

PRIORITY REVIEW VOUCHERS TO ENCOURAGE INNOVATION  
FOR NEGLECTED DISEASES

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## I. INTRODUCTION

Tropical diseases cause substantial suffering and loss of life around the world. Africa rightly receives considerable attention, but other regions also have limited resources to address enormous burdens from tropical diseases. Fortunately for people in developing Western Pacific countries (excluding Australia, Japan, New Zealand and the Republic of Korea), their share of the global burden of diseases (18%) is below their share of the world's population (24%), but unfortunately they have only 2% of the world's health resources (World Health Organization 2007, 19).

A recent policy change in the United States could provide treatments for tropical diseases in developing Western Pacific countries and other nations with low ability to pay. In September 2007, the U.S. Congress enacted legislation to increase research and development for treatments for neglected tropical diseases, including malaria, leishmaniasis, Chagas disease, and tuberculosis. A provision of the Food and Drug Administration Amendments Act of 2007 awards a transferable "priority review voucher" (PRV) to any company that gains Food and Drug Administration (FDA) approval for a new pharmaceutical or biological targeted to a neglected tropical disease. The bearer of this voucher is entitled to a priority review instead of a standard review for another drug product that is submitted for FDA approval.<sup>1</sup> The priority review voucher legislation was introduced into Congress by Senators Sam Brownback and Sherrod Brown (Brownback, 2007). The law is based on a policy proposal and economic analysis in Ridley, Grabowski & Moe (2006).

The value of a priority review voucher comes from the prospect of an earlier time to market for a new drug. The target FDA review times for priority drugs are six months compared to ten months for standard drugs. The *actual* median FDA review times for priority and standard

drugs since 2000 are about seven and fifteen months, respectively (Table 1). In a prior analysis we found that several months earlier entry to the market can be worth more than one hundred million dollars for pharmaceutical products with large expected market sales (Ridley, Grabowski & Moe, 2006).

Priority review vouchers raise a number of interesting issues for both policymakers and analysts. They include how the market for the vouchers will evolve, how they will be administered by the FDA, and what their ultimate effects will be in promoting R&D for tropical diseases. Other important issues to consider are how the vouchers will complement other public and private incentives, and whether the vouchers will lead to any important unintended consequences. Under the new law, companies that use the voucher will be required to pay a supplemental review fee so that the FDA can recoup the resource costs associated with additional priority reviews. The additional user fee is intended to prevent a PRV from slowing the review process for other drugs in the FDA queue.

In this paper we consider some of the important issues associated with the new PRV law. Section II of the paper provides background on diseases of developing countries and how the vouchers complement other push and pull incentive programs directed toward neglected diseases. Section III considers the PRV law in more detail and regulatory issues in administering the law. Section IV considers the economic value of a PRV under different scenarios. The final section summarizes our findings and discusses some of the key open issues for further analysis.

## II. THE PRV AND OTHER INCENTIVE MECHANISMS FOR NEGLECTED DISEASES

The Congressional Act establishing the PRV names sixteen tropical diseases for which treatments would be eligible for the vouchers.<sup>ii</sup> The law also states that vouchers could be obtained for “any other infectious disease for which there is no significant market in developed nations and disproportionately affects poor and marginalized populations, designated by regulation of the Secretary.”

The basic challenge to stimulating more R&D on new medicines for neglected diseases arises from the low income and ability to pay for health care that exists in developing countries. Average spending for health services in low-income countries was about \$29 per capita in 2003.<sup>iii</sup> The ability to pay barrier is compounded by other barriers, including an inadequate medical and political infrastructure in most countries for efficient delivery of drugs and other medical supplies. Insufficient revenues and infrastructure on the demand side are coupled with high fixed costs of R&D on the supply side. As a consequence, there have been relatively few drugs developed to address the high global disease burden posed by tropical diseases (WHO, 2004).

Figure 1 shows a graph of diseases that are highly concentrated in developing countries. Some of these diseases, like malaria and Tuberculosis (TB), have large annual global burdens and are the subject of targeted public-private development partnerships and other initiatives. The PRV law could complement these existing programs. At the same time, there are a large number of tropical diseases that have substantial disease burdens in the aggregate that have received less attention in terms of drug development efforts. These diseases could garner new interest and attention as a result of the new PRV law.

**A. *Push and Pull Incentive Programs***

Public and private strategies for stimulating R&D on neglected diseases are usually designated as “push” or “pull” programs. Strategies in the push category involve R&D cost sharing and subsidies which can be accomplished through tax credits, research grants, and public-private development partnerships (PDPs). Pull programs involve a specified prize or reward for research outputs—for example, guaranteed purchase arrangements for developing and gaining approval for new drugs for neglected diseases. The priority review voucher is a market oriented pull mechanism for gaining approval of a new drug for neglected disease. Its value derives from faster approval at the FDA for another drug targeted to the U.S. market. It can be combined with push mechanisms such as orphan drug tax credits.

Push and pull mechanisms have well-known benefits and limitations. Push mechanisms can allow direct donor control over product development, and might be especially beneficial at the earliest stages of research process where scientific and commercial risks are substantial, and where large uncertainties exist on the feasible set of product attributes. On the other hand, push mechanisms that are based on central control can suffer from asymmetric information and a misalignment of incentives between donors and developers, leading to resource inefficiencies.

Pull strategies reward output and do not require donor funding unless specific milestones are met such as regulatory approval or market distribution. Pull strategies are designed to create market type incentives through commitments for particular outcomes. A potential limitation, however, is the credibility of the commitment and the potential time inconsistency problem for pharmaceutical R&D programs than can span a decade or more.

A prominent example of a market oriented pull strategy is the Advanced Market Commitment (AMC) for stimulating R&D for neglected diseases, developed by Michael Kremer and his colleagues (Kremer, 2002; Berndt and Hurwitz, 2005). The AMC concept was adopted in 2007 when five countries (Canada, Italy, Norway Russia, and the United Kingdom) along with the Gates Foundation committed \$1.5 billion to launch the first AMC for pneumococcal vaccine for disease strains prevalent in developing countries. This pilot program provides for 7 to 10 years of funding with the goal of developing sustainable supply conditions for third-world countries. It has been estimated that a vaccine meeting the AMC criteria could save the lives of 5.4 million children by 2030 (GAVI Alliance, 2007).

One successful program that utilizes both push and pull incentives is the U.S. Orphan Drug Act. This Act provides tax credits, subsidies and other benefits such as market exclusivity to stimulate R&D on diseases with low prevalence in the United States (Grabowski, 2005). It has been very successful in encouraging new drug treatments for rare illnesses like Gaucher's disease and Wilson's disease. Neglected diseases like malaria qualify for orphan drug status because of their low disease prevalence in the United States. However, there have been relatively few drugs developed under the ODA for tropical diseases.<sup>iv</sup> Figure 1 illustrates that the burden for tropical diseases is great. As discussed in section III, the combination of orphan drug subsidies, together with the prize of a transferable PRV, could provide a more powerful set of incentives for increased R&D on neglected diseases.

***B. The PRV as a Complement to Other Incentive Programs for Neglected Diseases***

One advantage of the PRV is that it can complement other push and pull strategies. Many public-private development partnerships support a portfolio of development projects dedicated to

particular neglected diseases. A PRV could be valuable to these PDP activities in terms of resource support and incentives with their private partner. These non-profit foundations engage various public and private institutions with novel contractual relationships to support their clinical development programs. In effect, the PRV could be a *quid pro quo* for performing the expensive late stage trials. Alternatively, if the PDPs retained ownership of the PRV on a successful approval, they could auction it to the highest bidder and use the funds in further research.

The PRV also complements charitable and good will activities by for-profit corporations. Some important drugs targeted to neglected diseases have been developed under the philanthropic programs of major pharmaceutical firms. The most prominent example is Merck's development and donation of the drug ivermectin for river blindness. Other important initiatives by drug companies in progress include development programs targeted to filariasis, trachoma, and leprosy (Grabowski, 2005). The PRV could help broaden the scope of R&D on neglected diseases, and complement the philanthropic motivation underlying those programs.

The PRV also can reinforce other pull mechanisms proposed such as AMC programs that would provide purchase guarantees for a malaria or TB vaccine that meets particular specifications (Berndt and Hurwitz, 2005). While this might be a useful additional incentive, the primary contribution of the PRV might be to encourage R&D for lower profile neglected diseases without large, dedicated funding. In particular, the voucher could be particularly useful in building on development programs that were initiated for other disease indications to a new set of neglected diseases. The PRV also could allow smaller biotech firms to demonstrate proof of concept for new therapies before pursuing indications that target developed country markets.

### III. THE KEY ROLE OF THE FDA IN ADMINISTERING THE PRV

#### A. *Regulatory Requirements and Incentive Effects*

To earn a priority review voucher for a different drug, the drug developed for the tropical disease must be a novel treatment that is itself eligible for priority review under established FDA criteria. It must be a molecule (pharmaceutical or biological) that contains an active ingredient that was not previously approved by the FDA. This precludes new formulations, new indications and fixed combinations of previously approved drugs.

The PRV, once awarded, can be sold or transferred to another party. In order to use the PRV, however, the bearer will have to notify the FDA 365 days in advance of filing the new drug application (NDA) on which it is to be applied. This then binds the party to the supplemental priority user fee. The FDA will calculate and publish this fee each year based on its assessment of the average cost to review priority review drugs. The user fee for new drug applications requiring clinical data is \$1,178,000 for the 2008 fiscal year (Federal Register, Prescription Drug User Fee Rates for Fiscal Year 2008).

Under priority review, the target for FDA action is six months from the date of submission of a new drug application. This does not mean the application must be accepted or rejected in this period. The FDA can decide the drug is approved, approvable, or rejected. In the intermediate “approvable” case, the drug application is returned to correct deficiencies and might require that the sponsor perform additional tests (Berndt et al, 2005). The FDA, therefore, retains considerable discretion in the review of all drug applications.

FDA actions in administering priority review for voucher drugs will have an important influence on the value of the voucher. If, for example, FDA reviewers tend to issue approvable rather than approved outcomes for these drugs based on minor deficiencies or excess risk

aversion, this would significantly diminish the value and incentives for the PRV. This appears to be the biggest current concern of companies that are considering participating. Given that R&D is costly and risky, and can stretch over long time periods, there must be a credible expectation that the program will be administered in accordance with the law's objectives (i.e., they must avoid the time inconsistency problem). Many companies might wait to see if this is the case before initiating new R&D programs on neglected diseases, and markets for vouchers could be slow to develop.

***B. Potential Unintended Consequences***

From a social perspective, the concern of some observers is that priority review vouchers could slow the review of other drugs, or alternatively, a drug subject to a PRV would pose greater safety risks associated with faster reviews. The payment of the special user fee, and the 365 day notification period, provides the FDA with additional resources to handle the extra work load and this should ameliorate the first concern. In addition, since priority review does not lower the approval criteria for safety or efficacy, it should not increase safety risks provided adequate resources are available to undertake the faster reviews.

The general issue of whether faster review under the Prescription Drug User Fees Acts has led to greater safety risks has been investigated in some recent studies. The Acts introduced review time targets, but also gave the FDA significantly more resources to undertake new product reviews. Berndt et al (2005) found that the proportion of new drug withdrawals remained unchanged before and after the implementation of drug user fees in 1994. Similar findings were reported by the FDA (2005) and the Tufts Center for the Study of Drug Development (2005). On the other hand, Mary Olson (2004, 2008) in a multiple regression analysis found that drugs with

faster review times are subject to more adverse events. However her results are subject to some data limitations and potentially confounding factors.

Grabowski and Wang (2008) analyze the effect of review times on adverse events. They control for global launch lags, drug novelty, and utilization. Their results indicate that drugs approved abroad first are subject to fewer adverse events. This suggests some spillover knowledge benefits to FDA reviewers from a drug's experience in actual clinical practice with large patient populations in addition to the data obtained from controlled patient trials. From a policy perspective, however, priority review vouchers are unlikely to affect the country of first launch, since the United States is either the market of first launch, or a simultaneous global launch, for the vast majority of commercially important new drugs since the mid-1990s (Grabowski and Wang, 2008). After controlling for global launch lags and various other factors such as drug novelty and utilization, Grabowski and Wang find no significant relation between review times and adverse events.

In the deliberations leading to the passage of the FDA Amendments Act of 2007, Congress considered several policy options to enhance drug safety, including elimination of the FDA review time targets. However these targets were designed to reduce the lengthy delays of the pre-user fee period. There is evidence of significant health benefits from the timely access to new medicines under user fees (Philipson, Berndt, Gotschalk & Sun, 2008). Instead of rolling back these targets, Congress chose to institute new post-marketing safety measures. This focus on post-marketing measures is consistent with the recommendations of various experts including the Institute of Medicine (2007) and former FDA Commissioner, Mark McClellan (2007).<sup>v</sup> The 2007 Act dedicates significant funds from drug user fees to enhancing post-market surveillance and information disclosure. It also gives the FDA expanded risk management tools.

### III. VALUATION OF PRIORITY REVIEW VOUCHERS

The PRV has value from three perspectives: the company that utilizes the PRV to gain a speedier review, the company that is awarded the PRV for obtaining an approval for a new tropical medicine<sup>vi</sup>, and the overall global social value arising from new drugs and vaccines derived from the PRV.

#### A. *The Value of the PRV in Gaining a Priority Review*

In our earlier analysis, we considered the value to a company from obtaining a PRV that entitled it to a priority review instead of a standard review. This was a “time value of money” analysis. We showed that roughly half the “blockbuster” drugs introduced in the 1990s received standard rather than priority reviews (using the criteria for a blockbuster of \$1 billion in sales by year 5 after launch). The average difference in time over the 1992–2002 period between priority and standard reviews was 12 months. To estimate the value of a one year earlier approval time, we used as our baseline the after tax stream of income for the representative top decile product from the sample of 1990-1994 new drug introductions (Grabowski, Vernon & DiMasi, 2003). We found the value of one year earlier time to market for this typical top decile product to be over \$300 million (Ridley, Grabowski & Moe, 2006).

The value of the voucher is lower than prior estimates if the difference between priority review and standard review times is lower. In 2006 the difference in median review times was seven month rather than a year (Table 1). The value of the voucher might be greater than prior estimates, however, if the voucher i) increases time on the market (rather than just shifting it forward) and ii) creates early mover advantages vis-à-vis a competitor. First, given the workings

of the Hatch-Waxman Act on patent restorations, we assumed that effective patent life would remain unchanged. Specifically, we assumed that faster review time at the FDA would be offset by less patent term restoration awarded under the Hatch-Waxman Act. In that analysis, therefore, we only estimated the time value of money, assuming the voucher product's income stream was unchanged and shifted forward in time by exactly one year so.

There are many situations, however, where effective patent life would be increased by a product's earlier entry into the market. There are several scenarios discussed below where the product would both reach the market sooner with a PRV, and also experience an increase in effective patent life by the amount of the difference between priority review and standard review (i.e., an earlier market entry but the same patent expiration date). An expansion of patent life based on earlier entry on the front end can be worth a substantial amount in terms of the expected present value for a top decile product.

Another source of value that we abstracted from in our earlier analysis comes from the value that would accrue to firms in terms of early-mover advantages when companies are in a race to introduce a new class of therapeutics. These early mover advantages can be substantial in pharmaceuticals. The fact that the PRV is transferable and can be sold to the highest bidder could substantially increase its value if a bidding war were to occur between rival firms developing competing drugs in the same class. The value of the PRV from extra patent life and early mover advantages are considered further below.

## ***B. Effective Patent Life Scenarios***

Under the Hatch-Waxman Act, new molecular entities are eligible for patent restoration associated with losses in effective patent life during clinical development and FDA review.

Patent time is added equal to half the time lost in clinical development time and all the time lost during FDA review, subject to two constraints. The first constraint is that the maximum patent extension time is five years. Second, the amount of patent extension is capped by an effective patent life of 14 years from the date of first approval. Only one patent is eligible for patent restoration (usually the core product or composition-of-matter-patent). Process patents are not eligible for patent restoration.

As noted in our prior analysis, we assumed that earlier time to market from a PRV would be exactly offset by reduced patent restoration time (Ridley, Grabowski & Moe, 2006). For example, drugs subject to the 14 year cap on effective patent life would have a fixed 14 year effective patent life with and without the PRV. This fixed effective patent life would also occur when the extension is relatively short and neither of the Hatch-Waxman constraints hold (i.e., restored patent time is less than five years and effective patent life less than 14 years). On the other hand, products with lengthy development and review times typically reach the five year hatch-Waxman limit on patent time extensions prior to a 14 year effective patent life. Such products would obtain an extended patent life from a PRV.<sup>vii</sup>

There are a number of additional scenarios in which a product would realize longer patent life from a speedier review at the FDA. Especially relevant examples are products whose market exclusivity periods are not determined by its effective patent life expiration date. For example, a product's lifetime could be ended short of its extended patent period due to a successful patent challenge by a generic firm. Alternatively, a product's sales could be significantly curtailed due to a superior product introduction by a competitor. In other cases, a product's effective patent life might extend beyond that under the patent extension formula due to other patents or regulatory factors. These are all scenarios of increased effective patent life from the PRV.

## *1. Empirical Analysis of Effective Patent Life*

In order to gain insights into the relevance of various scenarios, we examined the experiences of blockbuster products experiencing initial generic competition in the five year period 2002 to 2007. In particular, we focused on the sample of new molecular entities which received a standard review by the FDA. We then selected products that had a billion dollars in sales or more in the year immediately preceding generic entry. There were 11 products that fit this criterion for 2002 – 2007. They are listed in Table 2. <sup>viii</sup>

Of the 11 products shown in Table 2, four of them had extended patent life of 14 years under Hatch-Waxman, plus an additional six months for undertaking pediatric clinical trials. <sup>ix</sup> As discussed, the patent life for these projects would be the same with or without the PRV. On the other hand, two products reached the five year constraint prior to a 14 year effective life (Coreg, Ambien). These products would have obtained increased patent life from an earlier launch with a PRV. <sup>x</sup> This would also have been the case for the other five products in Table 2 (Paxil, Celexa, Allegra, Norvasc and Protonix) because their generic entry points were determined by patent litigation rather than the Hatch-Waxman patent life formula. In summary, 7 of these 11 blockbuster products would have enjoyed increased effective patent life from an earlier launch through a PRV.

A prior analysis of market exclusivity periods by Grabowski and Kyle (2007) for new molecular entities experiencing their first generic entry in the 1995 to 2006 period also suggests that many products are in the cohort that would obtain increases in effective patent life from a PRV. In particular, the mean annual market exclusivity for drugs with sales above \$100 million varies between 10 and 12 years (Grabowski and Kyle, 2007). This study also found that drugs

subject to patent challenges had shorter effective lifetimes than drugs not subject to these challenges. There is a strong trend in recent years toward drugs with significant sales to experience generic challenges early in their product life cycle. (Berndt et al, 2007) Under Hatch-Waxman the first generic firm to file and successfully challenge an innovator's patent receives 180 days of exclusivity.

The issue of expected gains in exclusivity times is a useful topic to examine from a forecasting perspective with drugs currently gaining FDA approval. However, based on our historical analysis, many products would have obtained increases in effective patent life from the PRV. Since the PRV can be traded on a market, companies would be willing to bid more to obtain a PRV for these compounds with expected benefits from extensions in effective patent life. This would increase the value of the PRV in a market exchange framework.

## ***2. A Stylized Example***

To obtain further insights on the expected values associated with increased patent life from a PRV, we developed a stylized example illustrated in Figure 2. In this example we assume the product without a PRV would have a lifetime of 11 years, at which point the product loses the entire market to generic competitors.<sup>xi</sup> The PRV is assumed to permit the innovator company to gain entry into the market seven months earlier. (This is the average difference between priority and standard review in Table 1.)

We also assume that the time at which generic competition occurs remains unchanged (there is no offset due to Hatch-Waxman). Hence the product's lifetime increases to 11 years 7 months under a PRV. Product sales in the year prior to generic competition are assumed equal to \$1.5 billion in Figure 2. The values on sales and market life in this stylized example are

consistent with data on the seven products listed in Table 2 that would have been eligible for extended patent life from a PRV.

Under these assumptions, a seven month shift in the revenue stream would result in a total gain in the present value of product sales of \$599 million. This value can be decomposed into \$322 from earlier revenue (time value of money) and \$277 million from seven additional months of patent life.<sup>xii</sup> The value of additional sales before discounting is \$874 million. It should be borne in mind that all of these values are based on sales revenues rather than income. To obtain present values of income, one would need to subtract the variable costs of production, marketing, taxes, and other fees (see Grabowski, Vernon & DiMasi, 2002).

Under a number of plausible scenarios, the after-tax benefits from an earlier launch afforded by priority review are likely to in excess of one hundred million dollars. A product-specific present value analysis would include the product's forecasted sales revenues and patent life as well as contribution margins, cost of capital, marginal tax rates, etc. However, there also may be a significant discount factor for regulatory risks on the part of companies initially purchasing these vouchers until they see specific examples of how the FDA behaves with respect to PRVs.

### ***C. Early Mover Advantages***

The advantages of first entry have long been recognized in the economics and marketing literature. Theoretical work by Schmalensee (1982) shows that once consumers use a new product and become familiar with its quality, they might be reluctant to use a newly introduced competing product because they are uncertain about its quality. In the case of pharmaceuticals, being first to market gives the first entrant an opportunity to allow physicians to become familiar

with the therapeutic qualities of the drug, and to accustom physicians to thinking of the first entrant as the drug of first choice for treating the symptoms of concern.

Research on the pharmaceutical industry also provides empirical evidence that first-movers have an advantage over later entrants, all else being equal. In an early, oft cited analysis, Bond and Lean (1977) studied two prescription drug markets (diuretics and antianginals) and concluded that the “...the first firm to offer and promote a new type of product received a substantial and enduring sales advantage...” More recently, in analyses of sales of SSRIs and H2-receptor antagonists, Berndt and colleagues found that order of entry had significant effects on market share (Berndt et al, 1997; Berndt et al, 2002). Their analysis of the H2 blockbuster market, for example, finds that all else equal, the  $(n+1)$ th entrant can expect about forty percent lower sales than the  $n$ th entrant (Berndt et al, 1997).

To the extent that companies are involved in a competitive race to introduce a new class of therapies, the value to a bidder for a PRV to a firm projected to be second in this race could escalate to several hundred million additional dollars associated with expected long term gains in market share from an earlier introduction. Clearly this early mover component of value could be substantially more than the time value of money and increased effective patent life components under the right competitive scenarios. Since the PRV can be banked and sold to the highest bidder, its value will depend on both demand and supply availability at any point in time. The analysis here suggests that when all three components are applicable, the voucher could be worth a few hundred million dollars to potentially several hundred million dollars or more under a bidding war scenario for early mover advantages in a closely contested race where the expected market is very large. Of course, negotiating and bargaining strength as well as risk preferences could also play an important role in the value of the PRV.<sup>xiii</sup>

#### ***D. Value of Voucher to Developer for New Tropical Medicine***

To motivate development of a new drug for a neglected disease, the price of the PRV must exceed the R&D costs that the organization expects to incur for developing and gaining drug approval. For a profit making entity, the clinical development costs would be eligible for the 50% tax credit from an orphan drug designation. Sale of the voucher to a third party would, in turn, be subject to the corporate income tax. Revenues of several hundred million dollars obviously would support many neglected disease programs.

In the case of non profit public-private partnerships the PRV could be a valuable item to trade in exchange for support services. For example, a private firm might be willing to fund the phase III trials of a drug in its portfolio in exchange for obtaining the PRV in the event of a successful product approval. Alternatively, as discussed earlier, a PDP that has significant funding for its phase III trials from foundations and philanthropic sources could bank the PRV and eventually auction it to the highest bidder. It can then plow back the revenues to further work on other entities in its R&D program. In either event, the PRV could become a major source of R&D funding for public-private partnerships with neglected disease programs.

As discussed in our earlier article, we believe the cost for R&D for pursuing a neglected disease indication could be significantly less than the \$800 million mean estimated R&D cost for new chemical entities.<sup>xiv</sup> This is true even without taking account of the R&D tax credits from the Orphan Drug Act. First, infectious disease indications frequently have higher probabilities of success, shorter timelines, and lower R&D costs than the mean case. Second, drugs for neglected diseases of poverty would not normally need to undertake comparative trials for formulary and reimbursement purposes. Third, there are substantial spillover possibilities from other R&D

programs associated with bioterrorism and from public efforts to support vaccine and drug developments on pathogens in foreign countries by the U. S. military. These products could be investigated after some clinical trials have already occurred in these public programs. All of these factors suggest that the PRV valued at several hundred million dollars could be a valuable stimulus to increased R&D activity on neglected disease, just as the Orphan Drug Act stimulated a dramatic increase in activities on rare genetic diseases in developed countries.

### ***E. Global Social Welfare***

As discussed in our prior work, the largest social value would accrue from new pharmaceuticals and biologicals that address the high disease burdens for which adequate treatments are not currently available. A common threshold for health interventions in the poorest countries is \$100 per disability adjusted life year (DALY) (a fraction of the value utilized in more developed countries). Even utilizing this low DALY value per day, the benefits could be enormous for products that significantly reduce the disease burden for the 12 neglected diseases targeted by the new law. In addition, other diseases that disproportionately affect developed countries as shown in Figure 2 are likely to be added to the list of targets for the PRV in future regulatory actions.

A secondary component of social value arises from earlier United States availability of the medicines to which the voucher is applied. Several of the blockbuster drugs that received standard reviews in the 1990s went on to be leaders in their therapeutic class (e.g., Zocor, Norvasc and Ambien). If the voucher is applied to such cases, there also could be significant increases in consumer surplus and producer surplus from people in the U.S. having access to the voucher-applied product seven months earlier. This is an empirical issue for future work.

#### IV. CONCLUDING REMARKS

In 2007 Congress created a novel voucher award program to stimulate R&D for neglected diseases. We estimate that in a well functioning market, the priority review voucher could be worth hundreds of millions of dollars based on the time value of money associated with faster reviews, increases in effective patent life, and earlier mover advantages vis-à-vis competitors. The vouchers therefore could be a powerful stimulant for developing and filing new drug applications at the FDA for neglected diseases.

The voucher program complements other push and pull mechanisms such as public-private partnerships and Advanced Market Commitment incentive programs. Given that drugs developed for tropical diseases like malaria and dengue fever are eligible for orphan drug status in the United States, a 50% tax credit would also be applicable to the clinical trial costs for these diseases. The PRV in combination with these credits provides substantial incentives for companies to investigate a wider set of neglected diseases beyond those already targeted by dedicated programs.

The costs of the program appear to be small compared to potential benefits. The biggest concerns are the possibility of the PRV program slowing other FDA approvals, or subjecting patients to increased safety risks from faster reviews of the voucher drugs. However users of priority review program will pay an additional user fee and must give the FDA 365 days advance notice to allow the agency time to plan its resource allocations to handle the expedited reviews. Furthermore, priority review does not involve a lower standard for approval, or entitle the bearer to an actual approval in six months, but only a decision in that time frame. At the same time, however, for priority reviews to be an effective market oriented pull mechanism, there must be a

credible expectation that the program will be administered in the spirit of the law's objective so that voucher drugs will not be subject to inordinate delays unrelated to a product's efficacy or safety attributes.

To achieve the ultimate public health objective of reducing the large disease burden associated with tropical diseases, new medicines and vaccines emerging from the PRV program must be distributed to the relevant developing countries. This, of course, requires more than FDA approval. Nevertheless, development and approval of new medicines are essential first steps in the process.

The increased approvals by the FDA of effective new medicines for tropical diseases would likely be eligible for support by other government and non-government efforts dedicated to increased dissemination of effective therapies in the third world. This is currently a high priority of the Gates Foundation and other organizations. The U.S. government has also announced a \$350 million program to provide integrated treatment for seven neglected tropical diseases including lymphatic filariasis (elephantiasis); schistosomiasis (snail fever); trachoma (eye infection); onchocerciasis (river blindness); and three soil-transmitted helminthes (STHs—hookworm, roundworm, whipworm). The U.S. is working with other countries to support an additional global commitment of \$650 million to these efforts. As was true for the Orphan Drug Act, Europe and Japan could pass their own variants of the priority review voucher concept.<sup>xv</sup> They could also be integrated with other evolving programs for the distribution of established therapies to countries with low ability to pay.

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TABLE 1: Approval Times (Months) for Priority and Standard NMEs and New BLAs since 2000

Calendar Year	Standard Review Median Total Approval Time	Priority Review Median Total Approval Time	Differences for Median Total Approval Time	Standard Review Median FDA Review Time	Priority Review Median FDA Review Time	Difference for Median FDA Review Time
2000	19.9	6	13.9	15.4	6	9.4
2001	19	6	13	15.7	6	9.8
2002	15.9	16.3	-0.4	12.5	13.8	-1.3
2003	23.3	6.7	16.4	13.8	6.7	7.1
2004	24.7	6	18.8	16	6	10
2005	23	6	17	15.8	6	9.8
2006	13.7	6	7.7	12.5	6	6.5
Mean	20	8	12	15	7	7

Beginning in 2004, these figures include new BLAs for therapeutic biologic products. Source:

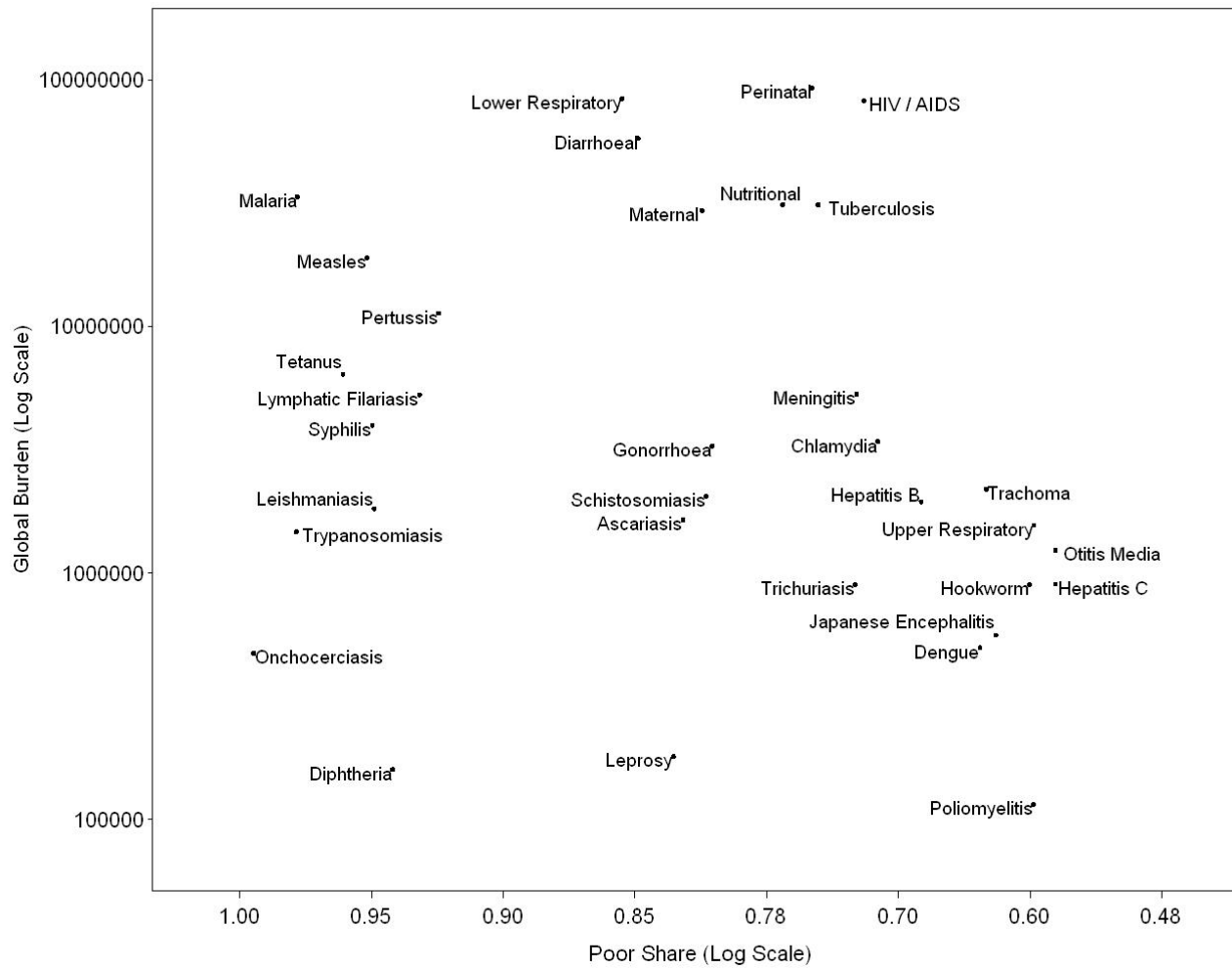
<http://www.fda.gov/cder/rdmt/NMEapps93-06.htm>

TABLE 2 Standard Review Drugs With More Than \$1 Billion in Sales in the Year Before Generic Entry

BRAND (CHEMICAL NAME)	GENERIC ENTRY	FDA APPROVAL	MARKET EXCLUSIVITY <sup>A</sup>	GENERIC TRIGGER EVENT
1 Zestril/Prinivil (lisinopril)	June 2002	December 1987	14 years 6 months	14 year Hatch-Waxman EPL
2 Paxil (paroxetine)	September 2003	December 1992	10 years 8 months	Litigation
3 Celexa (citalopram)	October 2004	July 1998	6 years 3 months	Litigation
4 Allegra (fexofenadine)	September 2005	July 1996	9 years 2 months	Litigation
5 Pravachol (pravastatin)	April 2006	October 1991	14 years 6 months	14 year Hatch-Waxman EPL
6 Zocor (simvastatin)	June 2006	December 1991	14 years 6 months	14 year Hatch-Waxman EPL
7 Zoloft (sertraline)	August 2006	December 1991	14 years 6 months	14 year Hatch-Waxman EPL
8 Norvasc (amlodipine)	March 2007	July 1992	14 years 8 months	Litigation
9 Ambien (zolpidem)	April 2007	December 1992	14 years 4 months	5 year Hatch-Waxman Extension
10 Coreg (carvedilol)	September 2007	September 1995	12 years	5 year Hatch-Waxman Extension
11 Protonix (pantoprazole)	December 2007	February 2000	7 years 11 months	Litigation

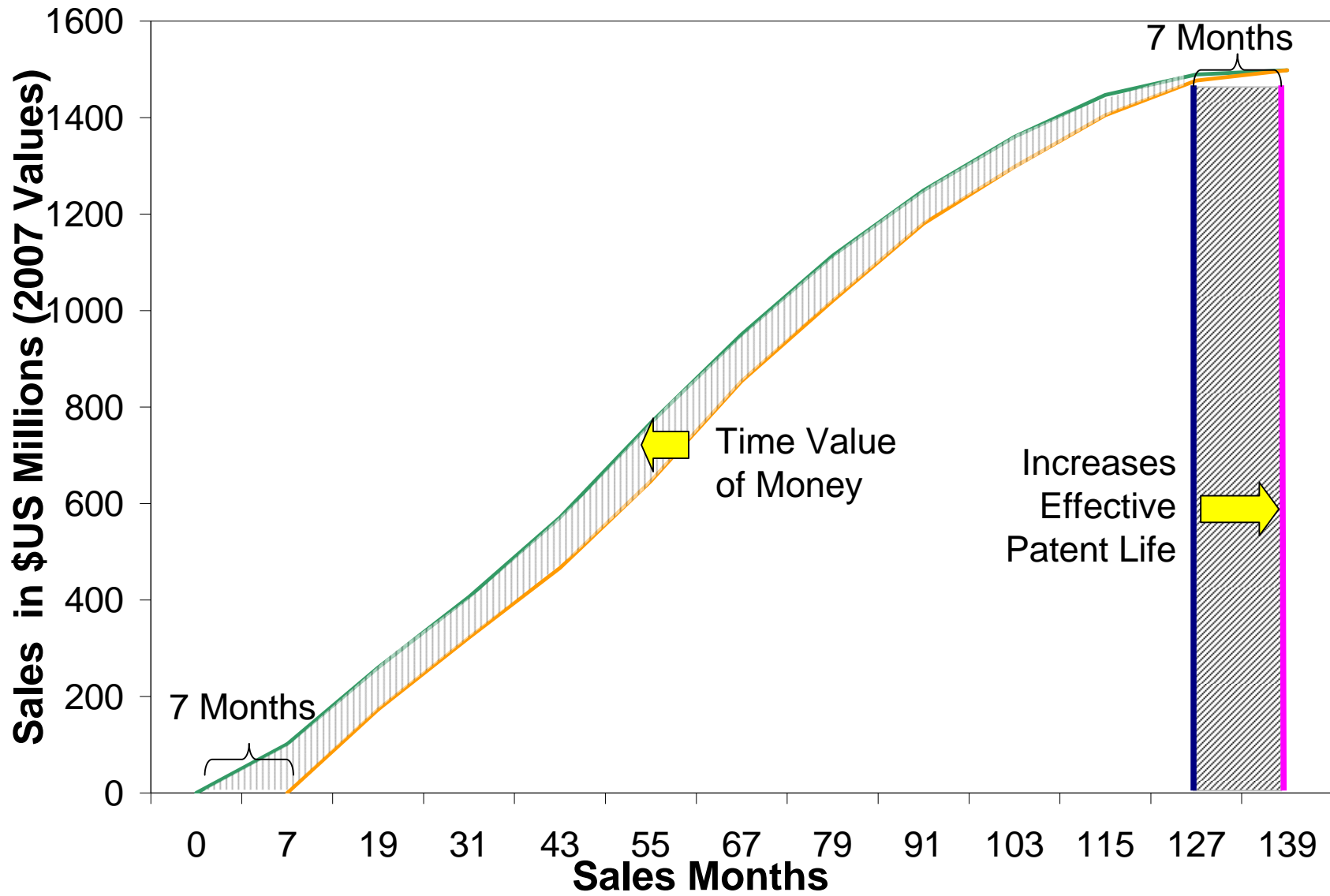
Note: <sup>A</sup> A 6 month pediatric exclusivity period was added to the listed patents for all these products except Protonix.

FIGURE 1: Annual Global Burden of Disease (DALYs) vs. Share of Burden in Developing Countries, 2005



Source: Authors' calculations based on World Health Organization 2006

FIGURE 2: The Priority Review Voucher shifts sales forward and increases effective patent life.



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<sup>i</sup> Section 1102 of the Act titled Priority Review to Encourage Treatments for Tropical Diseases.

<sup>ii</sup> The 16 diseases are tuberculosis, malaria, blinding trachoma, buruli ulcer, cholera, dengue/dengue haemorrhagic fever, dracunculiasis (guinea-worm disease), fascioliasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, soil transmitted helminthiasis, and yaws.

<sup>iii</sup> Per capita spending is estimated using World Health Organization data on health care spending in 2003, WHO data on population and population growth rates from 2005, and World Bank data on country income classification for 2004.

<sup>iv</sup> As of July 2003, there were only 12 orphan drugs approved in the United States targeted specifically to tropical diseases (Grabowski, 2005; Kettler, 2000).

<sup>v</sup> As various analysts have pointed out, serious adverse events that occur with relatively low incidence are only observable after regulatory approval in large patient populations rather than in the controlled pre-market clinical trials that typically involve a few thousand individuals. (Institute of Medicine, 2007) (Grabowski and Wang, 2008) Post-marketing safety activities have been relatively under-funded in both the public and private sector. (Ridley, Kramer, Tilson, et al, 2006).

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<sup>vi</sup> The company awarded the voucher, and its user, are not necessarily the same company since one firm might generate and utilize the PRV itself, or auction or trade it to another company.

<sup>vii</sup> Assume, for example, that the formula on clinical development time and review time yielded a restoration time of six years. In this case, the five year cap would be effective and added onto the original patent expiration date under either priority or standard review. Hence an earlier approval of seven months would also expand effective patent life by the same seven months.

<sup>viii</sup> Information on Hatch-Waxman times for specific drugs are available on the U.S. Patent Office's website ( <http://www.uspto.gov/web/offices/pac/dapp/opla/term/156.html> ). Information on the dates of initial generic launch were obtained from an IMS data collected through 2005 (Grabowski and Kyle, 2007) and also from sources on the internet such as Silver (2007). These latter sources also contained information on entry based on the successful challenges of branded firm patents.

<sup>ix</sup> A product can be granted an additional six months exclusivity for undertaking clinical trials and gaining an approved label for pediatric utilization. For an analysis of the value of six months pediatric exclusivity for a selective group of products (see Li, Eisenstein and Grabowski, et al, 2007).

<sup>x</sup> In the case of Ambien, the five year extension time under Hatch-Waxman plus pediatric exclusivity yields an effective patent life of 14 years and 4 months. Hence the extra time offered

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by a PRV would only be two months before it reaches the 14 year 6 month constraint under Hatch-Waxman.

<sup>xi</sup> Products with sales in excess of \$1 billion typically lose more than 90% of their sales to generic competitors within a matter of months. (Grabowski, 2004; Silver, 2007) However, where only a generic product enters with a six month Hatch-Waxman exclusivity due to a successful product challenge, the innovator firm will typically license an authorized generic. (Berndt et al, 2007) This enables the innovator to capture some of the lost sales from generic entry (albeit at reduced margins) for a short period of time before commodity pricing sets in with multiple generic entrants. We abstract from authorized generics in this stylized example, and assume that firm loses all of the product's sales at the time of generic entry.

<sup>xii</sup> For discounting purposes, this analysis treats the year 0 as the first seven months of product life and then each year after that is discounted based on an 11% cost of capital, compounded from the start of each calendar year. If one adopts an end of year calendar timing convention, total value would be \$550 million in this stylized example instead of \$599 million.

<sup>xiii</sup> It is not clear at this point whether there would be any requirement for transactions between firms to be publicly transparent in terms of the exchange of The PRV.

<sup>xiv</sup> This estimate includes discovery research and clinical development expenses as well as the costs of failed candidates, all capitalized to the date of marketing.

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<sup>xv</sup> In Japan, for example, priority review is granted for drugs treating orphan and other serious diseases (Japan Pharmaceutical Manufacturers Association 2007, 32-33).