources of funding. During the 63rd World Health Assembly in 2010, a Resolution was passed which established the Expert Working Group on Research and Development: Coordination and Financing (EWG). This resolution recognized the need to,

> "Explore and, where appropriate, promote a range of incentive schemes for research and development including addressing, where appropriate, the 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." (Resolution WHA 61.21)

This acknowledgment of the need for systemic change was somewhat radical for the WHO; they took the calls for delinkage to the highest levels of global health and showed the power that low- and middle-income countries have when voicing their concerns and negotiating together at the international level. This move created cautious optimism among the advocacy groups who had been in favor of delinkage for a long time. They recognized the legitimacy of the WHO in the global health world and the importance of having this agency behind their issue, but also acknowledged the slow and highly political nature of every decision that is made at this level.

The principle on which the EWG was founded was continuously supported by a number of countries in its mandate to explore solutions to the lack of private investment incentives for diseases impacting poor populations. However, there were criticisms about a lack of transparency and conflicts of interest in the EWG. In 2010, the WHA voted to continue the work of the EWG but make some necessary adjustments to address these issues; the result was the Consultative Expert Working Group: Funding and Coordination (CEWG).

In 2013, the CEWG issued a call for proposals from different parties across the spectrum of public and private sectors, for projects that would further R&D for neglected health

technologies and provide substantive evidence for the principle of delinkage. CEWG publications summarize the argument for investigating innovative ways of doing R&D:

> "Current incentive systems fail to generate enough research and development, in either the private or public sectors, to address the health-care needs of developing countries. In the case of developing countries, the market failure that intellectual property rights try to correct is compounded by a lack of reliable demand for the products generated by research and development (R&D). Thus the incentive offered by intellectual property rights fails to be effective in correcting the market failure. There is therefore an economic case, based on market failure, for public action. There is also a moral case. We have the technical means to provide access to life-saving medicines, and to develop new products needed in developing countries, but yet millions of people suffer and die for lack of access to existing products and to those that do not yet exist. This is also a matter of human rights as articulated, for instance, in WHO's constitution which states that 'the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition'."(CEWG, 2012)

This initiative, called the Health R&D Demonstration Projects, received numerous submissions including two from DNDi. The GEWG used their experience to evaluate the proposals according to delinkage principles and scientific feasibility, and then had member countries select finalist projects. One of the four final projects selected for WHO support was the DNDi submission regarding innovative mechanisms for funding and coordinating VL R&D, with the goal of ultimately delivering new health technologies that are "delinked" from the cost of R&D.

As described earlier in Chapter 1, the treatments currently available for VL are insufficient in many ways. Furthermore, other challenges for VL control include the presence of asymptomatic carriers and a painful skin rash (PKDL) that often develops after treatment, both of which may be sources of transmission. In addition, people living with HIV are especially prone to VL, but there is limited understanding of ideal treatment regimens for this special patient group.

DNDi's goal in developing "The Visceral Leishmaniasis Global R&D Access Initiative" as a demonstration project is to deliver safe and effective oral treatments for VL, treatments for

the PKDL rash and asymptomatic carriers, and also to develop diagnostics to detect carriers. A secondary goal of the Access Initiative is to create and allow open access to a database aimed at identifying determinants of treatment success and failure. The Visceral Leishmaniasis Global R&D Access Initiative involves a number of parallel projects including cross-regional coordination of a number of existing projects, creation of open source knowledge sharing tools, offering both push and pull incentive mechanisms, and building capacity in endemic countries. From the big-picture perspective, the goal of this demonstration project is to utilize a number of different incentive mechanisms and attach them to the different project objectives, in order to display the impact a diverse range of delinkage mechanisms can have on NTD drug development. In other words,

> "Because it is a holistic approach to VL that we are trying to have here, we had more freedom to see which innovative mechanisms would attach to each activities... Because it was really preclinical through the end of development phase, and with VL we have an activity in each of the sections, then it was easier to play with all of the different incentives and also funding mechanisms and partners. So, really for us, the demonstration project has always been a policy and advocacy exercise more than anything else, because we haven't developed some kind of new activities to fit into it. No, we said ok, here are all the R&D activities that we are doing anywhere on VL, and on each we are going to try and attach an incentive and we will show that it will boost the [activity]" (Heumber 2015).

A visual outline of the demonstration project can be found in **Appendix 3**. The graphic clearly shows the entire timeline of drug development for VL, what stages the different projects are in, and the ways in which DNDi hopes to tackle specific gaps in innovation with targeted incentive mechanisms.

For the first objective- developing a new, well-adapted first-line treatment- the first activity DNDi proposed was the creation of a drug accelerator consortium. This consortium would work to identify a new series of compounds from the oxabolore class to take into preclinical development. The proposed partners for this step include the University of Dundee,

Open Source Drug Discovery and other open source, and the European Innovative Medicines Initiative. Now that the Drug Discovery Booster is actually being implemented, the group has formed relationships with pharmaceutical partners, as well. As a second arm of this objective, they also proposed a grant with access clauses to advance a pre-clinical candidate (VL2098) to market. Lastly, they aim to complete the clinical development of either faxinidazole or VL2098 through building capacity, coordinating cross-regionally, and innovating improved regulatory pathways. This will involve partnership with the European and Developing Countries Clinical Trial Partnership (EDCTP), LEAP, Fiocruz/the Brazilian Ministry of Health, and the Indian Council of Medical Research.

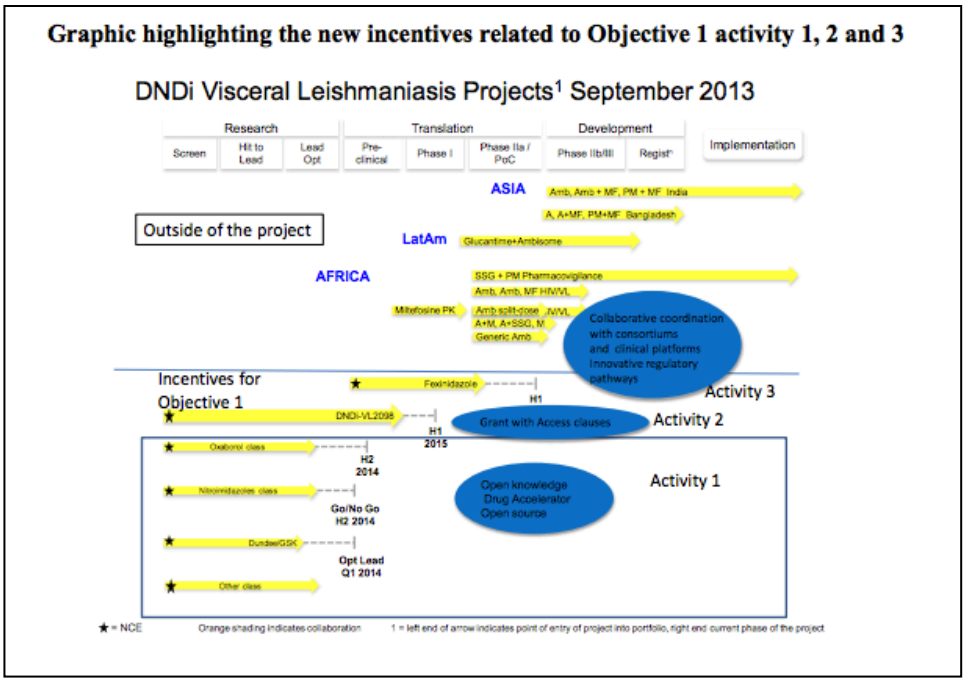


Figure 10: "The Visceral Leishmaniasis Global R&D Access Initiative." DNDi. 2016. <http://www.who.int/phi/implementation/DNDI_documents.pdf?ua=1>

The second objective of the demonstration project is to develop a diagnostic that would assist in assessing the role of asymptomatic carriers and PKDL patients. To achieve this objective they foresee collaboration with the University of Utrecht, the Institute of Endemic

Diseases, University of Caracas, the Ferrer Group, Salpetriere Hospital, Steifel, GSK, and SGS. These partners will implement the necessary capacity building, coordinate, and share data. DNDi also choose this objective as an area in which it could pilot a milestone prize, as described in Chapter 2, that would identify key thresholds in the development of a diagnostic and award developers who achieve these goals, with the result being an improvement in the appeal of investing in early-stage research.

Third, the Initiative hopes to begin research into a PKDL treatment and deliver a topical medication to market. This goal will utilize the same incentive package as is being used for Objective 1. It will involve collaboration with LEAP, the EDCTP, the International Center for Diarrheal Disease Research- Bangladesh (ICCDRB), PATH, and the IMI.

The fourth and final objective of the demonstration project, developing an open-access database with treatment effectiveness data, will work with many partners including Worldwide Antimalarial Resistance Network, ministries of health, Institute of Tropical Medicine, and the EDCTP. Currently, a model database exists for antimalarial efforts, and the goal is to replicate and improve upon this prototype for VL.

Unfortunately, the CEWG's powerful call to action in the declaration of the need for delinkage has yet to result in tangible action by the WHO. Although the demonstration projects raised many hopes that the goal would be advanced, the finalist projects have yet to see any real impact result from their participation in the WHO process. Mainly, they had hoped the WHO would set-up a "demonstration" R&D fund with mandatory contributions from member states or other innovative financing mechanism, that would give funding to the projects. This pooled funding mechanism was something the CEWG had been exploring for a while and that DNDi and others advocated for as part of the demonstration projects. Even though DNDi already had

some funding for their proposed activities, they thought it was important that the feasibility of a global fund be tested. However, the organization opted for a voluntary demonstration fund, and only a few countries have made minor contributions. Unsurprisingly, these donations have not met the financial needs of the demonstration projects. For example, the DNDi demonstration project proposed a budget of about 37 million Euros, but they have only received about 2 million Euros from the fund in addition to 9 million Euros from MSF and DFID (Chappuis 2015). For this reason, they have been able to implement parts of 8the proposal, such as the Drug Discovery Booster, but have not put the entire plan into action. In reality the WHO support is recognized as a kind of "rubberstamp" that participants hope will attract donations from other potential funders (Spangenberg 2015, pers. comm.).

3.4.6 Advocacy

The DNDi advocacy agenda is something relatively distinct from, but certainly complementary to, its product development agenda. Since its creation, DNDi's position has been that the current global R&D system is incompatible with global health goals and therefore should be reformed. In particular, DNDi advocates for public responsibility because only governments can provide the amount of financial support necessary for this work in a reliable and sustainable way. The 2013 CEWG decision to pursue demonstration projects rather than initiate a large-scale R&D treaty instituting these changes was a letdown to organizations like DNDi, which felt like the WHO was behind the times and making them "demonstrate" the effectiveness of work they had been doing for a decade. Alexandra Heumber, the Head of Policy Affairs at DNDi explained, "The reason why we still decided to be involved in this demonstration project, even though we would have preferred a more global political negotiation for a global fund, etc, is because it was this that was on the table at the end of the day. And we thought that being 'inside'

would help maybe to influence the process" (2015, pers. comm.). At the 2015 World Health Assembly in Geneva, when the idea of a global Framework and Fund was revisited, DNDi made its message clear both to delegates and global citizens; it advocated for an international fund for R&D, led by governments, that would promote delinkage and open innovation. Their point was that, while the organization remains committed to the demonstration project on leishmaniasis and their other internal operations, the innovation problem is much larger than what a single organization can overcome. The Executive Director of DNDi, Dr. Bernard Pécoul, co-authored an article right around the time of the 2016 WHA that argued for and outlined an umbrella framework under the WHO that would both finance and coordinate R&D for global health in areas of market failure. Specifically, the proposal recommends that the binding framework be responsible for implementation of national control programs, priority setting, regulatory harmonization, open innovation, innovative financing, and new R&D incentives (Balasegaram et. al 2015). Large, multi-lateral funds for global health purposes have been established in the past (UNITAID, Gavi, and the Global Fund are examples), but the recognition of a need for pooled support of R&D is just beginning to grow.

DNDi plays a large part in advancing this policy agenda and in creating coordination among those who seek reform. They also play a role in narrating stories from the ground and giving what they call "voices for neglected diseases" a platform to be shared with an international audience.

4. Conclusions

4.1 Summary of DNDi

Key principles:
• Focus on most neglected diseases (those ignored by market-driven R&D) • Not-for-profit organization working in the public interest • Use an alternative model for drug development • All work will be patient-driven, and field application is a crucial consideration • Provide equitable access to any approved health technologies and open access to knowledge • Raise awareness of the needs of NTD patients • Build capacity through collaboration with endemic countries and technology transfer

In the table above the key operating principles for DNDi, as apparent from their own publications and the author's interviews with organization employees, are listed. While studying this organization, these principles were reiterated over and over again; it is clear that they play a crucial role in organizational decision-making as the groups strives to reach the ambitious goals it has set for itself. Specifically, it is important to note how these principles show up in a document entitled "Ten Years of Experience & Lessons Learned by DNDi," in which the organization shares major lessons that DNDi has deduced from its own self-analysis. However, these themes also shape the author's own additional layer of analysis on the strengths and weaknesses of the organization.

This chapter positions DNDi in comparison to other PDPs and in a complex field of global access to medicines. Although each PDP operates in a distinct space, there are important considerations that can be garnered through contextualizing DNDi in the larger world of PDPs.

4.2 Analysis of Strengths

Overall, there has been a significant improvement in the NTD landscape since the inception of DNDi. A recent study reported that, of the 850 new therapeutic products registered in 2000–11, 37 (4%) were indicated for neglected diseases, comprising 25 products with a new indication or formulation and eight vaccines or biological products (Pedrique et. al. 2013). Even more noteworthy, a study done in 2005 showed that while multinational pharmaceutical company innovation in the field dropped since 2000, overall approval of new treatments for diseases of poverty has improved due to the increasing role of public-private partnership (Moran 2015). Figure 11 illustrates this unsurprising trend of decreased private investment, and how the "era of partnerships" has safeguarded public health needs and delivered important advancements through collaborative efforts.

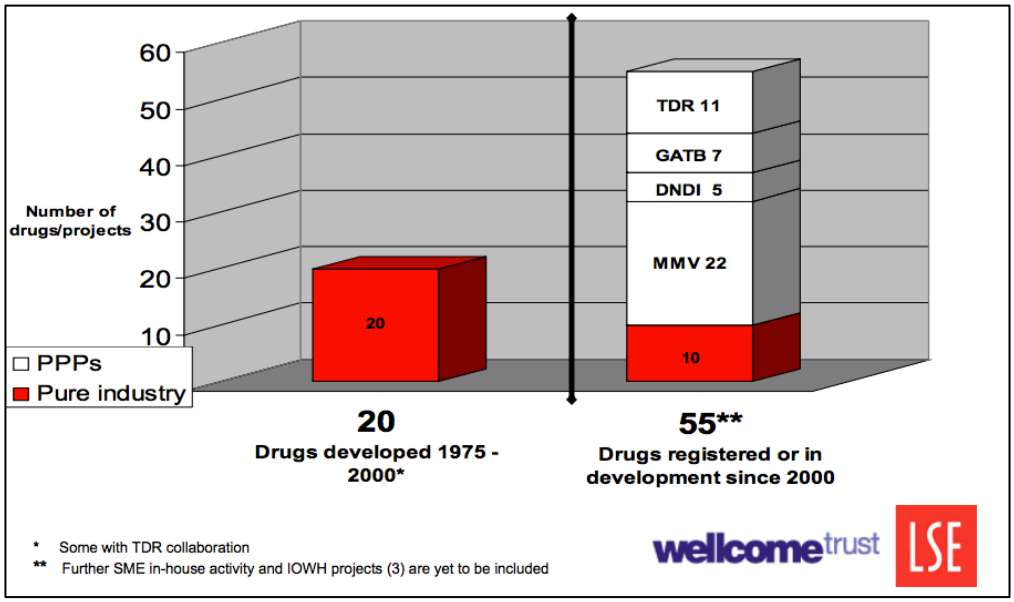


Figure 11: Moran, Mary. "New Approaches to Funding Drug R&D for Neglected Diseases." Jan 2005. London School of Economics and Wellcome Trust. Presentation to the Pharmaceutical R&D Policy Project. <http://www.who.int/intellectualproperty/submissions/Mary.Moran.pdf>

As this image shows, only a small number (5) of the total number of drugs registered since 2000 (55) were the result of DNDi. However, the organization has contributed significant

innovation in a thoroughly neglected field, and has also successfully advocated for larger global involvement in the field of NTDs. By taking a closer look at what exactly DNDi has done to achieve these results, this section of the paper identifies several trends for the success of PDPs.

4.2.1. Independence

One of the key pillars of DNDi is its independence. DNDi strives to protect its ability to work in the public interest by maintaining diversity of funding sources and remaining independent from any major funders. They also avoid ear-marked donations and, whenever possible, ask donors to contribute to their core funding. This means that the organization can pursue or stop project as they see necessary, rather than remain beholden to granting agencies. Importantly, this often leads to increased ability to pursue work that directly meets patient needs.

As of 2014, the organization had raised 350 million EUR, and funding sources were very balanced between public and private sources. On top of that, the organization will not accept donations exceeding 25% of the overall budget from any single funder. The purpose of this policy is that the organization remains independent of external influence and be able to operate in the ways that will best serve its vision and mission. This is a significant difference from many other PDPs. For example, it has been noted that many projects at PATH, which receives the majority of its funding from the Gates Foundation, are stopped and started per the decision of this major funder. This tenuous support essentially means that Bill and Melinda Gates have the power to decide which projects they are interested in pursuing, and PATH will follow in that direction regardless of their own perspective, interests, and larger vision (Barnes-Weise 2015, pers. comm.). Furthermore, DNDi has often felt that earmarked funding created silos whereby funding agencies can relegate a certain amount of money to research in certain disease areas. Ultimately, this narrow focus prevents efforts that are cross-sectoral, such as efforts toward

health systems strengthening or projects that might cross between different disease groups. DNDi views these efforts as an important part of their work that can often do more good than focusing a project in too narrowly or delineating restrictions for spending (Don 2015, pers. comm.).

The organization's commitment to having a balance of interests is also reflected in the representation of private and public affiliates on the organization's board; members include individuals from ministries of health, research institutions, pharmaceutical companies, NGOs, the WHO, patient representatives, and other experts. The scientific advisory committee for the organization also reflects a similar array of perspectives, with the goal being that no single agenda is prioritized, but rather that different members help keep each other in check and ensure the focus remains on DNDi's overall goals. This is important because, as the diagram below demonstrates, the Board of Directors plays an important role in determining organizational activities, and overrepresentation of any single interest could shift the organization's focus.

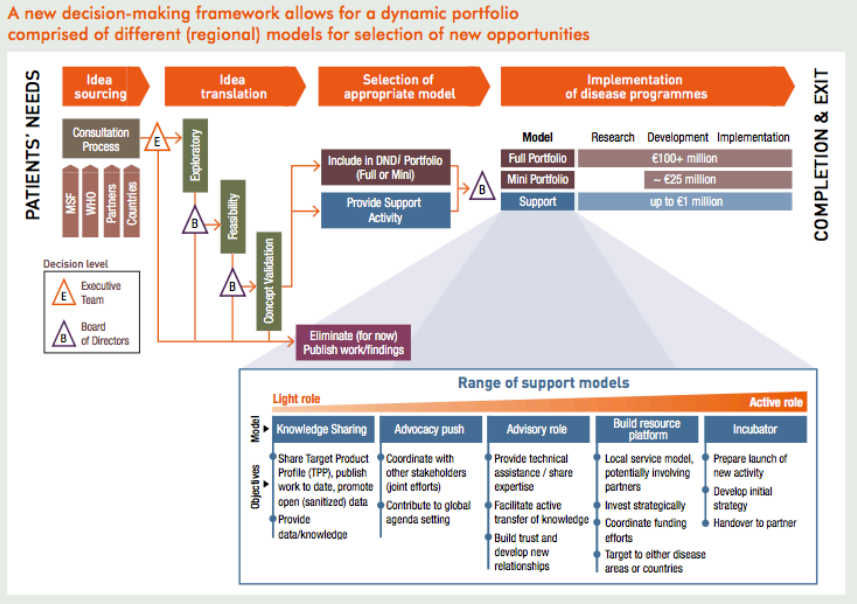


Figure 12: "Business Plan 2015-2023." DNDi. <http://www.dndi.org/wp-content/uploads/2009/03/DNDi_Business_Plan_2015-2023.pdf>

4.2.2 Health Systems Strengthening and Technical Capacity

DNDi's commitment to building capacity and being patient-driven, is clear in both its organizational structure and activities. First of all, DNDi's work in endemic countries vastly outweighs its work in high-income countries; the organization has offices around the world including in Switzerland, Brazil, India, Japan, Malaysia, Kenya, the Democratic Republic of the Congo, and the USA; importantly, their regional office staff outnumbers their headquarter staff. Furthermore, in addition to regional offices, DNDi's operations extend over 40 countries. This demonstrates that there is an emphasis on task shifting away from solely conducting work in high-income countries. Instead, DNDi sees a more powerful long-term solution in enabling endemic countries to be part of the solution to their problems.

First of all, DNDi has been successful at utilizing clinical trials for achieving improvements in overall health care. For example, some of the large-scale implementation studies they are engaged in are being used as evidence for national policy changes that will ensure patients are receiving the best available treatments. Another success in the realm of clinical trials is that DNDi conducted a Chagas trial in Bolivia that was the first of its kind, and in doing so the organization showed that it is possible to build the capacity necessary to execute a quality clinical trial in resource-limited settings. In addition to building clinical trial capacity, the organization's clinical work in endemic countries has worked alongside elimination campaigns. The DNDi regional clinical trial platforms not only represent a growth in clinical capacity and research training in these areas, but have also contributed to health systems strengthening efforts by supporting infrastructural improvements and training medical workers.

RedeLEISH and LOLA also represent efforts to strengthen the role of endemic countries in their ability to contribute to improvements for NTDs. The network of professionals and the

early-stage research program both demonstrate how Latin America, and Brazil in particular, are joining efforts previously led by institutions based mainly in high-income countries becoming more significant actors and leaders in global health. In terms of long-terms sustainability, this shift promises continued attention for diseases of poverty and less reliance on tenuous international support. As compared to other PDPs, which largely work in endemic countries only for clinical trial purposes, DNDi has shown a commitment to fundamentally changing the way low-income countries are involved in R&D today and especially in coming years.

4.2.3 Technology Transfer

DNDi's philosophy of ensuring long-term access has been demonstrated through its technology transfer agreements for ASAQ and ASMQ. ASAQ is currently under production in Morocco, made possible by DNDi's commitment to produce products without patenting them whenever this option is feasible. Based on market-forecasts DNDi pressed for further African production, and recently found another partner in Tanzania to manufacture enough doses to meet patient need. Additionally, technology transfer of ASMQ happened between a public pharmaceutical company in Brazil, Farmaguinhos, and a generic manufacturing company in India, Cipla. This was the first "South-South" technology transfer of its kind, meaning a contribution that originated in one endemic country was shared with another. Since this transfer occurred, ASMQ has been made available in India and Malaysia. Again, DNDi is unique in respect to its facilitation of partnerships between endemic countries, and not just between high-income governments and pharmaceutical companies with the countries with patient populations. Rather than relying on pharmaceutical companies based in the West to maintain registration and sales of their products in low-income markets, or alternatively to donate their global health products, local production of medicines helps ensure that even poor patients have access to the

products that result from the laborious R&D process. Clearly, like capacity building, technology transfer activities complement DNDi's objectives to both develop and ensure access to new treatments for NTDs.

4.2.4 Openness and Access

DNDi has demonstrated a commitment to open access of both new knowledge and new products throughout its work. When it comes to knowledge, it is important to know that DNDi's Intellectual Property Policy aims to, "Ensure that the results of the work carried out under its auspices are disseminated as widely as possible" (2016). This means that any research sponsored by DNDi must be presented and published in an open-access journal in a reasonable amount of time, unless there is a specific rationale for obtaining IP which publication of certain information might undermine. The goal of this requirement is to promote the circulation of any and all information relevant to NTDs and drug development. DNDi's Open Innovation Portal does this both through the free sharing of traditional academic publications, but also through the public sharing of data on chemical compounds. Open access publishing is becoming more and more common throughout the field of research, so there are a number of databases, such as Plos, that DNDi grantees can use which don't require user-fees. Two new tools for sharing data on medicinal chemistry are WIPO Re:Search and ChEMBL, which facilitate access to compounds and information about those compounds. The DNDi Open Innovation Portal compiles DNDi's work that is shared through these other open databases in a streamlined manner.

As for equitable access to new inventions, DNDi has developed a "gold standard" for licensing terms to which the organization agrees. As they stated in their publication outlining lessons from their ten-years in existence, this includes: "perpetual royalty-free, non-exclusive, sub-licensable"; "worldwide research and manufacturing rights"; "commitment to make the final

product available at cost, plus a minimal margin, in all endemic countries"; "non-exclusivity, enabling technology transfer and local production" (2014). These terms aim to de-link the cost of R&D from the price of the final product and ensure the progress of follow-on research. DNDi aims to introduce these principles into contracts starting from the very beginning so that partners' priorities are clear, and IP and access don't become an issue farther down the line. While many PDPs have similar goals for access and openness, DNDi is one of only a handful of PDPs with successfully approved products, and as the field grows and expands their successful access policies can potentially serve as a model for others looking to have similar success. This type of licensing model contrasts with some of the policy interventions discussed in Chapter 2, which may promote innovation but fail to achieve de-linkage and promote patient access. Clearly, PDPs are able to negotiate access provisions because of their position as "middle men" between funding and R&D, as well as their unique commitments to global health.

4.2.5 Breadth of Impact

In terms of tangible objectives, DNDi strives to improve the lives and health of patients in both the short- and long-term by establishing a strong portfolio of projects for their focus diseases and delivering 16-18 new treatments by 2023. Initially the organization focused on kinetoplastid diseases (leishmaniasis, sleeping sickness, and Chagas disease), for which treatments were unacceptably toxic, not adapted to the settings in which they were needed, or too expensive. This family of diseases was a logical combination for the organization to focus on as there are similarities and overlap between the diseases, and therefore the research could to applied and adapted across disease categories, and ultimately have a more efficient impact.

However, throughout the organization's lifetime it has also been called on by international organizations and its partners to work on other areas of patient need (including

malaria, helminths, and most recently pediatric HIV, HCV, and mycetoma) (DNDi 2016). Clearly, DNDi has taken a dynamic approach toward its portfolio while remaining committed to working in areas of market failure for the wellbeing of the most vulnerable patients who are unlikely to have their needs met by traditional drug development methods. When compared to the many PDPs that focus on the general HIV/AIDS population, TB, and malaria, for which there is more notable concern and at least some market incentive in high-income countries, it seems particularly important that DNDi has applied the PDP model in areas that are almost completely neglected. DNDi's work shows that partnerships that minimize investment risk can advance the needs of even the most marginalized patients in a global economy that favors those with higher purchasing power.

4.2.6 Strong Partnerships

One of the most distinct factors about DNDi is its commitment to using an alternative model for drug development that is based on a 'virtual' approach involving coordination of partnerships, rather than an in-house research effort. The organization arranges the ideal alignment of contributions from different partners and acts as a manager and channel for communication between them, but also works closely with partners at each stage. The goal of this approach is to bring together and leverage existing expertise and research capacity that is currently fragmented for the purposes of increased efficiency and reduced costs. As evidence of this, their ten-year publication reported that, as of 2014 DNDi had participated in over 350 collaborations across 43 countries. They work with over 50 public research institutes and universities, 20 pharmaceutical and biotech companies, many governments, and several other nonprofit organizations; each of these institutions dedicated their respective abilities, resources, and efforts to NTD drug development efforts under the auspices of DNDi. A list of the different

partners DNDi has worked with to-date is available in **Appendix 4**. Furthermore, the DNDi report "New Hope for Neglected Patients" says that the number of contracts the it signs with new partners has steadily increased every year, meaning there are a growing number of opportunities for innovative collaboration (2016). Overall, these figures represent DNDi's commitment to using an alternative model for R&D that relies on cooperation rather than exclusivity (as is the norm under a patent-driven model).

In particular, DNDi has been successful at involving for-profit pharmaceutical and research companies in their work. Initially, one of the biggest challenges facing DNDi was accessing compounds to screen for activity against NTDs. At the start, they were largely reliant on academic and biotechnology partners, but have been able to expand their efforts since then. By the end of 2013, the 28 partnership agreements had been signed with these companies to allow for access to their compound libraries, pre-clinical activities, and industrial development. All of these services were provided to DNDi at no cost, and agreements have been in line with DNDi's IP policies. This shift in pharmaceutical company focus has been the reflects both the corporate nature of these companies, as well as recognition of their moral obligations as public health actors. Representatives of these corporations consistently repeated that their global health activities are an important part of their company's role in the world, but separate from their business goals. As Dr. Benny Baeten of Janssen Pharmaceuticals said of his company's global health programs, "It was the only choice we had" (2015). Similarly, Dr. Thomas Spangenberg of Merck Serono cited the London Declaration as a compelling factor in Merck's decision to broadly engage in global health programs (2015, pers. comm.). Along the same vein, Dr. Julio Marten from GSK's Tres Cantos Open Lab recognized the importance that having a CEO who

cares about global health and having made a commitment to the London Declaration as reasons for their willingness to engage in more open, non-traditional research models for NTDs (2015).

Clearly, advocacy from DNDi and others has put NTDs on the global health agenda. The results of their activities, such as the signing of the London Declaration, have had important consequences for global health especially in their ability to mobilize the private sector. Importantly, DNDi has also offered pathways for sustained involvement that are logical from the point of view of these companies; because of the lack of incentive for pharmaceutical companies to engage in risky research for NTDs, it is important that DNDi has lowered the barriers to entry for their participation and provided the necessary avenue for their engagement. As the analysis of DNDi's successful products and promising pipeline has shown, a significant amount of successful and promising compounds originated from the libraries of these companies. Furthermore, their in-kind services, expertise, and implementation assistance have proved an essential part of the collaborations to achieve necessary new innovation. In summary, private sector contributions have been central to DNDI's success and the organization's engagement with these key partners will continue to be critical.

4.2.7 Cost-efficiency

Not only has DNDi created an environment that is less hostile to NTD R&D and managed to produce tangible results, but they have also done so at impressively low cost. The 6 new treatments that DNDi has received approval for were all accomplished with a budget of EUR 182.5 million, or about $250 million (2013). Compared to numbers published by the pharmaceutical industry about the costs they incur for R&D, which exceed $250 billion per new drug approval and are criticized because of their lack of transparency, it is clear that PDPs have managed to create a more cost-effective process. This fact is enlightening in that it shows the

way in which having a coordinating body, such as a PDP, can streamline research in a given disease area and prevent redundant research or similar errors. This fact is not unique to DNDi, but is reflected in the work of other PDPs, as well: PATH and the Serum Institute developed a meningitis vaccine at less than one-tenth the cost of typical vaccine development (PATH 2016). Overall, PDPs seem to have effectively utilized partnerships to introduce efficiency to the R&D process, as opposed to single-party development efforts.

4.3 Analysis of Weaknesses

Despite the many areas of success in the DNDi model, there are many challenges that remain as the organization pushes for the development of more NTD products. Ultimately, a long-term solution to the world's access to medicines problems depend on improvements in a number of key areas: financing, policy framework, regulatory capacity and priority setting in endemic countries, health systems, tech transfer, demand forecasting, and procurement strategies (DNDi 2013, 7). Most of these challenges can be summarized in one word: sustainability. Of course in some ways this is a problem that many non-profit organizations face, but DNDi would be well served to take lessons from other PDPs that don't face quite the same difficulties whenever possible, and think critically about potential solutions to their own unique challenges.

4.2.1 Financial Limitations

The financial situation of DNDi, as well as the organizations that they work with, is one area of constant struggle. **Appendix 4** lists the many entities that help fund their work; it is an impressively long list that has resulted in over EUR 350 million raised since they started their work in 2003. As much as DNDi strives to retain a diversity of funding sources and limit undue influence of any single funders, they are still largely dependent on high-income countries, a

handful of philanthropies, and corporate social responsibility efforts. More specifically, DFID, MSF, and the B&MGF are the three largest contributors to the organization and account for almost two-thirds of their income; undeniably, the commitment of these institutions is central to the future success of DNDi (2013, 55). To further complicate the picture, it is important to note from both **Appendix 1** and Figure 13 that these three major funders overlap between many PDPs- as do many of the smaller funders. As John-Arne Rottingen, former director of the CEWG, notes, this leads to inefficiencies such as fundraising and competition for financial support (2015)**.** As an example, MMV has consistently raised more money from its funders than DNDi; in 2014, the difference was an income of 41.7 million USD for DNDi compared to 79.2 million for MMV. One researcher has noted that perhaps the difference in successful fundraising results from the broad scope of DNDi being less appealing to donors versus the focused nature of MMV. While it is difficult to compare malaria with neglected diseases because of the difference in economics and international perception of the diseases, it is possible that donors are more inclined to give to an organization that targets one disease (Rahman 2016). This difference also suggests that DNDi would be well served to continue raising the profile of NTDs through education and communication efforts, as malaria's higher levels of recognition at the global level seems to correlate with successful fundraising efforts. Though the root of the problem is complicated, the result is straightforward: the financial instability in this field is a disincentive for essential players to stay involved in the NTD space. Experts who are aware of the success of these partnership-based organizations often cite unsustainable funding as their biggest remaining challenge and threat to the future. As Mary Moran, Executive Director of PolicyCures at the London School of Economics writes, "The current models are working and are a low-cost

effective way of targeting government funds, but lack of funding will lead to their collapse, leaving both the public and companies with restricted and expensive alternatives" (2005).

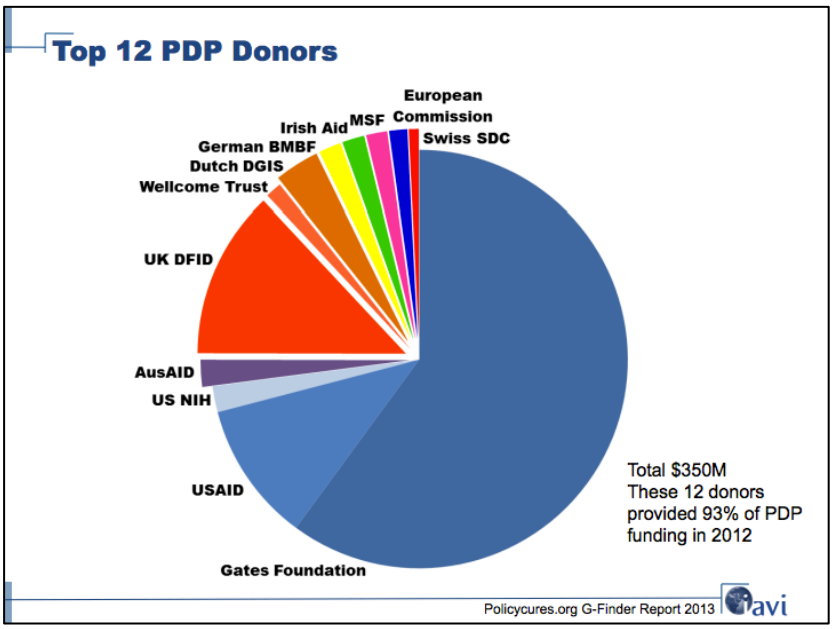


Figure 13: Dean, Hansi. 2016. "The Value of Product Development Partnerships in Vaccine Development."International AIDS Vaccine Initiative. Accessed March 21. https://ec.europa.eu/research/health/pdf/event17/s3-9-hansi-dean_en.pdf.

As a result, new incentives, and new, pooled funding mechanisms are an area of need. Mary Moran's research has come up with several incentive mechanisms that would be innovative improvements to the PDP business model. In terms of promoting engagement of small-scale commercial partners, she recommends a "draw-down fund" that would reimburse PDPs for their payments to companies. This would allow fee-for-service payments to happen as they would in a normal commercial setting, without the slow-down and uncertainty of a grant-based model. Raising money through auctioning off fast-track regulatory approval privileges could finance this draw-down fund, or any other incentive mechanism for that matter. Fast track designation is a regulatory pathway that is already in existence in the EU and has similar procedures in other countries, and is incredibly valuable to companies because it allows them to monetize their patent rights for longer. Auctioning just one or two of these privileges a year in

the form of a Transferrable Fast Track Regulatory Review privilege has the potential to raise enough money to be able to fund the type of R&D activities that need more sustainable financing. Even for big pharma who participate in the NTD space without commercial interest, financing is still a concern; they may be willing to do their global health duty at-cost, but they are often unwilling to operate at a profit loss because of their stakeholder interests. Therefore, securing financing for the PDP and reassuring large-scale multinational corporations that their partnership activities will be fully funded is essential to retaining their participation.

Alternatively, as DNDi's advocacy agenda promotes, there are calls for leadership from the WHO regarding R&D financing. In addition to a lot of NGOs, emerging economies that suffer the burden of NTDs, such as India, South Africa, Brazil, China, Uruguay, and Malaysia have all supported proposals for a Global Framework on R&D. This Framework outlines the need for an R&D Observatory that would coordinate global health R&D needs, as well as a financing mechanism to support priority efforts. On the other hand, there is lingering resistance from numerous high-income countries: most of the proposals suggest requiring all WHO member states contribute a percentage of their GDP or of their health development aid to the fund, which polarizes countries that don't want to be responsible for financing the needs of other countries. Furthermore, experts posit that those nations, which are home to multinational pharmaceutical companies, worry about the ramifications or are skeptical of a new innovation model, as it could undermine their current business models. Despite the resistance of certain parties and the political maneuvering at the WHO that has slowed down the advancement of a Framework for R&D, there are many proponents working to address the major hold-ups and push the idea forward. For example, there are proposals for innovative financing mechanisms, including discussion of an international financial transaction tax. Overall, the wastage and

uncertainty in the current PDP financing model and the failure of the voluntary fund that was part of the demonstration projects is strong evidence that some alternative mechanism for financing or a mandated contribution from different member states is needed.

4.2.2 Political Context

The largest ongoing problem that DNDi has recognized about the challenge of its work is the integral role that political context plays. One of the areas of weakness that DNDi has always emphasized, and which is related to all practically all of the other challenges they face in one way or another, is the lack of international governance over the NTD market failure. Despite the civil society's support of endemic countries in their advocacy for an International Framework on R&D that would coordinate WHO member states in the funding and implementation of R&D, and despite a growing amount of support from countries like Norway, Switzerland, and France, the idea lacks support from the strongest actors at the WHO (Sixty-sixth World Health Assembly 2015). Of late, the WHO has received a lot of criticism for being too weak, being under the influence of its largest donors, and failing to equally represent the needs of member states. For example, when they selected members for the CEWG, received a range of responses: the US maintained that it was "concerned about the unprecedented decision by the WHA" to establish a working group on R&D; the EU welcomed the new team; low-income countries were still concerned about conflict of interest issues (Wanis 2011). Specifically, low-income countries were concerned because Paul L. Herrling, an executive from the pharmaceutical company Novartis, was selected as the representative for the EURO zone (Love 2011). Civil society groups echoed the concerns of developing countries in a letter to the Chair and Vice-Chair of the CWG Executive Board. The complaints focused on the fact that Herrling represented an old

system of thinking and would be resistant to necessary reforms to the global R&D system, and also that he is an author of several of the proposals the CEWG was mandated to review (the Fund for R&D in Neglected Diseases, also known as FRIND, and the PDP Plus proposal). As James Love of KEI explained,

> "There has been considerable tension and controversy over proposals to de-link R&D costs from product prices. Proposals for a biomedical R&D treaty or the expanded use of innovation inducement prizes to replace product monopolies are particularly controversial, to the degree that they advance a de-linkage agenda. Paul Herrling's FRIND proposal was presented as the [International Federation of Pharmaceutical Manufacturers and Associations] alternative to reform proposals, and it was criticized in several areas… Whatever one thinks of the merits of the $10 billion Herrling proposal, it seems bizarre that Herrling would be asked to serve on the body that was asked to evaluate his proposal" (2011).

These statements not only voice hesitation about the membership of the CEWG, but more broadly reflect concerns that the WHO is failing to represent each member state and region in an equitable way. For nearly a decade the EWG and CEWG have recommended that there should be an international fund for health R&D that would sponsor the innovation of global health public goods. However, mandating contributions from every country and calling for pharmaceutical company contribution to the pot brings about negative pressure from the wealthiest and most powerful countries in the WHA as well as pharma lobbying groups. These groups have the political influence to hold up any proposal that they don't want to see passed, and they have clearly exerted their influence to halt any proposals resembling a treaty for R&D. Because the voluntary demonstration project fund fell short and left the proposal organizers to implement their projects without WHO support, there are still organizations, countries, and experts who insist that the only way to ensure we follow through on our economic, moral and human rights obligation to explore these proposals is through a global framework for an R&D fund. However, just recently, at the 68th World Health Assembly in Geneva, the suggestion was

voted down once more. More broadly, other experts in the field recognize that shortcomings in global R&D needs, including financing, coordination, leadership, and enforcement, reflect general trends international health. As such, there are proposals for an overarching Framework Convention on Global Health to address these needs (Gostin & Freidman, 2013). This potential solution would have an immense impact on health innovation, and could also address reform the global health system in a way that had cumulative effects for all of the barriers that impede access to medicines.

The groups who have experience working at the WHO are unsurprised that no such frameworks have been passed yet, but insist that this is how things happen, that they will continue to advocate for such a fund, and that in a few years they might succeed. As explained earlier, DNDi perceives its role as demonstration project finalists as a means to this end. Even those who remain optimistic agree that the WHO is failing to provide the financing and coordination it recognizes is necessary to address a very serious market failure. A lot of this trouble comes out of the budget-cuts that the WHO has suffered- if they had the financial ability to support these efforts, it seems as though they would. Overall, the type of policy solution that the Framework represents has a lot of potential benefits, and would likely make the work of DNDi much more efficient and stable. However, the downside to relying on policy reform is that the political situation at the current moment is highly unfavorable to the type of progressive changes that DNDi is calling for.

4.3.3 New Obstacles Moving Forward

As DNDi and other PDPs fill in weak pipelines and overcome market failures to produce innovations for global health, there are a number of barriers that come up farther down the

timeline of access. While the focus of this paper is on drug development, it is important to note the ways in which poor regulatory pathways, technology transfer efforts, demand forecasting and procurement strategies, and health systems all mediate the actual effect of new innovation on patient lives. PDPs such as DNDi are starting to tackle these emerging obstacles as they come up to them, as evidenced by DNDi's technology transfer agreements and efforts to work with the WHO on prequalification and registration of essential medicines. However, the impact of these activities would be even greater is, for example, national health systems were better equipped to procure and distribute locally produced products, or if regulatory capacities were streamlined at the international level. Ultimately, it seems beyond the scope of PDPs to take on solving these problems, but it is important that they are aware of the increasing relevance of these issues to their mission, and that they be creative about how to mitigate the effects of these challenges on their own efforts.

4.4 Conclusions

This evaluation of how a PDP model can fit into larger efforts of addressing market failures in global health suggests that DNDi is an effective and important part of the solution. Overall, the PDP model helps mitigate the concerns and risks for different partners that are essential to the drug development process, and by lowering barriers to entry for potential contributors ensures that their expertise is utilized for this cause. PDPs also allow for and coordinate collaboration, ultimately increasing the efficiency of the drug development timeline and leveraging the strengths of different partners to achieve the most rapid outcomes. Finally, the PDP model ensures a holistic pipeline approach rather than being limited to a single portfolio. These efforts de-link the cost of final products from R&D expenditures by recruiting

diverse funding sources rather than relying on retroactive cost recuperation via the exercise of IP rights. All in all, this has resulted in several product approvals and brighter future outlook for NTDs at a reduced cost as compared to traditional pharmaceutical innovation.

DNDi specifically offers unique capacity to address the needs around NTD drug development. Their commitment to the most neglected diseases is an important characteristic when considering the immense need and human rights considerations for these vulnerable populations. Furthermore, DNDi has been a success story in terms of delivering short-term therapeutic improvements as well as growing a strong pipeline for the future.

The past decade has seen an increase in resources devoted to R&D from a larger number of partners. There are more open models for innovation and new incentive mechanisms, which have resulted in a stronger pipeline for NTDs than ever before. That being said, the success of PDPs is highly contingent on political climate; in the future, increased support from governments could radically increase the impact that PDPs are able to have, whereas lack of interest could stifle their abilities. One DNDi policy brief on why an R&D convention is needed summarizes a point that cannot be ignored: "Successes have emerged from this trend, but they are by and large individual and limited advancements that would have greater overall impact if they were part of a coordinated framework for R&D" (2012). Looking ahead, it is important that DNDi not just consider what ideas are out there that might address the market failure around innovation for NTDs, but how to garner political will around the idea of creating a system designed to meet the health needs of everyone. With this is mind it makes sense to consider the actions of the World Health Organization, the international authority on global health. Although at present there are criticisms about the strength of the WHO and its bureaucratic nature, they have achieved incredible success in global health in the past and there is no other international agency poised to

be able to coordinate health R&D. It seems reasonable to hope that persistent and meaningful advocacy will prompt the organization to become a leader in the area, and this should continue to be a priority for DNDi.

Although the WHO has done wonders for global health, it is clear that it is a highly political organization. Also, even though pharmaceutical companies provide lifesaving drugs for a lot of the world and even donate significant amounts to important causes, there is no question that they are financially motivated institutions. However, these basic realities about two very important players in the world of global health do not have to result in perpetual neglect for NTDs; it is wrong to think that the status quo is the only way forward. In fact, there are a lot of intelligent people negotiating various delinkage proposals that aims to consider the motivations of developed countries and industry while addressing the needs of the poor. PDPs are enacting these visions for delinkage, and if we dare to garner political will and funding to push these options further, we might discover a new, more inclusive path forward.

Appendix 1

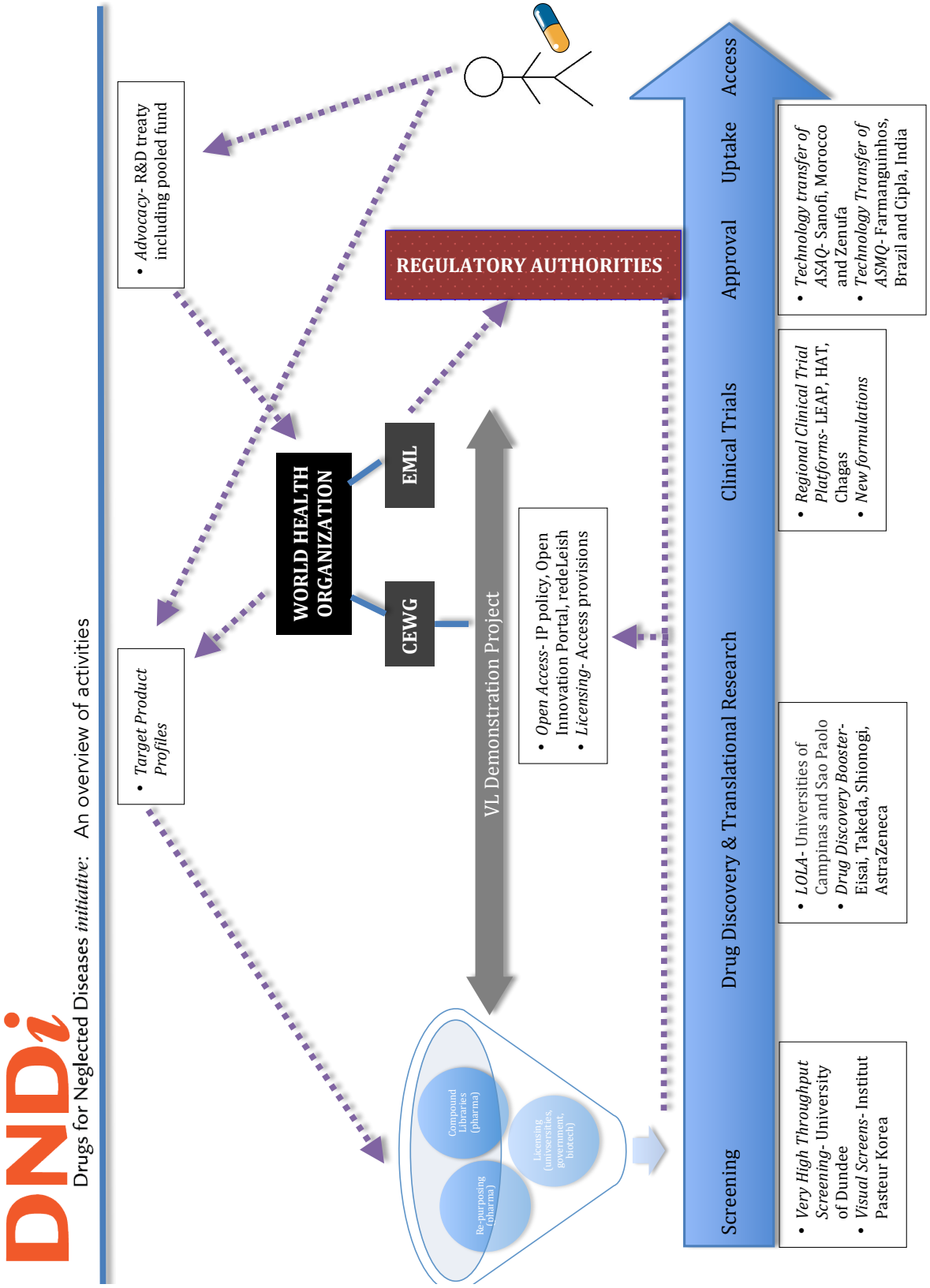
PDP	Mission	Revenue in 2014 (Adjusted to USD in 2014)	Funders (select examples)	Partners (select examples)	Projects/Strategies	Successes
Drugs for Neglected Disease Initiative (DNDi)	Innovate new drugs and formulations for communicable neglected tropical diseases (leishmaniasis, sleeping sickness, Chagas disease, malaria, helminths; recently added pediatric HIV, HCV, mycetoma)	36.5 million	Core funding: DFID, MSF, AECID, SDC, Rockefeller Foundation, Carlos Slim Foundation, Starr Foundation Portfolio funding: DGIS, AFD & MAEE, KFW & GTZ, Brazilian Ministry of Health Project funding: Gates Foundation, UNITAID, Wellcome Trust, European Union, Medicor Foundation, NIH/NIAID, Republic and Canton of Geneva, The Global Fund (See Appendix 4)	Founders: Institut Pasteur, Indian Council of Medical Research, Malaysia MOH, FIOCRUZ, WHO TDR (See Appendix 4)	Clinical trial platforms in endemic countries strengthen local capacity; NTD Drug Discovery Booster to increase molecule screening; strategic registration and access programs; participation in the WHO's health R&D demonstration projects	1 NCE approval (NECT for sleeping sickness); 5 new formulations approved (ASAQ and ASMQ for malaria, SSG&PM for VL in Africa, a pediatric dosage of benznidazol for Chagas, and a combination VL treatment for Asia); 15 NCEs in pipeline; 15 other pipeline products; 3 regional disease-specific clinical trial platforms (Leishmaniasis East Africa Platform, a HAT platform in Africa, and a Chagas platform in Latin America)
Medicines for Malaria Venture (MMV)	Discover, develop, and deliver new antimalarial medications	79.2 million	USAID, SDC, DGIS, Norad, DFID, World Bank, Irish Aid, NIH, AECID, Australian goverment, Rockefeller, Exxon Mobile Foundation, Novartis, Shin Poong, Guilin, Roll Back Malaria, Wellcome Trust, BHP Billiton, Newcrest Mining, MJC Amelior Foundation, Technology Innovation Agency, GHIT Fund, Merck Serono, UNITAID, Thailand NSTDA	Euratresim: Sigma-Tau Pyramax: Shin Poong Artesun: Guilin Coartem Dispersible: Novartis Transmission-blocking research: LSHTM, TropIQ, GSK, B&MGF Anti-relapse research: B&MGF, GSK *Over 300 partners in 50 countries	Working to improve medicines in order to combat resistance and prevent relapse; working to identify ways to block transmission of malaria; supports efforts to ensure access to artesunate over quinine therapies including finding generic manufacturers, mobilizing funding, and assisting in introduction studies; working with manufacturers to obtain WHO prequalification for essential products; scale-up of appropriate prevention methods among pregnant women	8 products in early-stage; 9 products in clinical trials; 4 antimalarial product approvals to-date; over 250 million courses of Coartem Dispersible have been given to children; 36 million vials of artesun injections have been given to treat severe malaria; 230 Malaria Boxes delivered to researchers to conduct further research on promising targets
PATH	Scale up international development, public health, and product development innovations; Within product development they aim to create vaccines, drugs, devices, diagnostics, systems and service innovations, especially for maternal and child health	305.5 million, about 55% of which goes toward product development as opposed to their other activites	Largest donor: B&MGF NIAID, Exxon Mobile, GHIT Fund, DFID	*More than 60 corporate partners Mosquirix: Janssen, NIH, HIV Prevention Trials Network for PreP; GSK and the Walter Reed Army Institute of Research MenAfriVac: Amyris, Inc. University of California, Berkeley; WHO Gates, and Serum Institute of India Other: BHP Billiton, Exxon Mobil, Medtronic, Sanofi, Microsoft, Merck, Tableau, Urbano	Global Health Innovation Hub promotes local innovation; started the Malaria Vaccine Initiative; created the Diarrhea innovations group; coordinates a symposium on cryptosporidium; runs a Center for Vaccine Innovation and Access; initiative for rice fortification	MenAfriVac meningitis vaccine has been delivered to over 235 million people; production of semisynthetic artemisinin to ensure sustainable production of antimalarials; river blindness diagnostic test; invented a Japanese encephalitis vaccine, CareHPV, Paromomycin Intramuscular Injection, Vaccine Vial Monitors, Woman's Condom, SoloShot, SILCS Diaphragm, Rapid Strip Test for Malaria, Non-Pneumatic Antishock Garment, Uniject with Hepatitis B Vaccine; 6 malaria vaccines in clinical development (Mosquirix is the most advanced malaria vaccine in development globally as it is in Phase III and promising results indicate protection): Phase 2 PreP formulation; Phase 1 trial for a novel rotavirus medication
International AIDS Vaccine Initiative (IAVI)	Develop a vaccine to prevent AIDS that is safe, effective, and acceesible thorughout the world	60 million	DFID, PEPFAR, Gates Foundation, Irish AID, NORAD, World Bank, NIH, B&MGF, GSK, BMS, BD Biosciences, Broadway Cares. Economic Development Corporation NYC, Google, Government of Japan, Hearst Foundations, Institut, Mériuex, Pendleton Charitable Trust, Spanish Ministry of Foreign Affairs, Indian Ministry of Science and Technology, Ministry of Foreign Affairs of the Netherlands, Robert Wood Johnson Foundation, Starr Foundation, United Airlines	HIV Translational Vaccines Discovery Program: Government of India's Translational Health Sciences and Technology Institute Neutralizing Antibody Consortium: Theraclone, Monogram Biosciences, NIAID's Vaccine Research Center, NIH Design Lab: NIH, Collaboration for Aids Vaccine Discovery of the B&MGF	Evaluates novel AIDS vaccine candidates at different labs including the AIDS Vaccine Design and Development Laboratory in New York, the IAVI Neutralizing Antibody Center at The Scripps Research Institute in California, the Human Immunology Laboratory at Imperial College in London, and the HIV Vaccine Translational Research Laboratory in New Delhi; works closely in endemic countries to build clinical research capacity while also engaging with communities and offering free HIV testing and counseling; ats as a policy analyst and advocate in the AIDS vaccines space; conducts R&D activities into neutralizing antibodies and replicating vecotrs	Established the Neutralizing Antibody Consortium leading to identification of conserved HIV targets and broadly neutralizing antibodies; coordinates a network of research labs in 5 African countries as part of the VISTA network; partner on 27 phase I/II trials; contributed to Kenya's National AIDS Strategic Framework, the WHO's Ebola task force, and impacted the UN's Sustainable Development Goals
TB Alliance	Develop beter, faster-acting, and more affordable TB drugs	45.9 million	Australian Aid, B&MGF, FDA, GHIT Fund, Indonesia Health Fund, Irish Aid, NIAID, Netherlands Ministry of Foreign Affairs, UKaid, UNITAID, USAID	Child-adapted medications: WHO, UNITAID, USAID, Stop TB, Macleods Pharmaceuticals NixTB: Janssen, Sizwe Hospital, TASK at Brooklyn Chest Hospital Screening: Daiichi Sankyo, Shionogi, Chugai, Daiichi Sankyo Novare, HyphaGenesis, Mitsubishi-Tanabe, OP-Bio, Sumitomo-Dainippon Compound libraries: GSK, Sanofi, Roche	Investigating multi-drug regimens to combat resistance; clinical trials on improvements to existing formulations; exploration of natural products as potential sources of promising compounds; joined the B&MGF TB Drug Accelerator	20 projects in the pipeline; 2 approved pediatric formulations; 5 clinical trials in phases 1-3; NixTB project is the world's first clinical trail for extensively drug resistant TB
FIND Diagnostics	Invent new diagnostic health solutions and link those tests to efforts to fight diseases of poverty (including TB, malaria, sleeping sickness, hepatitis C, Buruli ulcer, HIV, leishmaniasis, and Chagas)	31.4 million	B&MGF, DFID, KFW, PEPFAR, SDC, UNITAID, Global Fund, DGIS, WHO, UBS Optimus Foundation, JSI Research and Training, TI Pharma, Australian Department of Foreign Affairs, Stop TB Partnership, Canton of Geneva, NIH, government of Ireland, government of Australia, European Union, Paul G. Allen Family Foundation	MolBio, University of McGill, Mind, Titan, MSF Access Campaign, WHO, ReAct, TDR	Work across development, delivery, and implementation; ensures quality scale-up through lab-strengthening, quality assurance, and implementation; Support for Success program to build product development capacity in endemic countries; biomarker testing to distinguish bacterial from non-bacterial infections and reduce antimicribial resistance; shares samples for research and development from their specimen bank; clinical trial platform	11 new tests developed; strengthened specimen banks; developed new reagents; clinical trials and policy guidelines for 6 new TB tests and a new HAT rapid test; reformed WHO guidelines on malaria diagnosis

Innovative Vector Control Consortium (IVCC)	Discover new active ingredients that target disease vectors, especially malaria-transmitting mosquitoes, that will help create new formulations and mitigate the problem of insecticide resistance	15 million	B&MGF, DFID, USAID, SDC, UNITAID, Wellcome Trust	Agro-chemicals: Syngenta, Bayer, BASF, Sumitomo Chemical, DuPont, Dow NgenIRS: US President's Malaria Initiative, Abt Associates, PATH	NgenIRS to provide affordable indoor residual sprays to national control programs; evaluation of potential new paradigms for vector control; develop vector control tools; maintain a portfolio of active ingredients that could be developed into a new insecticide	Hundreds of thousands of molecules screened; 9 novel classes have been identified and will be moved into candidate selection; 2 new insecticide formulations have reached the market; Malaria Decision Support System to monitor and evaluate malaria control interventions; Insecticide Quantification Kit for quality-control; several testing sights have been brought up to industry standard for future involvement in clinical trials
International Partnership for Microbicides (IPM)	Fight the transmission of AIDS by developing microbicides that protect women in developing countries	28.9 million	B&MGF, Canadian International Development Agency, French Ministry of Foreign and European Affairs, AIDS Fund, Irish Aid, Flanders Department of Foreign Affairs, Norwegian Ministry of Foreign Affairs, OPEC Fund for International Development, Swedish Ministry of Foreign Affairs, Spanish Ministry of Foreign Affairs, UKaid, DFID, UNFPA, PEPFAR, World Bank, USAID, Swedish International Development Agency, Rockefeller Foundation, Netherlands Ministry of Foreign Affairs, German Ministry for Economic Cooperation and Development, DANIDA, Belgian Development Cooperation,	Manufacturing and analytical support: QPharma, Omnichem, Trelysit Product formulation: Particle Sciences, Inc.; Queens University- Belfast, Magee-Womens Research Institute, Oak Crest Institute of Science Preclinical evaluation: Huntingdon Life Sciences, ABL Inc., Tandem Labs Virology and compound screening: Imperial College Analytical support: PharmaVize, Microbiological Environments; Catelent, Parecal Clinical supply logistics: Penn Pharma; Almac; Fisher Clinical Services Scientific collaborations: CONRAD, Population Council, Inquest Biosciences, CHAARM, Advanced Biosciences Laboratory: Albert Einstein College of Medicine, Drexel University, Gynuity Health Projects Pharmaceutical licenses: Merck, Janssen, ViiV, BMS, Gilead Clinical research: MatCH, PHFVA, NDLOVU Medical Centre, Desmond Tutu HIV Foundation, MRC Uganda, Qhakaza Mbokodo, Madibeng Centre for Research	Empower and protect women by developing products that are discreet, safe, effective, and long-acting; incorporate contraceptive techniques into microbicide initiatives in order to address other reproductive health concerns	9 licenses for ARVs to distribute as microbicides to developing countries (5 non-exclusive licensises, 1 exclusive, royalty-free license, 1 exclusive worldwide rights agreement); Phase III studies of a slow-release vaginal ring for monthly use of one of these ARVs
Aeras	Develop new TB vaccines that are more effective and can be accessed by all who need them	49.7 million	Primary: B&MGF and European governments Other: NIAID, the NIH, GHIT Fund, pharmaceutical companies	Stage Gate criteria project: European TB Vaccine Initiative Clinical trials: China National Biotech Group, South African Tuberculosis Vaccine Initiative, European and Developing Countries Clinical Trials Partnership Clinical Development: GSK, Infectious Disease Research Institute, Statens Serum Institute, Dartmouth-Hitchcock Medical Center, Sanofi, NIAID Preclinical Development: Louis Picker of Oregon Health and Science University, Okairos	Develop TB vaccine criteria in collaboration with TB vaccine community; introduce innovative clinical trial designs; understand TB infection; advocacy and communications; expertise and advising across full spectrum of vaccine development	30 clinical trials completed; 13 vaccines in clinical development, a growing preclinical pipeline; improved animal models; improved vaccine capabilities including an exclusive license to vaccine technology from Vanderbilt to be used in the TB space; a "Stage Gate" decision-making criteria for global priority-setting
European Vaccine Initiative	Harmonize efforts among global stakeholders in vaccine development and develop effective, accessible, affordable vaccines against malaria and other diseases of poverty	842, 749	DANIDA, Irish Aid, KfW, DGS, Netherlands Organization for Scientific Research, Sida, DANIDA, EDCTP, Medical Research Council, B&MGF, GHIT Fund	Pregnancy Associated Malaria Project: Institut Pasteur, University of Copenhagen	Supports student working on EVI projects; exploring new vaccine technologies; clinical and preclinical development of vaccine candidates for diseases of poverty; harmonization efforts at the global level including projects such as EURHAVAC	Contributed to the development of 32 candidates in total, 16 of which reached Phase 1, 3 of which were transferred to partners and are undergoing further clinical development, 1 of which has reached phase 2; co-founder of the Malaria Vaccine Funders Group
Sabin Vaccine Institute	Develop vaccines for infectious and neglected tropical diseases (schistosomiasis, leishmaniasis, Chagas disease, ascariasis, trichuriasis, and severe acute respiratory syndrome- it is also the only vaccine development group targetting hookworm)	75.3 million	B&MGF, Accenture, GSK, The Hoffman Fund, Merck, the Inter-American Development Bank, Pfizer	AbbVie Foundation, Aeras, African Programme for Onchocerciasis Control, Aga Khan University, Agence de Medicine Preventive, American Public Health Association, Asian Development Bank, Association Society of Tropical Medicine and Hygiene, Bayer, College of Medicine, Bharat Biotech, B&MGF, Bio Farma, bioMerieux, BIRMEX, Blavatnik Family Foundation, Brazilian Society of Immunizations, Carlos Slim Foundation, Clinton Health Access Initiative, DNDi, Eisai, European Commission, Federal Ministry of Health of Nigeria, Gavi, GSK, GHIT Fund, Global Health Technologies Coalition, Indian Council of Medical Research, The Infectious Disease Research Institute, Institut Pasteur, LSHTM, Merck, Ministry of Health and Family Welfare of India, Brazilian Ministry of Health of Brazil, Novartis, OPEC Fund for International Development, Oxford Vaccine Group, PATH, Pfizer, RTI International, Sanofi Pasteur, Takeda, DFID, CDC, USAID, NIH, NIAID, UNICEF, Walter Reed Army Institute of Research, WASH Advocates, WaterAid, Wellcome Trust, World Bank, World Food Programme, WHO	Started the Global Network for Neglected Tropical Disease, provide funding for vaccine development and advocacy; builds capacity for vaccine introduction in endemic countries with ProVac; Sustainable Immunization Financing Program to help countries innovate sustainable financing solutions; Coalition against Typhoid promotes use of typhoid vaccine; education and advocacy amongst the global community; internal vaccine development activities	Started the International Association for Vaccine Managers; conducting clinical trials for schistosomiasis and hookworm vaccines; discovery of new potential target antigens for hookworm and ascariasis

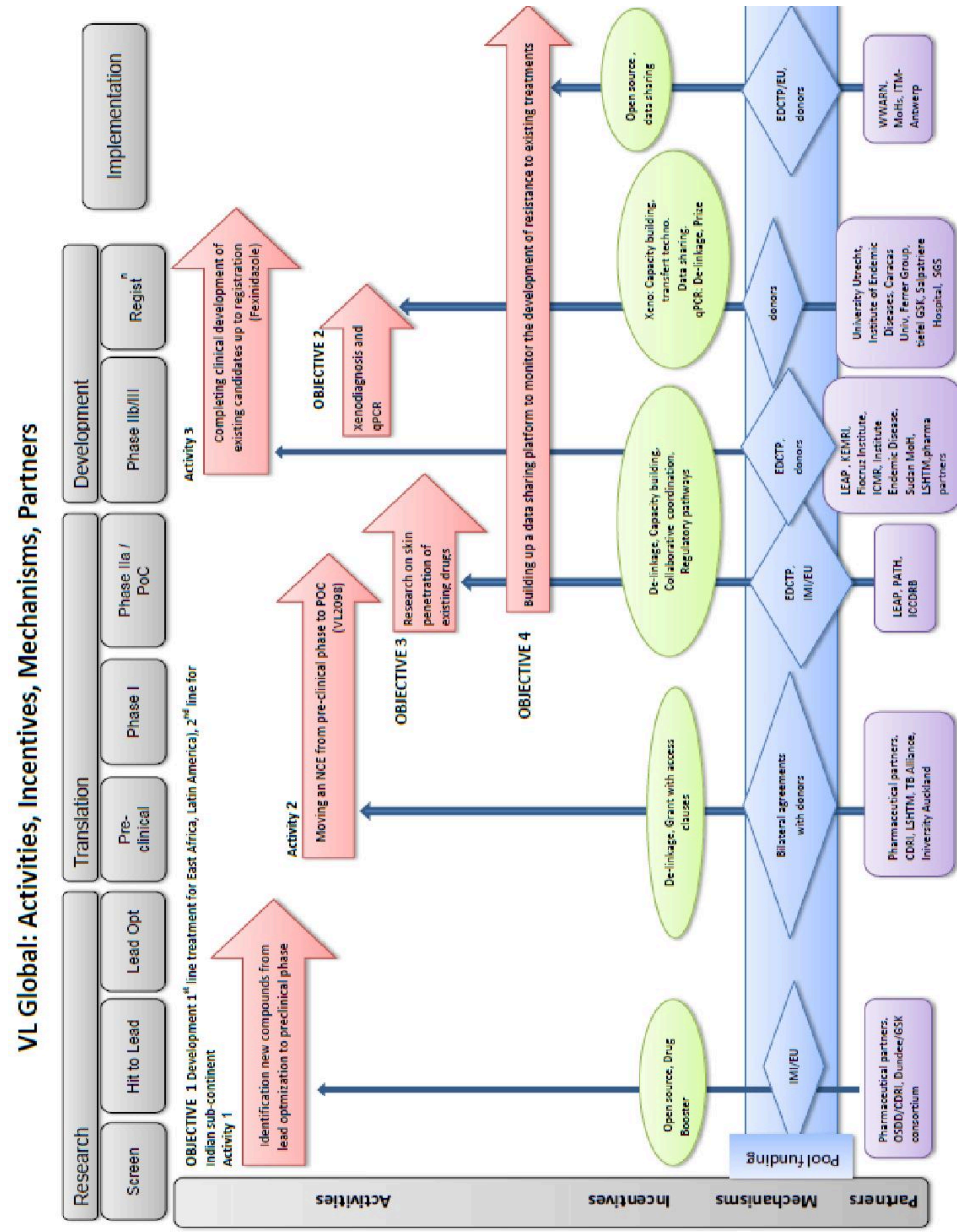
Infectious Disease Research Institute (IDRI)	Innovate vaccines, drugs, and diagnostics for global infectious diseases (such as leprosy, leishmaniasis, tuberculosis, malaria, HIV/AIDS, Chagas disease, pandemic flu and others)		22.5 million	B&MGF, NIH, Eli Lilly & Co., Paul G. Allen Family Foundation, Wellcome Trust, M.J. Murdock Charitable Trust, GSK, American Leprosy Missions, WHO, BARDA/DARPA, Other public/private partnerships	3M, Abbot Laboratories, Academia Sinica, Addis Ababa University, ADITEC, Aeras, Affigen Biologics, AIIMS, Amyris, Anvac, Anacor Pharmaceuticals, Anandaban Hospital, Athenese Dx, Banaras Hindu University, BARDA, Baylor College of Medicine, B&MGF, Bio-Rad, Bio Velo Test, Boston Children's Hospital, Brigham and Women's Hospital, Barnet Institute, Cantacuzino Institute, Case Western Reserve University, Cebu Leprosy and Tuberculosis Research Foundation, CDC, Chembio Diagnostics Systems, Duke University, Eli Lilly, European Vaccine Initiative, FIND, Imperial College London, Institute De Infectologia Emilio Ribas, NIH, LSHTM, NIAID, McGill University, MIT, Merck, FIOCRUZ, Pfizer, RTI International, Sabin Vaccine Institute, Sanofi Pasteur, Statens Serum Institute, Tel Aviv University, TDR, HIV Vaccine Consortium, Universidad Peruana Cayetano Heredia, Universidade de São Paulo, University of Banaras, University of California, University of Cape Town, University of Copenhagen, University of Delhi, University of Dundee, University of North Carolina, University of Virginia, USAID, Walter Reed Army Institute of Research, Wellcome Trust	Expertise in adjuvant and formulations development, antigen discovery and expression, clinical/regulatory support, diagnostic test development, drug discovery, GMP manufacturing, human immune monitoring, immunology, process sciences, quality assurance/quality control services, and vaccinology; Global Health Vaccine Center of Innovation project: new host-pathogen facility for drug discovery; manufacturing for pandemic preparedness	KalaazarDetect network for VL research; 10 leishmaniasis vaccine trials; over 13 million diagnostics used IDRI technology (for leishmaniasis, Chagas, and leprosy); undergoing 3 trials for TB vaccines; screened over 500,000 compounds against TB; one trial for pandemic flu under way
International Vaccine Initiative	Discover, develop, and ensure sustainable delivery of vaccines for infectious disease		22.9 million	Aeras, American Leprosy Mission, Army Research Office, BARDA, B&MGF, Eli Lilly Company, European Commission, FIND, Life Sciences Discovery Fund, MALTALEP, MJ Murdock Charitable Trust, New York Community Trust, NIH/NIAID, Novartis Foundation, Remala Foundation, Paul G. Allen Family Foundation, Renaissance Health Service Corporation, Sanofi Pasteur, Washington Research Foundation, The Wellcome Trust	Dengue Vaccine Initiative: Sabin Vaccine Institute, Initiative for Vaccine Research of the WHO, and International Vaccine Access Center Johns Hopkins University Cholera Vaccine Program: B&MGF, Sida, Republic of Korea	In-house basic and translational research; provide technical and field support to a network of collaborators for clinical trials; vaccine programs focused on cholera, enteric fever, dengue, Shigella, rotavirus, polio, and hepatitis E. Dengue Vaccine Initiative; Vi-based Vaccines for Asia Initiative; Typhoid Fever Surveillance in sub-Saharan Africa Program; Supporting Independent Immunizations and Vaccine Initiative Committees Program; Policy and Economic Research Unit	Inactivated oral cholera vaccine; technology transfer of typhoid vaccine production capabilities to Shantha Biotech; preclinical development of vaccine for enteric fever and typhoid/pneumonia
Population Council	Innovate new ways to help women have control over their family planning, protect people from HIV/AIDS, and empower young girls		84.3 million	USAID, B&MGF, NIH, CDC, DFID, NORAD, Sida, UNESCO, UNICEF, World Bank, WHO, FHI 360, Planned Parenthood, LSHTM, Marie Stopes, Nike Foundation, PATH, Population Services International, RTI, Kenyan Ministry of Health, government of Denmark, government of the Netherlands, United Nations Foundation, Bayer, B&MGF, Harvard School of Public Health, IBM, Plan International, Stanford, Yale	National AIDS strategies: USAID, Government of Tanzania, UNICEF, Tanzania Commission for AIDS, Ghana AIDS Commission, Government of India Other: Antares Pharma	Two journal publications (Population and Development Review and Studies in Family Planning); Center for Biomedical Research conducts basic science and does product development; clinical trials, product introduction, demographic research, implementation science research, policy analysis; looking for partners to license new products in development	3 models of a copper intrauterine device, Mirena intrauterine system; Jadelle & Norplant (implanted contraceptive devices); 170 million women worldwide using birth control with their technologies; Phase 3 trial microbicide; changed FDA policy on smoking while taking the pill; added contraceptive ring to WHO essential medicines list; dual action microbicide/contraceptive ring under development; vaginal ring to extend lactational amenorrhea; male contraceptive implant; contraceptive gel

AECID- Spanish Agency for International Development Cooperation
AFD- French Development Agency
B&MGF- Bill and Melinda Gate's Foundation
BARDA- US Biomedical Advanced Research and Development Agency
BMS- Bristol-Meyers Squibb
CDC- US Centers for Disease Control
DANIDA- Danish International Development Agency
DFID- UK Department for International Development
DGIS- Dutch Ministry of Foreign Affairs
EDCTP- European and Developing Countries Clinical Trials Partnership
FDA- US Food and Drug Administration
GHIT Fund- Global Health Innovative Technology Fund
GSK-GlaxoSmithKline
GTZ- German Agency for International Cooperation
KfW- German Development Bank
LSHTM- London School of Hygiene and Tropical Medicine
MAE- French Ministry of Foreign Affairs
MSF- Doctors Without Borders
NIAID- US National Institute for Allergy and Infectious Disease
NIH- US National Institute of Health
NORAD- Norwegian Agency for Development Cooperation
PEPFAR- President's Emergency Plan for AIDS Relief (US government)
SDC- Swiss Agency for Development and Cooperation
Sida- Swedish Development Agency
UNFPA- United Nations Population Fund
USAID- Unites States Agency for International Development
WHO (TDR)- World Health Organization (Research and Training in Tropical Diseases)

Appendix 2


DNDi
Drugs for Neglected Diseases *initiative*: An overview of activities
• *Advocacy*- R&D treaty including pooled fund
• *Target Product Profiles*
WORLD HEALTH ORGANIZATION
EML
CEWG
REGULATORY AUTHORITIES
VL Demonstration Project
• *Open Access*- IP policy, Open Innovation Portal, redeLeish
• *Licensing*- Access provisions
Compound Libraries (pharma)
Re-purposing (pharma)
Licensing (universities, government, biotech)
Screening
Drug Discovery & Translational Research
Clinical Trials
Approval
Uptake
Access
• *Very High Throughput Screening*- University of Dundee
• *Visual Screens*- Institut Pasteur Korea
• *LOLA*- Universities of Campinas and Sao Paolo
• *Drug Discovery Booster*- Eisai, Takeda, Shionogi, AstraZeneca
• *Regional Clinical Trial Platforms*- LEAP, HAT, Chagas
• *New formulations*
• *Technology transfer of ASAQ*- Sanofi, Morocco and Zenufa
• *Technology Transfer of ASMQ*- Farmanguinhos, Brazil and Cipla, India

Appendix 3


VL Global: Activities, Incentives, Mechanisms, Partners
Research
Translation
Development
Implementation
Screen
Hit to Lead
Lead Opt
Pre-clinical
Phase I
Phase IIa / PoC
Phase IIb/III
Regist n
OBJECTIVE 1 Development 1st line treatment for East Africa, Latin America), 2nd line for Indian sub-continent
Activity 1
Identification new compounds from lead optimization to preclinical phase
Activity 2
Moving an NCE from pre-clinical phase to POC (VL2098)
Activity 3
Completing clinical development of existing candidates up to registration (Fexinidazole)
OBJECTIVE 2
Xenodiagnosis and qPCR
OBJECTIVE 3
Research on skin penetration of existing drugs
OBJECTIVE 4
Building up a data sharing platform to monitor the development of resistance to existing treatments
Open source, Drug Booster
De-linkage, Grant with access clauses
De-linkage, Capacity building, Collaborative coordination, Regulatory pathways
Xeno: Capacity building, transfert techno. Data sharing; qPCR: De-linkage, Prize
Open source, data sharing
Pool funding
IMI/EU
Bilateral agreements with donors
EDCTP, IMI/EU
EDCTP, donors
donors
EDCTP/EU, donors
Pharmaceutical partners, OSDD/CDRI, Dundee/GSK consortium
Pharmaceutical partners, CDRI, LSHTM, TB Alliance, University Auckland
LEAP, PATH, ICCDRB
LEAP, KEMRI, Fiocruz Institute, ICMR, Institute Endemic Disease, Sudan MoH, LSHTM, pharma partners
University Utrecht, Institute of Endemic Diseases, Caracas Univ, Ferrer Group, tiefel GSK, Salpatriere Hospital, SGS
WWARN, MoHs, ITM-Antwerp
Activities
Incentives
Mechanisms
Partners

Appendix 4

PUBLIC INSTITUTIONAL DONORS

Department for International Development (DFID) / UNITED KINGDOM	Grant period: 2015 • Support to DND*i* initiative • Total amount: GBP 3 million Grant period: 2013-2018 • Support to DND*i* initiative • Total amount: GBP 30 million Grant period: 2014 • Support to DND*i* initiative • Total amount: GBP 3 million Grant period: 2009-2013 • Support to DND*i* initiative • Total amount: GBP 24.9 million Grant period: 2006-2008 • Support to DND*i* initiative • Total amount: GBP 6.5 million
Dutch Ministry of Foreign Affairs (DGIS) / THE NETHERLANDS	Grant period: 2015-2020 • Support to DNDi's disease programmes for human African trypanosomiasis (HAT), Chagas disease, leishmaniasis and mycetoma (from screening to clinical studies and implementation for new and improved products). • Total amount: EUR 16 million Grant period: 2011-2014 • Support to DNDi's disease programmes for human African trypanosomiasis (HAT), Chagas disease, and leishmaniasis (from screening to clinical studies and implementation for new and improved products). • Total amount: EUR 14 million Grant period: 2006-2010 • Support to DND*i* malaria project (FACT) • Total amount: EUR 2.9 million
European Union – Framework Programme 5 and 6	Grant period: 2004-2006 / 2006-2009 • Support to DND*i* malaria project (FACT) / to the Human African Trypanosomiasis Platform • Total amount: EUR 241,300 / EUR 340,000
European and Developing Countries Clinical Trials Partnership (EDCTP) / EUROPE	Grant period: 2010-2014 • Support to clinical studies for the assessment of the fixed-dose combination of ASMQ as an alternative antimalarial treatment for children in Africa • Total amount: EUR 577,900
European Union – Framework Programme 7	Grant period: 2009-2012 • Support to LEISHDNAVAX – Development of a DNA vaccine for visceral leishmaniasis • Total amount: EUR 253,800 Grant period: 2013-2016 • Support to AfriCoLeish – Development of a care package for treatment and control of visceral leishmaniasis in East Africa • Total amount: EUR 3 million

Federal Ministry of Education and Research (BMBF) through KfW / GERMANY and part of the EDCTP2 programme supported by the European Union	Grant period: 2011-2015 • Support to DNDi's disease programmes for human African trypanosomiasis, Chagas disease, leishmaniasis and filarial diseases (from screening to clinical studies for new and improved products as well as capacity strengthening activities through the disease platforms) • Total amount: EUR 9.1 million (including supplemental of EUR 1.1 million for 2015)
French Development Agency (AFD) / FRANCE	Grant period: 2015 – 2018 • Support to specific projects on visceral leishmaniasis in Africa • Total amount : EUR 2 million Grant period: 2012-2017 • Support to specific projects in Africa: technology transfer of ASAQ for Malaria, clinical trials for ASMQ (Malaria), development of a new oral treatment for human African trypanosomiasis (HAT), support to the HAT Platform and development of a new paediatric formulation of HIV • Total amount : EUR 5 million Grant period: 2006-2010 • Support to DND*i* malaria project (FACT) • Total amount : EUR 2 million
Global Fund To fight AIDS, Tuberculosis and Malaria / INTERNATIONAL	Grant period: 2010-2012 • Support to the Baseline and Endpoint Survey Work for the Independent Evaluation of Phase 1 of the Affordable Medicines Facility – malaria (AMFm) in Ghana • Total amount: EUR 532,800
Global Health Innovative Technology (GHIT) / JAPAN	Grant period: 2015-2016 • Support to lead optimization for visceral leishmaniasis and the Drug Booster • Total amount: EUR 3.75 million Grant period: 2013 • Support to screening activities • Total amount: USD 158,000 Grant period: 2014-2015 • Support to DNDi Chagas disease programme in joint collaboration with Eisai (E1224 combination study & benznidazole) • Total amount: EUR 2.8 million
GiZ on behalf of the Government of the Federal Republic of Germany / GERMANY	Grant period: 2008–2009 • Support to specific discovery, preclinical/clinical projects (screening, lead optimisation for Chagas disease, Fexinidazole for human African trypanosomiasis) • Total amount: EUR 1 million
Ministry of Foreign and European Affairs (MAEE) / FRANCE	Grant period: 2009-2011 • Support to specific discovery and lead optimisation projects for human African trypanosomiasis, Chagas disease, and leishmaniasis • Total amount: EUR 1.3 million Grant period: 2007-2010 • Support DNDi's disease programmes for human African trypanosomiasis and visceral leishmaniasis in Africa (preclinical, clinical and implementation

	activities and capacity building.) • Total amount: EUR 5.9 million
Ministry of Health / BRAZIL	Grant period: 2013-2015 • Support to DND*i* initiative, Chagas disease & Leishmaniasis • Total amount: BRL 995'000 (EUR 324'900)
Brazilian Development Bank (BNDES) / BRAZIL	Grant period: 2016-2018 • Support to DND*i* initiative, Chagas disease (Lead Optimisation Latin America programme – LOLA, Chagas Clinical Research Platform) and visceral leishmaniasis • Total amount: EUR 1 million
National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID) / UNITED STATES OF AMERICA	Grant period: 2010-2013 • Support to preclinical activities (K777 project) for Chagas disease • Total amount: USD 1.2 million Grant period: 2007-2012 • Support to Amphotericin B Polymer project for visceral leishmaniasis • Total amount: USD 1.5 million
The Norwegian Agency for Development Cooperation (Norad) / NORWAY	Grant period: 2013-2015 • Support to DNDi's disease programme for human African trypanosomiasis • Total amount: NOK 15 million
Region of Tuscany / ITALY	Grant period: 2007-2008 • Support to the development of SSG&PM (Paromomycin project) and capacity strengthening for visceral leishmaniasis • Total amount: EUR 200,000
Republic and Canton of Geneva, International Solidarity Office / SWITZERLAND	Grant period: 2013-2015 • Support to HAT (human African trypanosomiasis) activities • Total amount: CHF 500,000 Grant period: 2010-2012 • Support to the implementation of NECT (NECT-Field project) for human African trypanosomiasis • Total amount: CHF 600,000 Grant period: 2004-2009 • Support to the development of SSG&PM (paromomycin project) for visceral leishmaniasis • Total amount: CHF 1 million
Ruta-N / City of Medellin / COLOMBIA	Grant period: 2015-2016 • Support to DND*i* cutaneous leishmaniasis programme (Anfoleish) • Total amount: USD 317'500 (EUR 269'365)
Science and Technology Innovation Agency (FINEP) / BRAZIL	Grant period: 2015 • Support to DND*i'* s activities through the "Award for Innovation in Social Technology"

	• Total amount: EUR 67'000
Spanish Agency for International Development Cooperation (AECID) / SPAIN	Grant period: 2007-2012 • Support to DND*i* initiative • Total amount: EUR 12 million
Swiss Agency for Development and Cooperation (SDC) / SWITZERLAND	Grant period: 2013-2016 • Support to DND*i* initiative • Total amount: CHF 8 million Grant period: 2012-2013 • Support to DND*i* Malaria programme • Total amount: CHF 900,000 Grant period: 2010-2012 • Support to DND*i* initiative • Total amount: CHF 4 million Grant period: 2005-2006 • Support to DND*i* Malaria programme • Total amount: CHF 120,000
UNITAID	Grant period: 2013 – 2016 • Total amount: USD 17.3 million • Support to the development of child-adapted antiretroviral (ARV) formulation
United States Agency for International Development (USAID) / USA	Grant period: 2014 – 2019 • Support to the DND*i*"s portfolio on filarial diseases • Total amount: USD 10 million
World Health Organization/TDR (WHO/TDR)	Grant period: August 2015 – August 2016 • Support to the DND*i*"s Demonstration Projects on leishmaniasis (VL; CL) • Total amount: EUR 2,3 million

PRIVATE DONORS

Bill & Melinda Gates Foundation / UNITED STATES OF AMERICA	Grant period: 2015 – 2019 • Total amount: USD 60 million • Portfolio funding for human African trypanosomiasis (HAT), filarial diseases and visceral leishmaniasis Grant period: 2014-2016 • Total amount: USD 1 million • Support to DNDi activities through the "Innovative Fund Award" Grant period: 2011-2015 • Total amount: USD 9 million • Support to the adoption and implementation of new treatment options for visceral leishmaniasis in Asia

	Grant period: 2011-2014 • Total amount: USD 4.3 million • Support to the pre-clinical development of a macrofilaricidal drug candidate (flubendazole) for filarial diseases Grant period: 2011-2013 • Total amount: USD 2 million • Support to screening for neglected tropical diseases Grant period: 2013-2015 • Total amount: USD 2.3 million • Support to identify new drug candidate for filarial diseases (supplemental grant to the grant to support screening for NTDs) Grant period: 2009-2014 • Total amount: USD 19.4 million • Support to the clinical development of fexinidazole for human African trypanosomiasis Grant period: 2007-2012 • Total amount: USD 27.2 million • Support to lead optimisation, preclinical and start of clinical activities for human African trypanosomiasis/visceral leishmaniasis
Médecins Sans Frontières (Doctors without Borders) / INTERNATIONAL	Grant period: 2014-2018 • Total amount: EUR 20 million • Support to DND*i* initiative Grant period: 2009-2013 • Total amount: EUR 18.4 million • Support to DND*i* initiative Grant period: 2003-2008 • Total amount: EUR 25 million • Support to DND*i* initiative
Médecins Sans Frontières (Doctors without Borders) / ITALY	Grant period: 2010-2011 • Total amount: EUR 600,000 • Support to the development and registration of the paediatric dosage form of benznidazole for Chagas disease Grant period: 2009 • Total amount: EUR 100,000 • Support to DND*i* malaria project (FACT) – study in Liberia with ASAQ
Médecins Sans Frontières (Doctors without Borders) / NORWAY	Grant period: 2011-2013 • Total amount: EUR 1,135,000 • Support to R&D for paediatric HIV programme Grant period: 2010 • Total amount: EUR 165,000 • Support to R&D opportunities for filarial diseases and paediatric HIV programmes
Médecins Sans Frontières (Doctors without Borders) / BRAZIL	Grant period: 2011-2012 • Total amount: R$ 1 million • Support to the development and registration of the paediatric dosage form of benznidazole for Chagas disease

The Wellcome Trust / UNITED KINGDOM	Grant period: 2011-2014 • Total amount: EUR 1,999,801 • Support to the Phase II clinical trial of E1224 for Chagas disease Grant period: 2012-2015 • Total amount: USD 3,000,000 + USD 85'182 as supplemental funding • Support to a study to validate PCR and other biomarkers for Chagas disease

PRIVATE FOUNDATIONS AND PRIVATE INDIVIDUAL DONORS

UBS Optimus Foundation / SWITZERLAND	Grant period: 2013- 2016 • Total amount: CHF 750,000 • Support to Pediatric HIV – "Developing drug granules for children with HIV and TB" Grant period: 2006-2009 • Total amount: CHF 1,080,000 • Drug development for Chagas disease and Human African Trypanosomiasis Grant period: 2005 • Total amount: CHF 170,000 • Drug development for Chagas disease and Human African Trypanoyomiasis
Carlos Slim Foundation (through the Carlos Slim Health Award) / MEXICO	Grant period: 2013 • Total amount: USD 100,000 • Support to Chagas programme
Rockefeller Foundation (through the "Next Century Innovators Award") / USA	Grant period: 2013 • Total amount: USD 100,000 • Support to DND*i* initiative
BBVA Foundation (through the "Frontiers of Knowledge Award in Development Cooperation") / SPAIN	Grant period: 2012 • Total amount: EUR 400,000 • Support to DND*i* initiative
Medicor Foundation / LIECHTENSTEIN	Grant period: 2009-2013 • Total amount: USD 2.3 million • Support to VL programmes in Africa Grant period: 2009-2013 • Total amount: USD 2.3 million • Support to VL programmes in Africa Grant period: 2007 • Total amount: EUR 650,000 • Support to VL programmes in Africa

Other Private Foundations and Private Individual Donors:
Brian Mercer Charitable Trust, UK
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Leopold Bachmann Foundation, Switzerland

Marsha Fanucci, United States of America
Médecins Sans Frontières (Doctors Without Borders), International
Medicor Foundation, Liechtenstein
Moreau Family, Brazil
The Peter and Carmen Lucia Buck Foundation, United States of America
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Bennett Shapiro and Fredericka Foster, United States of America
Starr International Foundation, Switzerland
UBS Optimus Foundation, Switzerland
United States Agency for International Development (USAID), via the 4th Sector Health Project implemented by Abt Associates, Inc.
Wellcome Trust, United Kingdom
Wellspring Advisors, United States of America
Other private foundations and individuals who would like to remain anonymous

PHARMACEUTICALS	Projects	Description
AbbVie (formerly Abbott)- USA	Flubendazole Macrofilaricide (Helminth) / Screening	Since February 2009, compounds provider for research on Chagas disease, HAT, and leishmaniasis and since 2011, formulation development and toxicology studies for helminth infections.
Astellas Pharma Inc.- Japan	Screening	Since June 2012, DND*i* partner for drug discovery, provider of compounds for screening activities for leishmaniasis, Chagas disease, and sleeping sickness.
Astra Zeneca- Sweden	Screening	Since 2012, DND*i* discovery partner. Since 2013, DND*i* partner for screening.
Bristol Meyers Squibb- USA	Screening	Since August 2012, DND*i* partner for screening and testing in the field of visceral leishmaniasis.
CIPLA- India	ASMQ (Malaria) / Two 4-in-1 LPV/r-based fixed-dose combinations (Paediatric HIV)	Since January 2007, DND*i* partner against malaria, by developing and producing the combination of the product (ASMQ) as well as file application, registration and distribution in endemic countries at cost (in the public sector). Since 2012, DND*i* partner for the development and registration of two solid taste-masked LPV/r-based fixed-dose formulations, also known as the 4-in-1s.
Debiopharm- Switzerland	Discovery	Material transfer agreement, beginning April 2011, for discovery activities.
E.I du pont Nemours- USA	Screening	Since June 2012, DND*i* partner for screening of compounds against helminths and kinetoplastids.
Eisai- Japan	Azoles E1224 & Biomarker (Chagas) / Screening	Since September 2009, DND*i* partner through collaboration and license agreement on clinical studies for Chagas disease using the E1224 compound. Eisai has the option of becoming a pharmaceutical partner for manufacturing and distribution.

Farmanguinhos (Fiocruz)- Brazil	ASMQ (Malaria)	Since 2006, various agreements for production and distribution of ASMQ at cost in endemic countries.
GILEAD- USA		Since 2008, donation program of Ambisome® for clinical studies on VL.
GNF Novartis, Genomics Institute of the Novartis Research Foundation- USA	Screening	Since October 2009, DND*i* partner for discovery phase on kinetoplastids.
GSK, Tres Cantos, Open Lab Foundation- Spain	Screening	Since May 2006, various partnerships through screening, discovery activities, and clinical trials for CL.
Humax Pharma- Colombia	Anfoleish	Since 2011, partner for pre-clinical research on CL.
Janssen Research & Development, LLC- Belgium	Flubendazole (Filarial diseases)	Since September 2013, DND*i* partner for discovery and pre-clinical activities for flubendazole.
LAFEPE, Laboratorio Farmacêutico do Estado de Pernambuco- Brazil	Paediatric Benznidazole (Chagas)	Since June 2008, Preclinical agreement and collaboration agreement for Chagas disease: to manufacture the paediatric formulation of benznidazole.
Merck & Co.- USA	Screening	Since 2008, Merck granted access to compounds through a non-exclusive, worldwide license, for research on NTDs.
Novartis Centre de Recherche Santé Animale S.A.- Switzerland	Screening & Lead Optimization	Since November 2013, DND*i* partner for screening and lead optimization activities on filarial diseases.
Paladin Labs- Canada	New VL treatments- Africa	Since 2009, Paladin Labs provides miltefosine for clinical studies on VL in Eastern Africa.
Pfizer Limited- UK	Screening & Lead Optimization	Since 2004: material transfer agreement to provide amodiaquine for ASAQ; 2009, research and license agreement to access compound libraries. Since 2012, DNDi lead optimization partner (access to series identified out of a Pfizer screening).
Sanofi and affiliates- France	ASAQ (Malaria) / Fexinidazole (HAT) / Screening	Since 2004, DND*i* partner through manufacture, registration, and distribution partner for ASAQ in endemic countries. Since January 2011, R&D license agreement to allow research and development on various NTDs, aiming to provide affordable treatments in endemic countries of low -middle income economies and Latin America. More specifically, Sanofi partners with DND*i* on Fexinidazole clinical studies for HAT. Since November 2012, DND*i* partner for capacity strengthening and technology transfer to Tanzania in the field of malaria.
TAKEDA Pharmaceutical Company Limited- Japan	Screening	Since June 2013, DND*i* partner for screening.
Zenufa Laboratories Ltd– Tanzania	ASAQ (Malaria)	Since March 2011, recipient of DND*i*'s technology transfer of ASAQ. Partner for manufacture and distribution.

BIOTECHS		
Anacor- USA	Oxaborole backup (HAT) / Oxaborole SCYX-7158 (HAT) / Screening	Since December 2007, DND*i* partner through research collaboration and license agreement to provide compounds of the oxaborole class for

		research on HAT, VL-CL, and Chagas disease.
Celgene- USA	Screening	Material transfer agreement since 2011 for screening on HAT, Chagas disease, and Leishmaniasis. Since 2014, DND*i* partner for screening.
Genzyme biotechnology company part of the Sanofi group- USA		Material transfer for research and development on HAT, Chagas disease, and Leishmaniasis.
Evolva- Switzerland	Discovery	Since 2008, DND*i* partner in discovery for kinetoplastids.
iThemba- South Africa	Lead Optimization	Since 2012, lead optimization partner.
Polytherics- UK		Since October 2006, DND*i* partner on formulation of amphotericin B, in collaboration with Imperial College.
Scynexis- USA	Oxaborole SCXY-7158 (HAT) / Lead Optimization	Since December 2005, DND*i* partner through screening and material transfer for research and development on kinetoplastids.
Sequella, Inc- USA	Screening	Since February 2015, material transfer agreement for screening on kinetoplastids.
Vertex- USA	Screening	Since January 2010, DND*i* partner through material transfer agreement for R&D, in the field of kinetoplastids.

UNIVERSITIES		
Addis Ababa University- Ethiopia	Fexinidazole (VL) / HIV/VL / New VL treatments (Africa) / SSG&PM (VL in Africa)	Leishmaniasis East Africa Platform (LEAP) partner. Since April 2005, clinical trial partner for leishmaniasis.
Antwerp University, Laboratory of Microbiology, Parasitology and Hygiene (LMPH)- Belgium	Lead Optimization	Since June 2006, DND*i* partner for screening and discovery activities.
Baylor College of Medicine- USA		Since August 2013, works with DND*i* on study of seroprevalence of Chagas in USA.
Bonn University Hospital, Institute of Medical Microbiology, Immunology and Parasitology- Denmark		Since December 2012, DND*i* partner for testing of repurposed compounds in animal models for filarial infections.
Brasilia University- Brazil	New VL treatments (Latin America)	Since 2004, DND*i* partner through research and development license agreement on HAT, and Leishmaniasis.
FAPUNIFESP, Fundaçao de Apoio Universidade Federale de Sao Paolo- Brazil		Since March 2009, DND*i*partner in the field of Chagas disease.
Gondar University Hospital- Ethiopia	HIV/VL / New VL treatments (Africa)	Leishmaniasis East Africa Partner (LEAP) partner. Since March 2005, DND*i* partner for clinical trials for VL.
Imperial College- UK		Since October 2006, DND*i* partner on formulation of amphotericin B with Polytherics.
London School of Pharmacy- UK		Since October 2006, partner on formulation of amphotericin B, in collaboration with Imperial College.
LSHTM, London School of	HIV/VL / Lead	Since January 2005, DND*i* partner for screening,

Hygiene and Tropical Medecine- UK	Optimization / New VL treatments (Africa) / New VL treatments (Asia) / Nitroimidazole backup (VL) / VL-2098 / Biomarkers (Chagas) / Screening & Lead Optimization	clinical trials and discovery. Since November 2013, works with DND*i* on comparison of benznidazole and posaconazole for Chagas disease.
Makerere University and Amudat Hospital- Uganda	New VL treatments (Africa)	Since November 2008, DND*i* partner for clinical trials for VL.
McGill University- Canada	Biomarkers (Chagas)	Since January 2014, DND*i* partner for pre-clinical work on Chagas disease.
Michigan State University- USA	Flubendazole Macrofilaricide (Filarial diseases)	Since 2011, DND*i* pre-clinical research partner for helminth infections.
Monash University, Centre for Drug Candidate Optimization	Fenarimol series (Chagas) / Nitroimidazole (Chagas) / Lead Optimization	Since July 2008, DND*i* partner through a technical agreement for Chagas disease.
Murdoch University, School of Veterinary and Biomedical Science- Australia	Fenarimol series (Chagas) / Nitroimidazole (Chagas) / Lead Optimization	Since August 2006, technical agreement, and since July 200, R&D agreement on Chagas disease.
Pace University- USA	Nitroimidazole backup (HAT) / Oxaborole backup (HAT) / Lead Optimization	Since April 2007, DND*i* partner for pre-clinical studies in the field of HAT.
Stellenbosch University- South Africa	"Superboosting" – TB/HIV	Since November 2012, DND*i* partner for clinical trials in the field of HIV/TB.
UCSF, University of California, San Francisco- USA	K777 (Chagas) / RTV Superbooster for HIV/TB co-infection (Paediatric HIV)	Since January 2011, DND*i* partner for pre-clinical studies on Chagas disease. Since April 2014, works with DND*i* on clinical analysis for the RTV Superbooster project.
University of Antoquia, PECET, Programme for the study and control of tropical diseases- Colombia	Anfoleish	Since 2011, DND*i* partner on pre-clinical studies for CL.
University of Auckland- New Zealand	SCYX-2035811 / Nitroimidazole backup (VL) / VL-2098 / Lead Optimization	In 2009, DND*i* partner for HAT, and since 2010, partner on VL.
Universidade Estadual de Campinas UNICAMP- Brazil	Lead Optimization	Since July 2013, DND*i* partner for lead optimization in the field of Chagas disease and leishmaniasis.
Universidad Mayor de San Simon- Bolivia	Azoles E1224 & Biomarker (Chagas)	DND*i* partner for clinical trials for Chagas disease.
University of North Carolina, Office of Technology Development- USA		Since 2007, DND*i* partner through information sharing and discovery for NTDs.
Universidade Ouro Preto- Brazil	Fenarimol series (Chagas) / Nitroimidazole (Chagas) / Lead Optimization	Since April 2005, DND*i* partner in the field of Chagas disease through discovery and R&D agreement.

University of Oxford, Worldwide Antimalarial Drug Resistance Network- UK	ASAQ (Malaria) / ASMQ (Malaria)	Since October 2009, DND*i*partner through data collection on malaria.
University Sains- Malaysia	ASAQ (Malaria) / ASMQ (Malaria)	Since April 2004, DND*i* partner on malaria.
Utrecht University- The Netherlands	VL-0208 (Africa)	Since 2009, DND*i* partner for clinical trials for VL.

UNIVERSITY "SPIN-OFF"		
Epichem- Australia	Fenarimol series (Chagas) / Nitroimidazole (Chagas) / Lead Optimization	Product and service provider in synthetic and medicinal chemistry to the drug discovery and pharmaceutical industries. Since 2008, provides medicinal chemistry lead optimization for series on kinetoplastids.
Eskitis, The Eskitis Institute for Cell and Molecular Therapies. Griffith University- Australia	Lead Optimization	Since 2009, partner on drug discovery for HAT. Setup and validation of in *vitro* assays.

RESEARCH INSTITUTES		
Broad Institute, MIT and Harvard- USA	Fenarimol series (Chagas) / Nitroimidazole (Chagas) / Lead Optimization	Since September 2010, DND*i* partner through discovery activity for Chagas disease.
CRESIB, Centre de Recerca en Salut Internacional de Barcelona- Spain	Azoles E1224 & Biomarker (Chagas)	Since September 2010, DND*i* partner for the clinical phase for Chagas disease.
FIPEC: Fundacion Para el Estudio de las Infecciones Parasitarias y enfermedad de Chagas- Argentina		Since 2010, DND*i* partner on clinical studies for Chagas disease.
Georges Institute for International Health- Australia		Since May 2009, DND*i* partner through research.
IMEA Consulting France : Institut de Médecine et d'Epidémiologie Appliquée, Département de Santé Tropicale- France		Since January 2010, DND*i* partner for clinical phase of ASAQ (malaria).
IEND, Institute of Endemic Disease, Khartoum University- Sudan	Fexinidazole (VL) / VL-0208 / SSG&PM (VL in Africa)	Leishmaniasis East Africa Platform(LEAP). Since December 2004, DND*i* partner for clinical trials for VL patients.
Ifakara Health Institute- Tanzania	ASMQ (Malaria)	Since June 2012, DND*i* partner for clinical studies on ASMQ against malaria.
IRD, Institut de Recherche pour le Développement- France	ASAQ (Malaria)	Since 2007, various partnerships on VL and currently partner for clinical trials of ASAQ (malaria).
Institut Pasteur- France		Since December 2008, discovery and screening partner for leishmaniasis.
Institut Pasteur Korea-Korea	Fenarimol series (Chagas)/Nitroimidazole (Chagas)/Screening & Lead Optimization	Since April 2008, DND*i* partner on Chagas disease and leishmaniasis for high throughput screening and discovery activities.
Institut René Rachou IdP- Brazil	New VL treatments (Latin America)	Since October 2007, DND*i* partner for pre-clinical studies for VL.
Institute of Tropical Medicine- Belgium	VL-0208 / HIV/VL	Since September 2006, DND*i* partner for HAT, malaria and since May 2011, partner for clinical trials on VL, and HIV co-infected patients). Since

		September 2012, DNDi partner and supplier of reagents and accessories for diagnostic tests in the clinical phase of fexinidazole against sleeping sickness.
KEMRI, Kenya Medical Research Institute- Kenya	ASAQ (Malaria) / ASMQ (Malaria) / Fexinidazole (VL) / VL-0208 / SSG&PM (VL in Africa)	Since January 2005, various partnerships for clinical trials of malaria (ASAQ and ASMQ) as well as VL.
KIT, Koninklijk Instituut voor de Tropen- Netherlands	Fexinidazole (VL)	Since January 2014, DND*i* partner for PD analysis on the fexinidazole VL study.
Medical Research Council (MRC), publicly-funded organization- UK	Two 4-in-1 LPV/r-based fixed-dose combinations (Paediatric HIV)	Since May 2012, DND*i* partner for clinical trial in the field of paediatric HIV.
Northwick Park Institute for Medical Research (NPIMR)- UK		Since 2012, partner for screening for helminth infections.
Pasteur Institute of Iran- Iran		Since 2012, partner for pre-clinical research for CL.
Seattle Biomedical Research Institute- USA		Since October 2008, DND*i* partner for discovery on NTDs.
Swiss Tropical and Public Health Institute- Switzerland	Fexinidazole (HAT) / NECT (HAT) / Nitromidazole backup (HAT)	Since 2006, various partnerships through discovery, screening (kinetolastids), and clinical trials for HAT, leishmaniasis.
Texas Biomedical Research,private research institute- USA	Azoles E1224 & Biomarker (Chagas)	Since October 2012, DND*i* partner for pre-clinical research in the field of Chagas disease. Evaluation of potential indicators of parasitological cure following drug therapy.
University of Georgia Research Foundation- USA	Azoles E1224 & Biomarker (Chagas)	Since October 2012, DND*i* partner for pre-clinical research in the field of Chagas disease. Evaluation of potential indicators of parasitological cure following drug therapy.

NATIONAL RESEARCH CENTERS		
Administración Nacional de Laboratorios e Institutos de Salud (ANLIS)- Argentina		Since 2012, DND*i* partner for clinical trials for Chagas disease.
B.P Koirala Institute of Health Sciences- Nepal		DND*i* partner for clinical trials for VL.
Centro National de Pesquisa em Energia e Materiais (CNPEM) LN BIO- Brazil	Screening	Since October 2013, DND*i* partner for screening.
CNRFP, Centre National de Recherche et de Formation sur le Paludisme- Burkina Faso	ASMQ (Malaria)	Since August 2010, DND*i* partner for clinical trials for malaria.
CSIR, Council of Scientific and Industrial Research- India		Since August 2008, various partnerships for leishmaniasis and HAT through screening and discovery activities of anti-leishmaniasis compounds.
CDRI, Central Drug Research Institute- India	VL-2098 / Nitroimidazole backup (VL)	Since June 2007, various discovery partnerships for leishmaniasis and HAT.
Fiocruz, Fundaçao Oswaldo Cruz- Brazil	Azoles E1224 & Biomarker (Chagas)	Since 2003, various partnerships through information sharing, discovery, clinical trials,

		research on malaria (ASMQ) and Chagas disease.
ICDDR, International Centre for Diarrheal Disease Research- Bangladesh	New VL treatments (Asia) / New VL treatments (Bangladesh)	Since November 2009, DND*i* partner for clinical trials for VL.
ICMR, Indian Medical Research Council- India	ASAQ (Malaria) / ASMQ (Malaria) / New VL treatments (Asia)	Since 2006, DND*i* partner for clinical trials for VL.
Instituto de Salud Carlos III- Spain		Since May 2013, scientific collaboration in the field of neglected tropical diseases.
Kala Azar Medical Research Center- India		Since January 2007, DND*i* partner for clinical trials for VL.
National Institute for Medical Research (NIMR) – Tanzania	ASMQ (Malaria)	Since 2012, DND*i* partner for ASMQ clinical trials for malaria.
RMRIMS, Rajendra Memorial Research Institute of Medical Sciences- India	New VL treatments (Asia)	DND*i* partner for clinical trials for VL.
State Health Society, Bihar- India	New VL treatments (Asia)	Since 2011, collaboration for the VL Asia Phase IV clinical studies for VL.

NGOs/IOs		
AEDES- Belgium		Consulting firm for Social and Public health sector. In 2008, partner for malaria CMC manufacture. Since January 2011, partnership for the technology transfer of ASAQ to Zenufa.
CEADES, Collective of Applied Studies and Social Development- Bolivia	Azoles E1224 & Biomarker (Chagas)	Since September 2010, DND*i* partner for clinical trials of benznidazole against Chagas disease.
Communauté Baptiste du Congo- Democratic Republic of Congo	Fexinidazole (HAT)	Since August 2012, DND*i* partner for clinical trials of fexinidazole in the field of sleeping sickness.
Epicentre- France	ASAQ (Malaria) / ASMQ (Malaria)	Non-for-profit organization which groups health professionals specialized in public health/epidemiology. Since November 2005, various partnerships for clinical phases on malaria and HAT.
IDA Foundation- Netherlands	VL-0208	Since December 2008, DND*i* partner for clinical phase for VL.
i+solutions- Netherlands	VL-0208 / SSG&PM (VL for Africa)	Continuation of the partnership with IDA Foundation: Leishmaniasis East Africa Platform (LEAP) partner.
Médecins Sans Frontières	ASAQ (Malaria) / Azoles E1224 & Biomarker (Chagas) / Fexinidazole (VL) / HIV/VL / NECT (HAT) / VL-0208 / New VL treatments (Asia) / SSG&PM (VL in Africa)	Since 2003, various partnerships in financing, discovery, and clinical trials.
Microbial Chemistry Research Foundation- Japan	Screening	Since September 2013, DND*i* partner for screening.
Mundo Sano Foundation- Argentina	Paediatric Benznidazole (Chagas)	Signed a memorandum of understanding with DND*i* on Chagas disease in 2011. Since November 2013, collaborative agreement with DND*i* aimed at ensuring availability and access to sustainable and affordable treatments for Chagas disease to both adults and children.

OTECI, Offre Technique d'Etude et de Coopération Internationale- France	ASMQ (Malaria)	Since January 2008, DND*i* partner through technology transfer support for ASMQ.
Royal Society of Chemistry- UK		Since September 2009, MoU to promote open source discovery.
WHO-TDR	ASAQ (Malaria) / ASMQ (Malaria) / New VL treatments (Asia) / Screening	World Health Organization, TDR, Special Programme for Research and Training in Tropical Diseases and co-sponsored by UNICEF, UNDP, the World Bank and WHO. Founding partner since 2003. Various collaboration projects on malaria and kinetoplastids.

PDPs/PPPs		
FIND, Foundation for Innovative New Diagnostics- Switzerland		Since August 2010, collaboration and material transfer agreement to develop an ELISA-based diagnostic test for leishmaniasis. Since December 2013, MoU for collaboration in the field of neglected tropical diseases.
OWH, Institute for One World Health- USA	VL-0208 / New VL treatments (Asia) / SSG&PM (VL in Africa)	Since April 2009, DND*i* partner for VL.
MMV, Medicines for Malaria Venture- Switzerland	ASAQ (Malaria) / ASMQ (Malaria) / Screening	Since September 2004, various partnerships through information sharing, discovery on malaria.
NITD Novartis Institute for Tropical Diseases- Singapore	Screening	Since April 2007, partnership in discovery on kinetoplastids.
TB Alliance: Global Alliance for Tuberculosis Drug Development - USA	Nitroimidazole (Chagas) / Nitroimidazole backup (HAT) / Nitroimidazole backup (VL) / VL-2098 /Screening and Lead Optimization	Since January 2007, various partnerships through screening and discovery in the field of kinetoplastids.
TI Pharma- Netherlands		DND*i* partner for discovery activities.

HOSPITALS		
Arba Minch Hospital- Ethiopia		Leishmaniasis East Africa Platform (LEAP) partner. Since April 2005, clinical trial Agreement for VL.
CHUV, Centre Hospitalier Universitaire Vaudois- Switzerland	ASMQ (Malaria)	Since June 2009, technical agreement for discovery.
Hospital de Ninos Ricardo Gutierrez / Jaime Altcheh- Argentina	Paediatric Benznidazole (Chagas)	Since January 2014, works with DND*i* on analysis of sera samples.
KATH, Komfo Anokye Teaching Hospital- Ghana	ASAQ (Malaria)	Since 2008, DND*i* partner for access and data management for ASMQ (malaria).
Shaheed Suhrawardy Medical College and Hospital- Bangladesh	New VL treatments (Asia) / New VL treatments (Bangladesh)	Since November 2009, DND*i* partner for clinical trials for VL.

MINISTRIES OF HEALTH/ GOVERNMENTAL ORGANIZATIONS		
Department of Health (South Africa)	RTV Superbooster for HIV/TB co-infection	Since 2013, donating free treatments for TB/HIV clinical trial. Since April 2014, MoU on improving

	(Paediatric HIV) / Two "4-in-1" LPV/r based FDC granules (Paediatric HIV) / LPV/r pellets with dual NRTI FDC (Paediatric HIV)	access to paediatric HIV treatment in South Africa.
Ministry of Health (Brazil)	New VL treatments (Latin America)	DND*i* partner for clinical trials for VL.
Ministry of Health (Cambodia)	ASMQ (Malaria)	Since July 2010, DND*i* partner for clinical research in the field of malaria.
Ministry of Health (Ethiopia)	New VL treatments (Africa)	Since 2004, Leishmaniasis East Africa Platform (LEAP) partner.
Ministry of Health (Kenya)	New VL treatments (Africa) / SSG&PM (VL in Africa)	DND*i* partner for clinical trials for VL.
Ministry of Health (Rep. Dem. Congo)		Since January 2006, various partnerships (financial and clinical trial agreement) in the field of HAT.
Ministry of Health (Uganda)	New VL treatments (Africa) / SSG&PM (VL in Africa)	Since 2004, Leishmaniasis East Africa Platform (LEAP) partner.
CeNDIE, Centro Nacional de Diagnostico e Investigacion de Endemo-epidemias, Ministry of Health, (Argentina).	Paediatric Benznidazole (Chagas)	
Gedarif MoH (Sudan)	New VL treatments (Africa) / SSG&PM (VL in Africa)	Leishmaniasis East Africa Platform (LEAP). Since December 2004, various partnerships for clinical trials in the field of leishmaniasis.
National Trypanosomiasis Control Programmes (Democratic Republic of Congo and Central African Republic)	NECT (HAT)	DND*i* partners for clinical trials for HAT.

CONTRACT RESEARCH ORGANIZATIONS		
Accelera- Italy		Since September 2007, works with DND*i* on pre-clinical studies.
Advinus Therapeutics- India	Nitroimidazole backup (VL) / Oxaborole SCXY-7158 (HAT) / VL-2098	Since January 2006, works with DND*i* on discovery, pre-clinical, lead optimization and clinical activities. Since November 2013, works with DND*i* on CMC and manufacturing activities.
Aptuit- Italy	VL-2098	Since December 2008, provides research services concerning pre-clinical activities as well as CMC and manufacture phases.
BaseCon- Denmark	Fexinidazole (VL)	Since September 2012, DND*i* partner for a pharmacovigilance database on fexinidazole against sleeping sickness. BaseCon is an "in-kind contributor".
Bertin Pharma- France	ASAQ (Malaria) / VL-2098 / Oxaborole SCYX-7158 (HAT) / Fexinidazole (HAT)	Since March 2011, works with DND*i* for capacity strengthening and technology transfer of ASAQ to Zenufa in Tanzania. Since May 2013, works with DND*i* on the packaging and shipment of SCYX-7158. Since November 2013, works with DND*i* on the preparation of fexinidazole.
Calvert Labs- USA		Since June 2012, DND*i* partner for pre-clinical phase for topical formulation against cutaneous

		leishmaniasis.
Cardiabase- Frnace		Since 2011, research service agreement on cardiac safety studies for new chemical entities (NCEs) in clinical stage (Phases I, II/III).
Cardinal System- France	Azoles E1224 & Biomarker (Chagas)	Since January 2004, works with DND*i*: clinical activities in the field of malaria and other NTDs.
Catalent- USA		Since November 2007, works with DND*i*: screening, discovery, clinical activities as well as registration and regulatory issues in the field of malaria.
Central Diagnostics- India		Since September 2012, DND*i* partner in the field of visceral leishmaniasis.
Centipharm- France		Since November 2007, works with DND*i*: CMC/manufacture of fexinidazole for HAT.
Clinwin Research Services- Kenya	ASMQ (Malaria)	Since August 2013, works with DND*i* on clinical research project management and monitoring of ASMQ.
CONICET INGEBI- Argentina	Azoles E1224 & Biomarker (Chagas) / Paediatric Benznidazole (Chagas)	Since October 2010, works with DND*i* for clinical phases in the field of Chagas disease.
CoreLab Partners- USA		Since April 2011, works with DND*i* for clinical activity for Chagas disease.
Covance- UK	VL-2098	Since December 2013, works with DND*i* on pre-clinical activities for VL-2098.
Creapharm- France	Fexinidazole (Chagas)	Since March 2014, works with DND*i* on CMC activities for fexinidazole for Chagas.
Drugabilis- France	Screening & Lead Optimization / Fexinidazole (HAT) / Oxaborole SCYX-7158 (HAT) / Flubendazole (Filarial diseases) / VL-2098	Since 2009, works with DND*i* on lead optimization and pre-clinical activities for HAT, VL and filarial diseases. Since May 2013, works with DND*i* on small scale tests for filariasis.
Endolytics- USA	VL-2098	Since February 2014, works with DND*i* on pre-clinical activities for VL 2098.
Eurofins Optimed- France	Oxaborole SCYX-7158 (HAT) / Two "4-in-1" LPV/r based FDC granules (Paediatric HIV)	Since April 2013, works with DND*i* on clinical trial of Oxaborole SCYX-7158. Since June 2013, works with DND*i* on activities for the phase 1 study of LPV/r.
Frontage- USA	Azoles E1224 & Biomarker (Chagas)	Since August 2013, works with DND*i* on analysis of E1224 in plasma.
GVK Biosciences- India		Since October 2006, works with DND*i* in the clinical phase for malaria and VL.
Harlan Laboratories- Switzerland		Since 2011, pre-clinical research agreement for Chagas disease.
Huntingdon Life Sciences Limited- UK	VL-2098	Since June 2013, works with DND*i* on pre-clinical activities for VL-2098.
LAT Research- Argentina	Azoles E1224 & Biomarker (Chagas)	Since December 2010, works with DND*i* on the clinical studies of benznidazole against Chagas disease.
JSS Medical Research- Canada	Anfoleish (CL) / Fexinidazole (Chagas)	Since October 2013, works with DND*i* on clinical trials of Anfoleish and fexinidazole for Chagas.
NUDFAC, Nucleo de	Azoles E1224 &	Since 2012, works with DND*i* on data analysis of

desenvolvimento farmacêutico e cosméticos- Brazil	Biomarker (Chagas) / Paediatric Benznidazole (Chagas)	clinical studies for Chagas disease.
Patheon- UK		Since 2012, works with DND*i* on formulation development and manufacturing for HAT.
Penn Pharmaceuticals Services- UK	Oxaborole SCYX-7158 (HAT)	Since May 2010, works with DND*i* on pre-clinical study (formulation) for HAT.
PhinC Development- France		Since 2010, works with DND*i* on Pk/PD and statistics for HAT and, since 2012, on PK/PD analysis for Chagas.
RCTs- France	NECT (HAT) / Fexinidazole (HAT)	Since May 2009, works with DND*i* on clinical study of NECT for HAT. Since February 2014, works with DND*i* on clinical studies for fexinidazole for HAT.
Roowin- France		Since 2012, works with DND*i* on CMC activities for HAT.
Sandexis LLP- UK	Lead Optimization	Since August 2012, works with DND*i* on research in discovery activities (hit to lead, lead optimization).
Selcia- UK	VL-2098	Since November 2013, works with DND*i* on radiosynthesis service for VL-2098.
Sigma-Aldrich- UK	VL-2098	Since November 2013, works with DND*i* on CMC activities for VL-2098.
SGS- France		Since November 2008, initially worked with DND*i* on clinical study of fexinidazole for HAT, subsequently performing bioanalyses.
Theradis Pharma- France	Fexinidazole (HAT)	Since June 2012, provides logistical support for the clinical trials of fexinidazole for sleeping sickness.
WuXi AppTec- China	Lead Optimization	Since 2011, lead optimization partner and pre-clinical animal studies and formulation work for HIV paediatric projects.

Reference List

"2014 Ebola Outbreak in West Africa." Centers for Disease Control. Accessed March 9, 2016. http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/.

"About Us." 2016. *DNDi*. Accessed April 11. http://www.dndi.org/about-dndi/.

"Agreement on Trade Related Aspects of Intellectual Property." 2016. *WTO*. Accessed April 11. https://www.wto.org/english/docs_e/legal_e/27-trips_03_e.htm.

"An Innovative Approach to R&D for Neglected Patients: Ten Years of Experience & Lessons Learned by DNDi." 2016. DNDi. Accessed March 9. http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_Modelpaper_2013.pdf.

"Approved Medicines." 2016. *PhRMA*. Accessed March 9. http://www.phrma.org/few-approved-medicines-are-commercially-successful.

"Around 10 million people living with HIV now have access to antiretroviral treatment." UNAIDS. 2013. Geneva. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2013/june/20130630prtreatment

Balasegaram, Manica, Christian Bréchot, Jeremy Farrar, David Heymann, Nirmal Ganguly, Martin Khor, Yves Lévy, et al. 2015. "A Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance." *PLOS Med* 12 (5): e1001831. doi:10.1371/journal.pmed.1001831.

Ballel, Lluís (Director of External Opportunities at Tres Cantos Open Lab Foundation), interview with Jason Cross, Julia Barnes-Weise, Sejal Lahoti, and Julia Tuttle. 5 Mar. 2015.

Barnes-Weise, Julia & Rutschman, Ana Santos. "Ebola and the Accidental Consortia." HuffPost. 7 April 2015. http://www.huffingtonpost.com/julia-barnesweise/post_9271_b_7019058.html

Bilbe, Graeme. 2016. "Breakthrough Treatments for the Most Neglected Diseases: Diversifying Approaches Is Required to Expand the Development Pipeline with New Chemical Entities." *DNDi*. Accessed April 11. http://www.dndi.org/2015/viewpoint/viewpoint-graeme-bilbe-november-2015/.

"Biopharmaceutical Research and Development: The Process Behind New Medicines." 2015. PhRMA. http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

"Biopharmaceutical Sector." 2016. *PhRMA*. Accessed April 11. http://www.phrma.org/about/biopharmaceutical_sector.

"Business Plan 2015-2023." 2016. DNDi. Accessed March 9. http://www.dndi.org/wp-content/uploads/2009/03/DNDi_Business_Plan_2015-2023.pdf.

Carroll, John. 2016. "AbbVie Hands United a Record $350M Payoff for a Speedy FDA Review Voucher." *FierceBiotech*. Accessed February 18. http://www.fiercebiotech.com/story/abbvie-hands-united-record-350m-payoff-speedy-fda-review-voucher/2015-08-19.

Consultative Expert Working Group on Research and Development. "Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination." World Health Organization. April 2012. Pp. 8.

Dean, Hansi. 2016. "The Value of Product Development Partnerships in Vaccine Development." International AIDS Vaccine Initiative. Accessed March 21. https://ec.europa.eu/research/health/pdf/event17/s3-9-hansi-dean_en.pdf.

"DNDi Awarded USD 2.34 Million from New Pooled Fund Mechanism at WHO-TDR in Support of Global Leishmaniasis R&D Demonstration Project." 2016. Accessed April 8. http://www.dndi.org/2015/media-centre/press-releases/pr-demo-project/.

"DNDi's Intellectual Property Policy." n.d. DNDi. http://www.dndi.org/images/stories/pdf_aboutDNDi/ip%20policy.pdf.

"DNDi, the Drugs for Neglected Diseases Initiative: A Global Initiative to Develop Drugs for Those in Need." 2016. *MSF Access Campaign*. Accessed March 22. http://www.msfaccess.org/content/dndi-drugs-neglected-diseases-initiative-global-initiative-develop-drugs-those-need-eng-4-pg.

Drugs for Neglected Diseases initiative. 2016. *The NTD Drug Discovery Booster*. Accessed April 6. https://www.youtube.com/watch?v=t1OQo6CyVv8&feature=youtu.be.

"Ebola Hemorrhagic Fever: 2014 Ebola Outbreak in West Africa." 2016. *CDC*. Accessed March 9. http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/.

"Experience Treating the Most Neglected of the Neglected Tropical Diseases." Doctors Without Borders. New York, NY. http://www.doctorswithoutborders.org/sites/usa/files/MSF-NTD-Briefing-Paper.pdf

Fehr, Angela, Petra Thürmann, and Oliver Razum. 2006. "Drug Development for Neglected Diseases: A Public Health Challenge." *Tropical Medicine & International Health* 11 (9): 1335–38. doi:10.1111/j.1365-3156.2006.01714.x.

Ferguson, Steve. "Licensing from the NIH to Address Global Health." Rubenstein Hall, Duke University, Durham, North Carolina. 20 Apr. 2015. Lecture.

Fisher, William W. & Rigamonit, Cyrill P. "The South Africa AIDS Controversy A Case Study in Patent Law and Policy." *The Law and Business of Patents*. Harvard Law School. 10 Feb. 2005. http://cyber.law.harvard.edu/people/tfisher/South%20Africa.pdf

Foege, William. "Smallpox Eradication Lessons." Duke University, Durham, NC. 1 Feb. 2016. Class lecture.

Gostin, Lawrence 0. & Friedman, Eric A. (2013) "Towards a Framework Convention on Global Health: A Transformative Agenda for Global Health Justice," *Yale Journal of Health Policy, Law, and Ethics*: Vol. 13: Iss. 1, Article 1. http://digitalcommons.law.yale.edu/yjhple/vol13/iss1/1

"How the pneumococcal AMC works." Gavi. 2015. http://www.gavi.org/funding/pneumococcal-amc/how-the-pneumococcal-amc-works/

Incentives for Global Health. "Making New Medicines Available." Health Impact Fund. 2015. http://healthimpactfund.org/

Intellectual Property Watch. 2016. "Alleged R&D Costs: Not A Transparent Driver Of Drug Prices." *Intellectual Property Watch- International IP News*. March 4. http://www.ip-watch.org/2016/03/04/alleged-rd-costs-not-a-transparent-driver-of-drug-prices/.

Lewis, Tracy R., Reichman, Jerome & So, Anthony. "The Case for Public Funding and Government Oversight of Clinical Trials." *Economist's Voice.* The Berkley Electronic Press: Jan. 2007.

Liu, Joanne. "Remarks by International President of MSF Dr. Joanne Liu at the Gates Foundation Global Partner Forum." Médecins Sans Frontières. 8 May 2015. http://www.msf.org/article/remarks-international-president-msf-dr-joanne-liu-gates-foundation-global-partner-forum

Love, James. "KEI Comment on the New Tufts Study on Drug Development Costs." *Knowledge Ecology International.* 18 Nov. 2014. http://keionline.org/node/2127

Love, James. "Senator Sanders introduces two medical innovation prize bills in U.S. Senate to de-link R&D costs from drug prices." Knowledge Ecology International. 27 May 2011. http://www.keionline.org/node/1147

Love, James. "The WHO EB debate over membership of the new R&D Financing consultative expert working group (CEWG)." Knowledge Ecology International. 17 Jan. 2011. http://keionline.org/node/1056

Mahoney, Richard T. 2011. "Product Development Partnerships: Case Studies of a New Mechanism for Health Technology Innovation." *Health Research Policy and Systems* 9 (August): 33. doi:10.1186/1478-4505-9-33.

Medicines Patent Pool. "Building Partnerships, Accelerating Access." UNITAID. Apr. 2015. Geneva. http://www.medicinespatentpool.org/wp-content/uploads/WEB_EN_BROCHURE_MPP_201504.pdf

"Meningitis Vaccine Project: Ending the Epidemics." 2016. *PATH*. Accessed April 10. http://www.path.org/menafrivac/overview.php.

Moran, Mary. 2005. "New Approaches to Funding Drug R&D for Neglected Diseases." presented at the Pharmaceutical R&D Policy Project, January. http://www.who.int/intellectualproperty/submissions/Mary.Moran.pdf.

MSF Access Campaign. "About Us." Médecins Sans Frontières. http://www.msfaccess.org/the-access-campaign

MSF, Drugs for Neglected Disease Working Group. 2016. "Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases." *SciDev.Net*. Accessed March 7. http://www.scidev.net/index.cfm?originalUrl=global/key-document/fatal-imbalance-the-crisis-in-research-and-develo.html.

Mueller-Langer, Frank. 2013. "Neglected Infectious Diseases: Are Push and Pull Incentive Mechanisms Suitable for Promoting Drug Development Research?" *Health Economics, Policy, and Law* 8 (2): 185–208. doi:10.1017/S1744133112000321.

"Neglected Tropical Diseases." 2016. *WHO*. Accessed April 11. http://www.who.int/neglected_diseases/diseases/en/.

"New Hope for Neglected Patients." 2016. DNDi. Accessed March 9. http://www.dndi.org/wp-content/uploads/2009/02/DNDi_Brochure_2014_ENG.pdf.

"NIH Budget." National Institutes of Health. 29 Jan. 2015. http://www.nih.gov/about/budget.htm

Nisen, Max. "The Top 10 Best Selling Prescription Drugs in the United States." Business Insider. 28 June 2012. http://www.businessinsider.com/10-best-selling-blockbuster-drugs-2012-6#lipitor-77-billion-1

"NPPD Products Developed as of 2013." 2013. Global Health Technologies Coalition. http://www.ghtcoalition.org/files/NPPDnewproductslist_10.21.13.pdf.

"Open Source Malaria: Looking for New Medicines." OSM. <http://opensourcemalaria.org/#>

Orbinski, James. 1999. "Médecins Sans Frontières - Nobel Lecture." Oslo, Norway, December 10. http://www.nobelprize.org/nobel_prizes/peace/laureates/1999/msf-lecture.html.

"Patient Access to Miltefosine in Developing Countries Not Secure Despite Award of US FDA Priority Review Voucher Sold for USD 125 Million." Drugs for Neglected Disease Initiative. 25 Nov. 2014. New York, NY. http://www.dndi.org/media-centre/press-releases/2028-pr-miltefosine-prv.html

Pedrique, Belen, Nathalie Strub-Wourgaft, Claudette Some, Piero Olliaro, Patrice Trouiller, Nathan Ford, Bernard Pécoul, and Jean-Hervé Bradol. 2013. "The Drug and Vaccine Landscape for

Neglected Diseases (2000–11): A Systematic Assessment." *The Lancet Global Health* 1 (6): e371–79. doi:10.1016/S2214-109X(13)70078-0.

Peña, Imanol, & Martin, Julio. Assembly of Three Kineto Boxes. GlaxoSmithKline, Tres Cantos. ISNTD d^3 Research Handbook. May, 2015.

"Pharmaceutical Industry." 2016. *WHO*. Accessed April 11. http://www.who.int/trade/glossary/story073/en/.

Powaleny, Andrew. 2016. "Fact Check Friday: The Truth about Industry's Role in R&D." *PhRMA*. Accessed February 16. http://catalyst.phrma.org/fact-check-friday-the-truth-about-industrys-role-in-r-and-d.

"Product Development Partnerships (PDPs)." 2016. Deutsche Stiftung Weltbevoelkerung. Accessed March 21. http://www.dsw.org/uploads/tx_aedswpublication/1408_PDP_UK_A4_web.pdf.

Rahman, Samir. (2015.) "Pharmaceutical Progress for Neglected Tropical Diseases:Using Non-Traditional Development Models to Overcome Market Deficiencies." Unpublished master's thesis, Duke University, Durham, North Carolina

Rai, Arti K., Reichman, Jerome H., Uhlir, Paul F., and Crossman, Colin. "Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery," *Yale Journal of Health Policy, Law, and Ethics*: Vol. 8: Iss. 1, Article 1 (2008). http://digitalcommons.law.yale.edu/yjhple/vol8/iss1/1

Reichman, Jerome H. "Compulsory Licensing of Patented Pharmaceutical Inventions: Evaluating the Options." *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics* 37.2 (2009): 247–263. *PMC*. Web. 10 July 2014. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893582/

Reichman, Jerome. 2009. "Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach." *Marquette Intellectual Property Law Review* 13: 1–68.

Resolution WHA61.21, Annex, Element 5, paragraph 5.3a.

Ridley, David. "The Priority Review Voucher System: Flaws and Fixes." Presented at Alliances and Incentives in an Era of Outbreaks. 1 April 2016. Durham, North Carolina.

Rottingen, John- Arne. Presentation at Achieving Access to New Innovations. 18 May 2015. Global Health Technologies Coalition and Council on Health Research for Development.

Schubach, Armando, Lyra, Marcelo, Ferandes, Maria Ines, and Valete, Claudia Maria, interview with the author. 11 June 2015. Rio de Janeiro.

Scherer, F.M. "The Pharmaceutical Industry." *Handbook of Health Economics.* 252. Vol 1. Eds. Culyer, A.J. & Newhouse, J.P. Elsevier Science. 2000.

"Sixty-sixth World Health Assembly: daily notes on proceedings". 27 May 2013. WHO

Sorenson, Corinna. 2009. "Product Development Partnerships (PDPs) for Neglected Diseases: Considerations on Governance." *Health Economics, Policy and Law* 4 (01): 1–10. doi:10.1017/S1744133108004702.

Spangenberg, Thomas. Personal conversation. 21 May 2015.

"TDR History: Making a difference since 1974." TDR. http://www.who.int/tdr/about/history/en/

"The Pathogen Box: Catalysing Neglected Disease Drug Discovery." 2016. Accessed April 6. http://www.pathogenbox.org/.

Topal, Claire. "The Value of Product Development Partnerships: An Interview With Rob Lin." The National Bureau of Asian Research. 11 Aug. 2014. http://www.nbr.org/research/activity.aspx?id=477

Troy, Daniel. 2003. *Testimony - Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)*. http://www.fda.gov/newsevents/testimony/ucm115033.htm.

Tufts Center for the Study of Drug Development. "Backgrounder." Tufts University. 18 Nov. 2014. Boston. http://csdd.tufts.edu/files/uploads/cost_study_backgrounder.pdf

United Nations General Assembly. 1948. "Universal Declaration of Human Rights." *Refworld*. December 10. http://www.refworld.org/docid/3ae6b3712c.html.

Uniting to Combat NTDs. "The London Declaration of Neglected Diseases." 30 Jan 2012.

Wanis, Heba. "New R&D Group entangled in conflict-of-interest issues." *North South Development Monitor.* Geneva: 28 Jan. 2011. People's Health Movement.2 Feb. 2011. <http://www.phmovement.org/en/node/4142>

"Why Innovative Biopharmaceutical Companies Are Different." 2016. *PhRMA*. Accessed March 9. http://www.phrma.org/graphic/why-innovative-biopharmaceutical-companies-are-different.

Wiley, Ryan. 14:39:41 UTC. "Product Development Partnerships." presented at the Product Development Bootcamp. http://www.slideshare.net/shifthealth/product-development-partnerships.

WTO/WIPO/WHO. "Promoting Access to Medical Technologies and Innovation." 2012. 107-109. https://www.wto.org/english/res_e/booksp_e/pamtiwhowipowtoweb13_e.pdf