2015

The Economics of Orphan Drugs: The Effectiveness of Priority Review Vouchers on the Development of Drugs to Combat Neglected Tropical Diseases

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Abstract
Neglected tropical diseases (NTDs) such as malaria and cholera affect more than 1.4 billion people a year. Pharmaceutical companies have historically neglected these diseases, as the affected populations are also some of the world's poorest. In 2007, a bill was signed into US law that created a Priority Review Voucher (PRV) program. This program grants developers of drugs for neglected diseases a waiver that reduces the time needed for FDA drug approval. This waiver can be sold to other pharmaceutical companies hoping to expedite the process for potential blockbuster drugs. This law is still in its early stages at the time of this paper, and it would not be feasible for any drugs to be fully approved due to the long drug development timeline. By analyzing FDA clinical trial data, though, initial trends can be analyzed for the development of drugs for NTDs. The clinical trial data does not fully support the effectiveness of the PRV program, but recent sales prices support that the market incentives are working correctly.

Keywords
FDA, economics, orphan drugs, priority review vouchers, tropical diseases

Disciplines
Business

THE ECONOMICS OF ORPHAN DRUGS:

THE EFFECTIVENESS OF PRIORITY REVIEW VOUCHERS ON THE DEVELOPMENT OF DRUGS TO COMBACT NEGLECTED TROPICAL DISEASES

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ABSTRACT

Neglected tropical diseases (NTDs) such as malaria and cholera affect more than 1.4 billion people a year. Pharmaceutical companies have historically neglected these diseases, as the affected populations are also some of the world's poorest. In 2007, a bill was signed into US law that created a Priority Review Voucher (PRV) program. This program grants developers of drugs for neglected diseases a waiver that reduces the time needed for FDA drug approval. This waiver can be sold to other pharmaceutical companies hoping to expedite the process for potential blockbuster drugs. This law is still in its early stages at the time of this paper, and it would not be feasible for any drugs to be fully approved due to the long drug development timeline. By analyzing FDA clinical trial data, though, initial trends can be analyzed for the development of drugs for NTDs. The clinical trial data does not fully support the effectiveness of the PRV program, but recent sales prices support that the market incentives are working correctly.

INTRODUCTION

Purpose

The purpose of this paper is to analyze the effectiveness of the Priority Review Voucher program on the development of drugs to combat neglected tropical diseases.

Motivation

I have been personally motivated by this topic after analyzing the orphan drug landscape. My initial literature review made it very clear that many researchers had analyzed the proliferation of orphan drugs in the US since 1984 for classic rare diseases such as cystic fibrosis. Far less thought and research, though, focused on the subgroup of paradoxically named 'rare diseases' that kills millions every year. This paradox of some of the world's most common diseases being labeled a 'rare disease' in the US was what I found initially so intriguing. Looking further into these diseases, I found the Priority Review Voucher program, which I found to be a fascinating program developed to incentivize the private sector to create 'profitless' drugs by utilizing the bureaucracy and inefficiency of the US Food and Drug Association.

Methods

This paper analyzes data from ClinicalTrials.gov: an online registry supported by the U.S. National Institutes of Health. The data was analyzed using tools from Microsoft Excel. All cases of clinical trials applying to multiple diseases were discounted. Trial dates are based on the trial start dates as reported to ClinicalTrials.gov.

Findings

There has been an increase in the percentage growth of clinical trials for the NTDs observed in the years since the passage of the PRV program in 2007.

The market price of the vouchers has exceeded expectations and will likely continue to rise.

BACKGROUND

Drugs and devices to treat rare diseases are increasingly common in today's national and international health care landscape, but this was not always the case. New laws and regulations have altered the natural markets and created economic incentives to encourage the development and sale of drugs and medical devices for diseases that individually affect less than 1 in 1250 individuals in the United States (Orphan Drug Act, Pub. L. no 97-414, 96 Stat. 2049 (1984 as Amended).

Rare diseases are called "orphan diseases" and the drugs that treat these orphan diseases are called "orphan drugs." The term 'orphan' is a reference to the "pharmacological neglect" these diseases suffered in the early to mid twentieth century (Institute of Medicine (IOM) 2009). Diseases with a population prevalence of less than 200,000 people are labeled "rare" or "orphans" in the United States, but this cut off varies by country (Orphan Drug Act, Pub. L. no 97-414, 96 Stat. 2049 (1984 as Amended). According to this definition, "it is estimated that over 7,000 rare diseases affect an estimated 25-30 million people […] in the U.S." constituting 8-12% of the US population (Griggs et al. 2009, 20-26). Advances in pathophysiology are leading to more strictly defined diseases, leading to the identification of about 250 new orphan diseases each year (Hernberg-Ståhl and Reljanović 2013). Lacking constraints, the health care industry would work to cure all rare diseases, but money and time impose large hurdles in the development of every drug—be it for a rare disease or not. New drugs are estimated to cost between $800 million and $1.3 billion dollars and take between 10 and 15 years to develop (IOM 2009). Drugs to treat rare diseases are often just as expensive and take just as much time as possible 'blockbuster drugs' that affect a large swath of the population, rendering

this system of treating the "far less commercially attractive" orphan drugs "simply infeasible" (IOM 2009). With increased public awareness and a new law, there was a significant shift in the economic incentives to encourage pharmaceutical companies to develop orphan drugs.

Late in the 1970s, "several American rare disease organizations united to address the need for medical research and translation of that research into drugs and therapies for their members" (Largent and Pearson 2012, 27-34). Abbey Meyers, then-president of the National Organization for Rare Diseases, "embarked on a public relations campaign, bringing television cameras and newspaper reporters into the laboratories where recovered patients helped to fill capsules with lifesaving medicines that drug companies refused to manufacture" (Largent and Pearson 2012, 27-34). Increasing pressure from the general public and patient advocacy groups pushed the US government to pass the Orphan Drug Act (Largent and Pearson 2012, 27-34). Passed in 1983, the law affirms that "there is reason to believe that some promising orphan drugs will not be developed unless changes are made […] to reduce the costs of developing such drugs" and that "it is in the public interest to provide […] incentives for the development of orphan drugs" (Orphan Drug Act, Pub. L. no 97-414, 96 Stat. 2049 (1984 as Amended). These economic incentives include "grants, tax credits, a waiver of the $1 million Prescription Drug User Fee Act filing fee, FDA assistance with protocol development, priority review of new drug applications (a 6-month review rather than the standard 10-month review), and [most importantly] a 7-year U.S. market exclusivity following approval of a designated orphan product" (IOM 2009). In the decade preceding the passage of the Orphan Drug Act, "only ten new drugs for rare diseases were developed," while "more than 1,100 new orphan treatments have entered

the research pipeline" since the law passed in 1983 (Largent and Pearson 2012, 27-34). Today, orphan drugs make up about one third "of all newly approved drugs and biologics" (Largent and Pearson 2012, 27-34). The FDA estimates that roughly 12 million people who suffer from orphan diseases have benefited from the Orphan Drug Act (IOM (Institute of Medicine) 2009). Analysis of the effects of the Orphan Drug Act have pointed to positive achievements of many of the bill's initial goals, but raise concerns for the future viability and efficacy of the funding mechanisms.

Many initial concerns about the Orphan Drug Act have been found to be nonissues. Despite initial concerns that drug developers would focus on the more common rare diseases and ignore the truly rare ones, an in depth study by the US Department of Health and Human Services found that "in no year was the average patient population for designated products more than 90,000, whereas in general the prevalence for designated products was between 50,000 and 70,000" (Haffner, Torrent-Farnell, and Maher 2008, 2041-2044). Additionally, the technological advances introduced by fighting rare diseases have dissuaded those who question the larger impact of the legislation, as "development of orphan products has been and is part of the discovery of innovative treatments" such as "RNA interference, antisense therapies, new gene therapy, and others" (Haffner, Torrent-Farnell, and Maher 2008, 2041-2044).

It has become increasingly more difficult to determine population sizes in recent years than in the bill's conception in 1983. The development of targeted therapies and personalized medicine has increased the number of subpopulations (Hernberg-Ståhl and Reljanović 2013). Additionally, the practice of "salami slicing" occurs when companies apply for orphan drug designation by taking a disease with a prevalence greater than

200,000 people, and narrow it into a subpopulation of that group that's less than 200,000 people in order to reap the rewards of the orphan drug label. While this practice is acceptable "when a disease subset is clearly demarcated, has its own specific pharmacological mechanism, and the proposed orphan drug has no effect in the rest of the population," it is *not* acceptable when "the proposed orphan product might also have value in the rest of the condition" (Hernberg-Ståhl and Reljanović 2013). The extremely high costs of some orphan drugs have been constantly dismissed by the National Organization for Rare Diseases as "a small overall expense to a health insurance company," but as the number of subpopulations grow, health insurance companies will find themselves footing more and more expensive drug treatments (Largent and Pearson 2012, 27-34).

"One unexpected consequence of orphan legislation" has been the incentives it created for the US to combat very common diseases abroad (Haffner et al., 2008). Diseases such as tuberculosis and malaria, "two of the top five infectious disease killers in the world," are called "neglected tropical diseases" and are very rare in the US despite their prevalence in other, mostly developing, nations (Haffner et al., 2008). More specifically, neglected tropical diseases (NTDs) are a subset of infectious diseases that share two main characteristics. First, NTDs are mostly found in the tropics, "but their predilection for hot places results principally from the fact that poverty is found in greatest concentration in the remote rural communities, urban slums and displaced populations near to the equator" (Feasey et al. 2010, 179-200). Although the diseases are designated as tropical, in reality "all low-income countries are affected by at least five NTDs simultaneous" which are "at least in part attributable to inadequate access to safe water, sanitation and appropriate housing" (Feasey et al. 2010, 179-200). The second main characteristic of NTDs is that by

and large they have "been neglected by funders, researchers and policy-makers" (Feasey et al. 2010, 179-200). The rarity of these diseases in the US typically qualifies them for Orphan Drug designation and attached benefits, another factor encouraging pharmaceutical companies to develop drugs and medical treatments for these NTDs.

It cannot be overlooked, though, that "little is invested in developing treatments" for NTDs because "most of the people suffering from these diseases are poor" (Ridley, Grabowski, and Moe 2006, 313-324). Three researchers from the Fuqua School of Business, Duke University published a research paper outlining a proposal to incentivize drug development for NTDs in 2006. The researchers proposed a "priority-review voucher" (PRV) program (Ridley, Grabowski, and Moe 2006, 313-324). Under this program, drug companies that developed treatments for NTDs would receive a "transferable voucher" which "would entitle the bearer to priority FDA review for another drug and orphan drug tax credits" (Ridley, Grabowski, and Moe 2006, 313-324). This voucher could be sold to a pharmaceutical company pursuing FDA approval for a potential blockbuster drug. The authors estimated that cutting the FDA approval time in almost half (from a typical 10-12 month timeline down to a promised (but not mandated) six months) "would be worth more than $300 million" (Ridley, Grabowski, and Moe 2006, 313-324). A year later, the academic proposal became US law, as it was included in the Food and Drug Administration Amendments Act of 2007, or "FDAAA". Although the law is not the exact proposal of the three authors, the general model is clearly based on their work. Section 1102 of the FDAAA defines a 'priority review' as "review and action" by the FDA "not later than 6 months after receipt" (US Food and Drug Administration 2007, 150). The law lists 16 tropical diseases, but also allows for the addition of "any other infectious disease for which there is no

significant market in developed nations and that disproportionately affects poor and marginalized populations" (US Food and Drug Administration 2007, 150). The law was strengthened in December 2014 when President Obama signed "Adding Ebloa to the FDA Priority Review Voucher Program Act" into law. The law reduced the previous one-year waiting period to 90 days, eliminated the limit on the number of time that PRV "may be transferred before such voucher is used," and added "filoviruses" which include strains of Ebola to the list of tropical diseases (113th Congress, Sen. Harkin, Tom 2014). The first two changes more closely aligned this PRV program for NTDs to a similar one that exists for rare pediatric diseases. In August 2015, the FDA utilized its power and added Chagas disease and neurocysticercosis to the PRV program.

This paper will analyze how effective the PRV program has been since its creation in 2007 by analyzing clinical trial data as well as market prices of the vouchers.

DATA

Source

The following data are from ClinicalTrials.gov: an online registry supported by the U.S. National Institutes of Health. Dates from trials are based on the trials' start date. The data focuses on the initial 16 diseases listed in the 2007 law, as enough time has not elapsed to add the two new additions from Congress and the FDA since.

No data was available for the diseases Dracunculiasis or Fascioliasis as there has yet to be clinical trials targeting the two diseases.

Clinical Trial Results

In order to investigate the possible effect of the PRV program on the development of drugs treating neglected tropical diseases, the long-term data on clinical trial start dates need to be analyzed. Figure 1 clearly shows a general increase in the number of these clinical trials started. The 4-6 years following 2007 should be treated with caution as any drugs for which clinical trial data was submitted in that time period likely were already in the drug pipeline before the FDA agreed to the PRV program.

Figure 1. Number of US Clinical Trials sorted by start date for all preceding diseases.

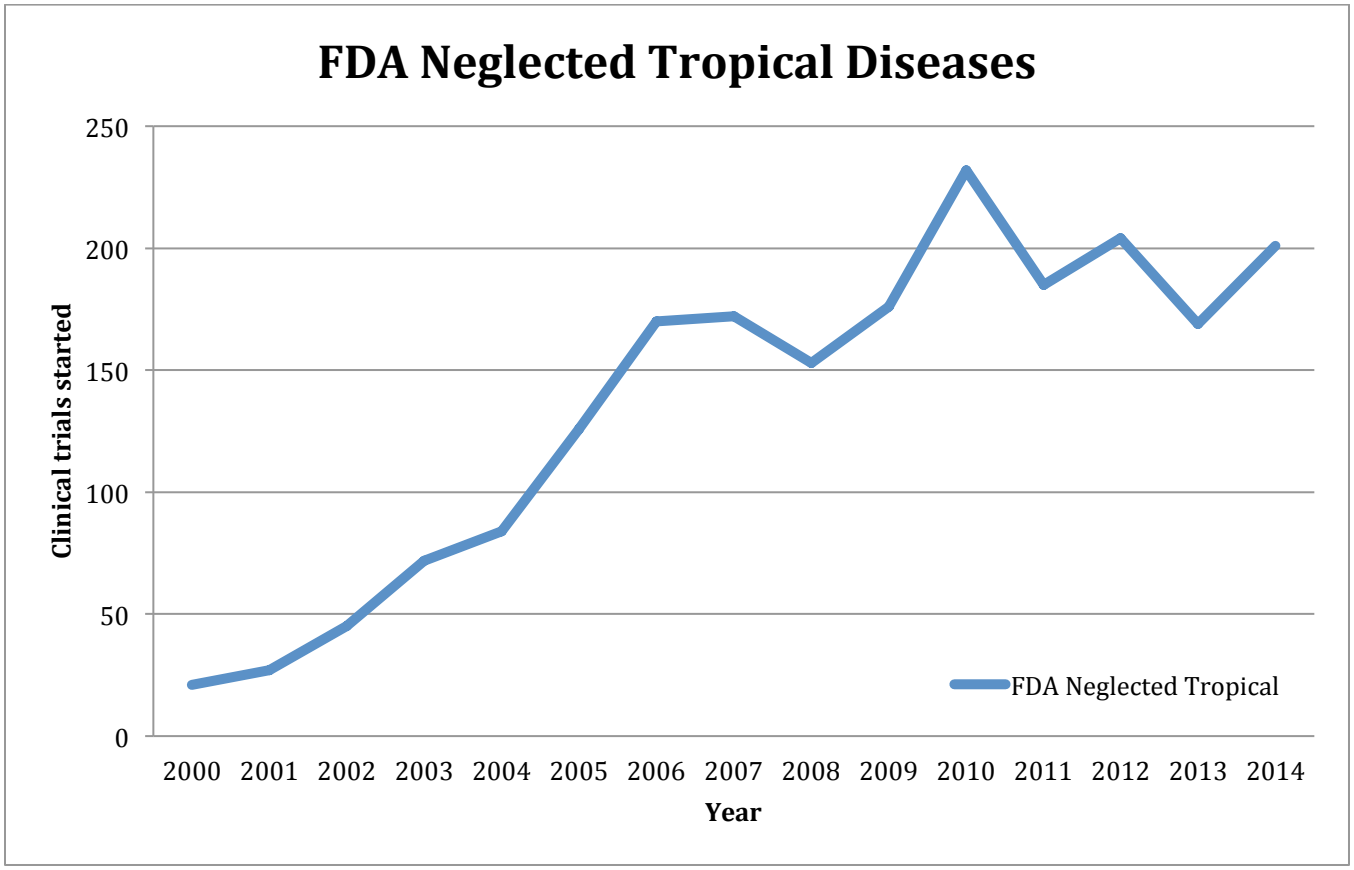


Figure 2 shows the differing number of clinical trials started for some of the neglected tropical diseases for which there were generally higher levels of total clinical trial submissions.

Figure 2. Number of US Clinical Trials sorted by start date for some select diseases.

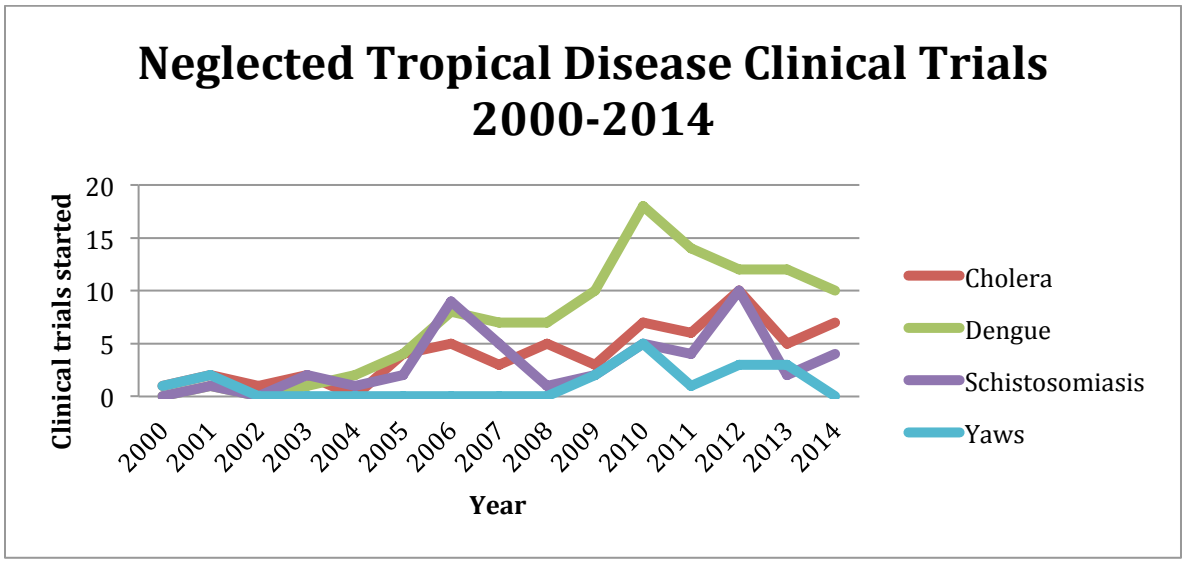
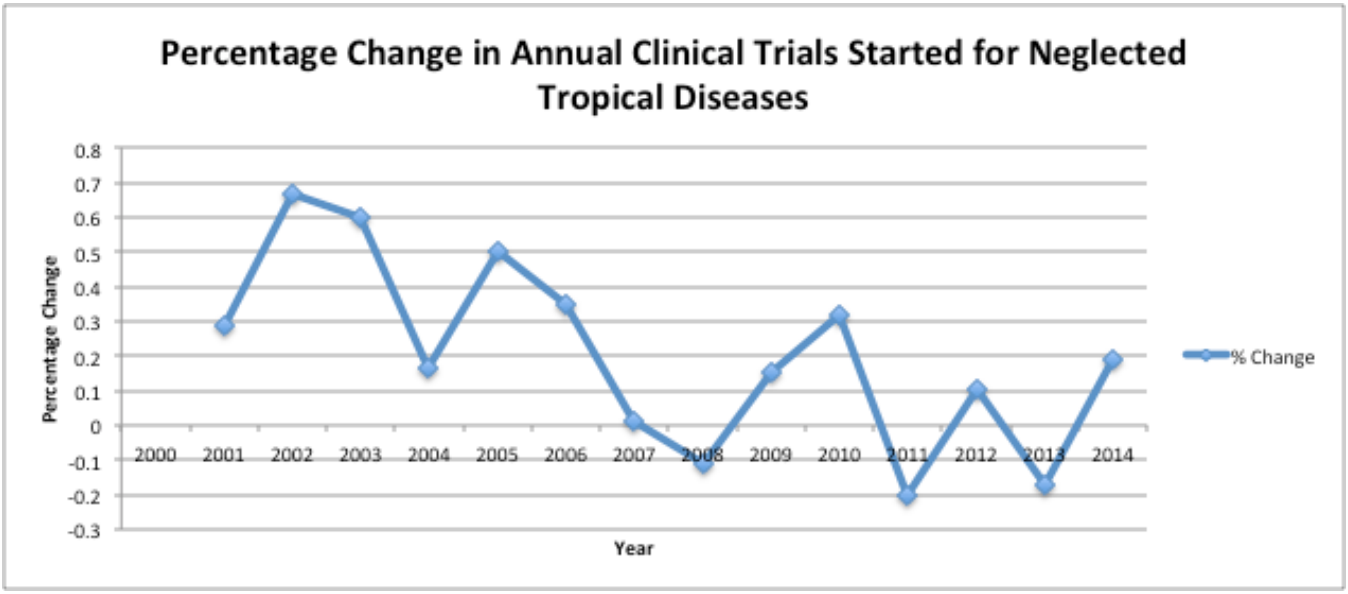


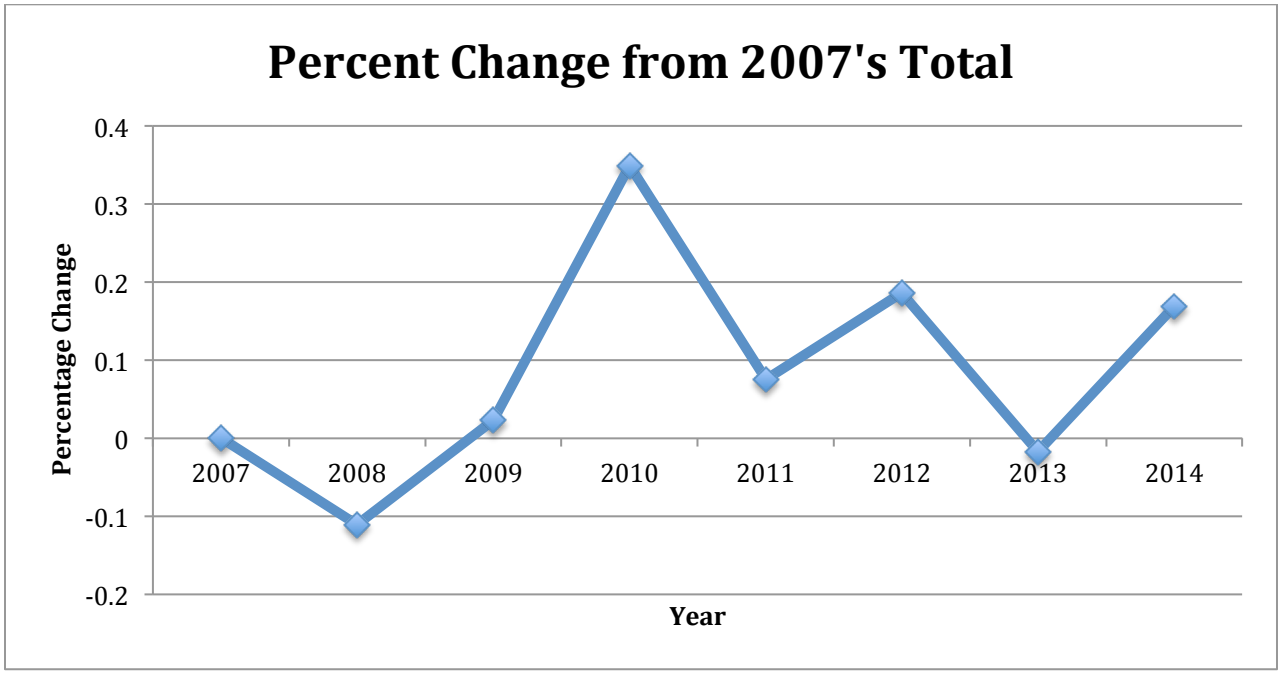
Figure 3 illustrates the general decrease in percentage change from year to year between 2001 and 2014 for the number of clinical trial start dates cataloged for neglected tropical diseases.

Figure 3: Percent change in number of US Clinical Trials started in that year compared to the previous year.



While the data point towards a generally positive percentage change, the number of trials are clearly increasing decreasingly, which is especially pronounced in 2011 and 2013 when there are negative percentage changes. Due to the length of the drug development pipeline, these are years one would expect to see a large increase if the implementation of the PRV program did in fact spur the development of more drugs to combat neglected tropical diseases. When looking at the percentage change between 2007 and each subsequent year in reference to 2007 in Figure 4, the data are still inconclusive. The percentage difference between 2007 and 2014 is 16.8%, which appears noteworthy, but 2013's percentage difference between 2007 is -1.7% and the largest spike occurred in 2010 with an almost 35% percentage difference. The 2010 data were too early to be affected by the PRV program, and the negative change in 2013 also corroborates doubts about a causative link between the PRV program and increased neglected tropical disease drug development.

Figure 4: Percent change from 2007's count in number of US Clinical Trials sorted by start date for all preceding diseases by year.



While the clinical trial data are inconclusive regarding any effect from the implementation of the PRV program, there are other indicators of success. Table 1 details sales of a FDA Priority Review Voucher. It is important to note that the FDA offers Priority Review Vouchers not only for the pharmaceutical companies that develop drugs to treat neglected tropical diseases but also for those who create drugs targeting rare pediatric diseases. While the diseases differ, the priority review vouchers received in each instance are virtually identical. The increasing prices in Table 1 point to a marketplace that values these vouchers at continuously higher prices.

Table 1. Voucher sale prices since the program's inception.

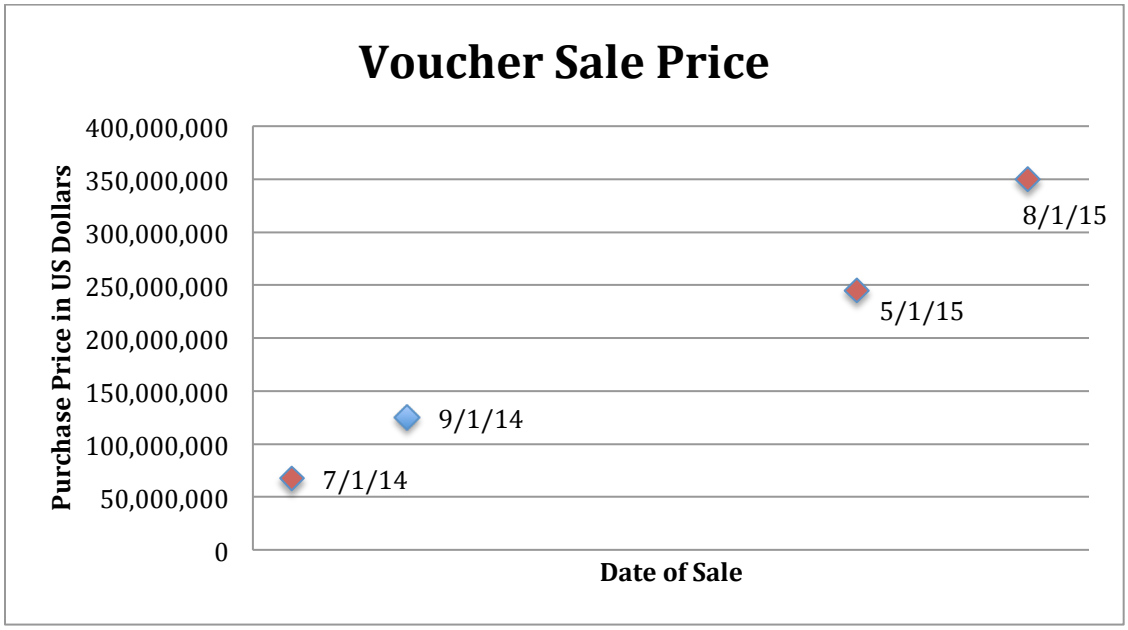
Date	**Purchase Price**
July 2014*	$67.5 million
November 2014	$125 million
May 2015*	$245 million
August 2015*	$350 million

*These vouchers were awarded for rare pediatric diseases and not neglected tropical diseases.

Source: Data from the Regulatory Affairs Professional Society: www.raps.org

This increase in market prices for vouchers is easily seen in Figure 5.

Figure 5. Voucher sale prices since the program's inception.



Markers in red represent vouchers that were awarded for rare pediatric diseases and not neglected tropical diseases.

Source: Data from the Regulatory Affairs Professional Society: www.raps.org

FINDINGS

Effects of Priority Review Voucher program on Clinical Trial Commencement

The implementation of the 2007 PRV program coincided with a general increase in the number of clinical trials started over the following 7 years for drugs that would treat neglected tropical diseases. The annual percentage change decreased over the following 7 years, but generally remained positive, indicating a nominal increase as seen in Figure 3. The percentage change when comparing 2007 and 2014 was 16.86%. It is clear from Figure 4 that there have been almost exclusively positive percentage differences since 2007. The data from each year were not rich enough to support the use of a difference of means test. There are a couple of issues with the current data available, though, which make it difficult to declare causation. First, it's unclear from FDA clinical trial start data when the researchers began the first steps of the process of developing a drug. Due to this and the variance in the drug development timeline, it's unclear whether drug manufacturers with clinical trials in 2014 began the process before the PRV program became law in 2007. Second, the data do not give information as to whether those beginning clinical trials were aware or incentivized by the PRV program. Third, cross correlation is an obvious issue with the data, as the number of trials in a certain year is often contingent on trials in the preceding years due to the need for multiple clinical trials in the drug approval process. Lastly, control data was unable to be found, as any diseases with the needed similar characteristics to those on the list would already be on the list.

Effects of Priority Review Voucher program on Priority Review Voucher Prices

As can be seen in Figure 5, the sales price for the vouchers has increase greatly since the first sale in July 2014. The last sales price of $350 million is in line with the initial researchers'

estimate that a "priority-review voucher would be worth more than $300 million for a potential blockbuster drug" (Ridley, Grabowski, and Moe 2006, 313-324) despite initial doubts from the public that the price would reach that level. The increase in price signals an increase in both the awareness of these vouchers and their value to large pharmaceutical companies. Comparing lines of best fit in Graph 4, it can be seen that the prices appear to be growing exponentially. It's important to realize that three of the four vouchers have come from the development of drugs for rare pediatric diseases rather than neglected tropical diseases, but the awarded vouchers are virtually identical. Thus, the market incentives to receive and then sell a voucher are the same for those looking to manufacture drugs to treat neglected tropical diseases as they are for those who have manufactured drugs to treat rare pediatric diseases. From a simple supply and demand model, it is likely that more companies will be incentivized to receive a voucher and then sell it as the market price continues to increase. Whether these companies will receive a voucher by creating a drug to treat rare pediatric diseases or neglected tropical diseases is still unclear. Some question why so few sales have taken place, but by looking at Table 18 and Table 19 it's clear that few vouchers have been awarded in general, and some are still unused and unsold as companies continue to track the market price of the vouchers. While it's likely that the voucher prices will continue to rise, it remains unclear whether these vouchers will serve their purpose in spurring the development of drugs to combat neglected tropical diseases.

Appendix

Blinding Trachoma

Table 1. Number of US Clinical Trials sorted by start date for the disease: Blinding Trachoma.

Year	**Number of trials started**
2000	1
2001	0
2002	0
2003	1
2004	0
2005	2
2006	1
2007	0
2008	1
2009	0
2010	0
2011	0
2012	0
2013	0
2014	1

Buruli Ulcer

Table 2. Number of US Clinical Trials sorted by start date for the disease: Buruli Ulcer.

Year	**Number of trials started**
2000	0
2001	0
2002	0
2003	0
2004	0
2005	0
2006	1
2007	0
2008	0
2009	0
2010	0
2011	1
2012	1
2013	1
2014	1

Cholera

Table 3. Number of US Clinical Trials sorted by start date for the disease: Cholera.

Year	**Number of trials started**
2000	1
2001	2
2002	1
2003	2
2004	0
2005	4
2006	5
2007	3
2008	5
2009	3
2010	7
2011	6
2012	10
2013	5
2014	7

Dengue

Table 4. Number of US Clinical Trials sorted by start date for the disease: Dengue.

Year	**Number of trials started**
2000	0
2001	1
2002	0
2003	1
2004	2
2005	4
2006	8
2007	7
2008	7
2009	10
2010	18
2011	14
2012	12
2013	12
2014	10

Human African Trypanosomiasis

Table 5. Number of US Clinical Trials sorted by start date for the disease: Human African Trypanosomiasis,

Year	**Number of trials started**
2000	0
2001	2
2002	1
2003	1
2004	0
2005	0
2006	0
2007	0
2008	0
2009	2
2010	0
2011	2
2012	3
2013	1
2014	2

Leishmaniasis

Table 6. Number of US Clinical Trials sorted by start date for the disease: Leishmaniasis.

Year	**Number of trials started**
2000	0
2001	1
2002	1
2003	4
2004	9
2005	8
2006	11
2007	15
2008	11
2009	10
2010	12
2011	11
2012	2
2013	7
2014	9

Leprosy

Table 7. Number of US Clinical Trials sorted by start date for the disease: Leprosy.

Year	**Number of trials started**
2000	2
2001	0
2002	2
2003	0
2004	1
2005	1
2006	7
2007	7
2008	3
2009	1
2010	6
2011	1
2012	1
2013	4
2014	1

Lymphatic filariasis

Table 8. Number of US Clinical Trials sorted by start date for the disease: Lymphatic filariasis.

Year	**Number of trials started**
2000	0
2001	2
2002	0
2003	2
2004	1
2005	2
2006	6
2007	3
2008	0
2009	3
2010	3
2011	2
2012	5
2013	2
2014	4

Malaria

Table 9. Number of US Clinical Trials sorted by start date for the disease: Malaria.

Year	**Number of trials started**
2000	5
2001	9
2002	24
2003	37
2004	42
2005	57
2006	72
2007	73
2008	57
2009	62
2010	95
2011	70
2012	78
2013	70
2014	79

Onchocerciasis

Table 10. Number of US Clinical Trials sorted by start date for the disease: Onchocerciasis.

Year	**Number of trials started**
2000	0
2001	0
2002	0
2003	1
2004	0
2005	0
2006	2
2007	0
2008	0
2009	1
2010	0
2011	2
2012	1
2013	1
2014	2

Schistosomiasis

Table 11. Number of US Clinical Trials sorted by start date for the disease: Schistosomiasis.

Year	**Number of trials started**
2000	0
2001	1
2002	0
2003	2
2004	1
2005	2
2006	9
2007	5
2008	1
2009	2
2010	5
2011	4
2012	10
2013	2
2014	4

Soil transmitted helminthiasis

Table 12. Number of US Clinical Trials sorted by start date for the disease: Soil transmitted helminthiasis.

Year	**Number of trials started**
2000	0
2001	0
2002	0
2003	0
2004	0
2005	1
2006	7
2007	1
2008	1
2009	1
2010	4
2011	4
2012	4
2013	1
2014	7

Tuberculosis

Table 13. Number of US Clinical Trials sorted by start date for the disease: Tuberculosis.

Year	**Number of trials started**
2000	11
2001	7
2002	16
2003	21
2004	28
2005	45
2006	41
2007	58
2008	67
2009	78
2010	77
2011	66
2012	74
2013	59
2014	74

Yaws

Table 14. Number of US Clinical Trials sorted by start date for the disease: Yaws.

Year	**Number of trials started**
2000	1
2001	2
2002	0
2003	0
2004	0
2005	0
2006	0
2007	0
2008	0
2009	2
2010	5
2011	1
2012	3
2013	3
2014	0

Combined results

Table 15. Number of US Clinical Trials sorted by start date for all preceding diseases.

Year	**Number of trials started**
2000	21
2001	27
2002	45
2003	72
2004	84
2005	126
2006	170
2007	172
2008	153
2009	176
2010	232
2011	185
2012	204
2013	169
2014	201

Combined Results

Table 16. Percent change in number of US Clinical Trials sorted by start date for all preceding diseases by year.

Year	% Change
2000	--
2001	0.286
2002	0.667
2003	0.600
2004	0.167
2005	0.500
2006	0.349
2007	0.012
2008	-0.110
2009	0.150
2010	0.318
2011	-0.203
2012	0.103
2013	-0.172
2014	0.189

Combined Results

Table 17: Percent change from 2007's count in number of US Clinical Trials sorted by start date for all preceding diseases by year.

Year	% Change
2007	--
2008	-0.110
2009	0.023
2010	0.349
2011	0.076
2012	0.186
2013	-0.017
2014	0.169

Voucher History

Table 18. Vouchers awarded since the programs inception.

Priority Review Vouchers Awarded to Date		
Date Voucher Awarded	*Voucher Type*	*Company Voucher Awarded to:*
2009	Tropical Disease	Novartis
2012	Tropical Disease	Janssen
2014	Rare Pediatric Disease	BioMarin
2014	Tropical Disease	Knight Therapeutics
2015	Rare Pediatric Disease	United Therapeutics
2015	Rare Pediatric Disease	Asklepion Pharmaceuticals
2015	Rare Pediatric Disease	Wellstat Therapeutics
2015	Rare Pediatric Disease	Alexion Pharmaceuticals
2015	Rare Pediatric Disease	Alexion Pharmaceuticals

Source: Table comes directly from the Regulatory Affairs Professional Society: www.raps.org

Voucher Status

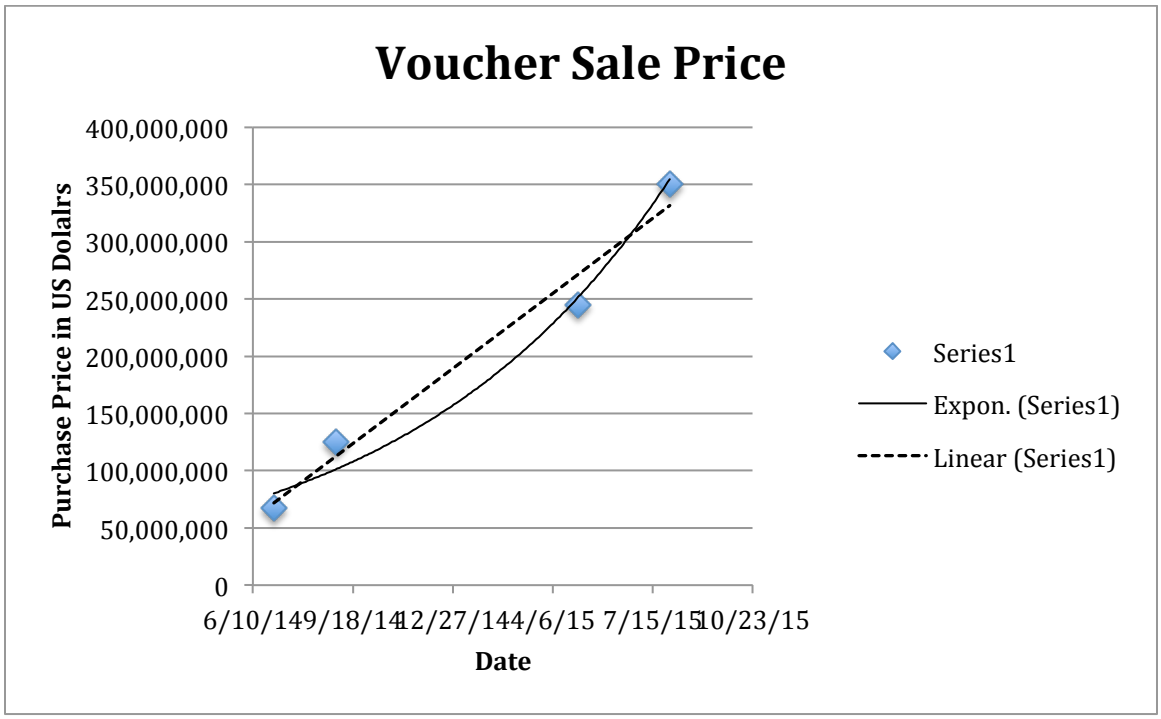
Table 19. Status of vouchers awarded.

Status of Existing Priority Review Vouchers		
Company	*Voucher Type*	*Status of Voucher*
Novartis	Tropical Disease	Unsuccessfully used by Novartis to accelerate the review of its Biologics Licensing Application (BLA) for Ilaris (canakinumab).
Janssen	Tropical Disease	Unused.
BioMarin	Rare Pediatric Disease	Sold to Sanofi and Regeneron for $67 million. Used successfully to speed the approval of Praluent.
Knight	Tropical Disease	Sold to Gilead Sciences for $125 million. Gilead is using the voucher in support of its NDA filing for a new HIV drug.
United Therapeutics	Rare Pediatric Disease	Sold to AbbVie for $350 million in August 2015. AbbVie has not disclosed how it plans to use the voucher.
Asklepion Pharma	Rare Pediatric Disease	Transfered to Retrophin under an existing agreement. Sold to Sanofi for $245 million in May 2015.

Source: Table comes directly from the Regulatory Affairs Professional Society: www.raps.org

Voucher Sale Price

Graph 1. Voucher sale prices since the program's inception with a linear and exponential trend line.



*These vouchers were awarded for rare pediatric diseases and not neglected tropical diseases.

Source: Data from the Regulatory Affairs Professional Society: www.raps.org

REFERENCES FOR BACKGROUND

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