

ENCOURAGING INNOVATIVE TREATMENT OF NEGLECTED DISEASES THROUGH PRIORITY REVIEW VOUCHERS

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Tropical diseases cause substantial suffering and loss of life around the world. Africa rightly receives considerable attention in its efforts to fight them, but other regions too have limited resources to mitigate their impact. Fortunately, the developing nations of the Western Pacific (excluding Australia, Japan, New Zealand, and the Republic of Korea) have a disease rate (18 percent of the global average) below their share of the world's population (24 percent). But they have only 2 percent of the world's health resources (World Health Organization 2007, 19).

A recent shift in U.S. policy could help fight tropical diseases in developing Western Pacific countries and elsewhere. In September 2007 the U.S. Congress enacted the Food and Drug Administration Amendments Act of 2007, which increased funding for the research and development (R&D) of treatments for neglected tropical diseases including malaria, leishmaniasis, Chagas disease, and tuberculosis (TB). Introduced into Congress by Senators Sam Brownback and Sherrod Brown (Brownback 2007), the law is based on the policy proposal and economic analysis of this chapter's authors (Ridley, Grabowski, and Moe 2006). One of its provisions involves awarding a transferable priority review voucher (PRV) to any company that gains Food and Drug Administration (FDA) approval for a new pharmaceutical or biological treatment targeting a neglected tropical disease. The bearer of this voucher is entitled to a priority review (instead of a standard one) for another drug product submitted for FDA approval.²

A PRV thus speeds the process of getting a new drug to market. The FDA's target review times for priority and standard drugs are six and ten months, respectively, but the *actual* median review time (since 2000) is about seven months for priority drugs and fifteen months for standard drugs (table 20.1). In an earlier analysis we found that a difference of several months can be worth hundreds of millions of dollars for pharmaceutical products with large expected sales (Ridley, Grabowski, and Moe 2006).

PRVs raise a number of interesting questions for both policymakers and analysts. How will the PRV market evolve? How will vouchers be administered by the FDA? And how effective will they be in promoting the R&D of tropical

disease treatments? Other important issues to consider are how the vouchers will complement other public and private incentives, and whether they will have 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 chapter we consider several important aspects of the new PRV law. We first provide background information on tropical diseases in developing countries and how the vouchers complement other push-and-pull incentive programs directed at mitigating these diseases. We then consider the PRV law in more detail and examine regulatory issues in administering it. After analyzing the economic value of a PRV under different scenarios, we summarize our findings and discuss some key issues for further analysis.

The PRV and Other Incentives for Treating Neglected Diseases

Under the Food and Drug Administration Amendments Act of 2007, companies that make treatments for any of sixteen tropical diseases are eligible to receive PRVs.³ The law also states that vouchers can be obtained for treatment of “any other infectious disease for which there is no significant market in developed nations and [which] disproportionately affects poor and marginalized populations, designated by regulation of the Secretary.”

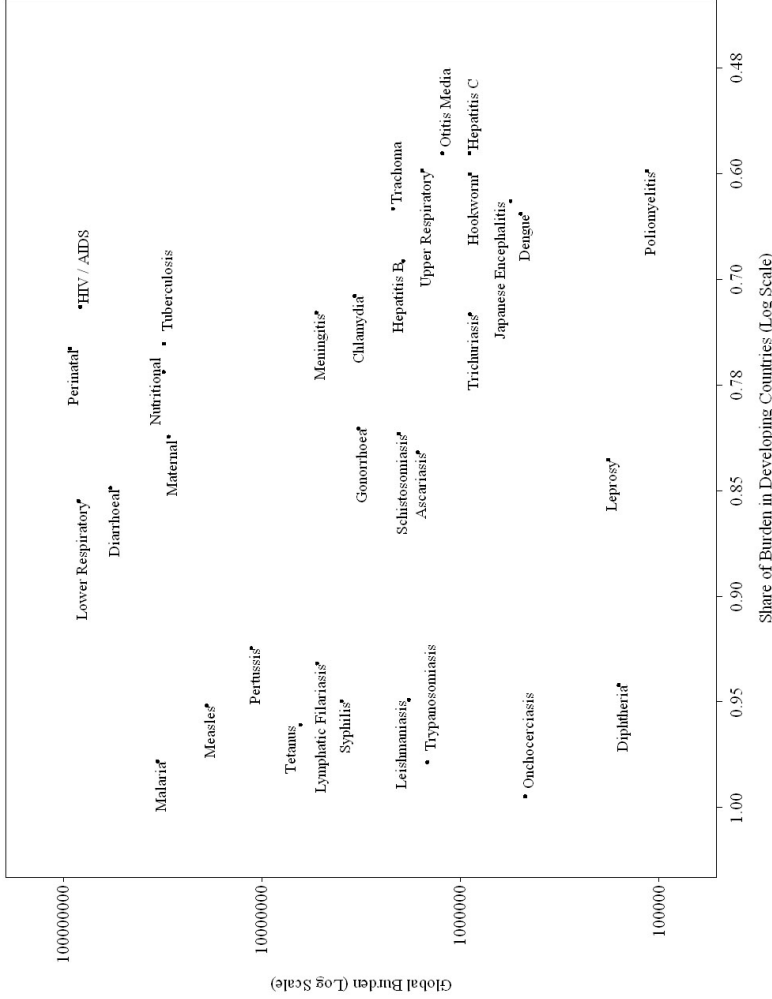
The major obstacle to stimulating the R&D of new medicines for neglected diseases is low-income nations’ inability to pay for such medicines. Average spending on health services in low-income countries was about \$29 per capita in 2003.⁴ This barrier is compounded by others, including ineffective policies and inadequate medical infrastructure, both of which impede the efficient delivery of drugs and other medical supplies. Insufficient revenue and infrastructure on the demand side are coupled with the high fixed cost of R&D on the supply side. As a consequence, relatively few drugs have been developed to address the high global disease burden posed by tropical diseases (WHO 2004).

Figure 20.1 shows diseases that are highly concentrated in developing countries. Some of these, such as malaria and TB, have large annual global burdens and are the subject of targeted Public-Private Development Partnerships (PDPs) and other initiatives. The PRV law could complement existing programs. At the same time, a large number of tropical diseases have substantial disease burdens in the aggregate but are targeted by few drug development efforts. These diseases could garner more interest and attention as a result of the new PRV law.

Push-and-Pull Incentive Programs

Public and private strategies for stimulating R&D of treatments for neglected diseases are usually designated as “push” or “pull” programs. Strategies in the “push” category involve R&D cost sharing and subsidies such as tax credits,

Figure 20.1 Annual Global Burden of Disease versus Share of Burden in Developing Countries, 2005



Source: Authors' calculations based on World Health Organization data (2006) on disability-adjusted life years lost from disease.

research grants, and 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 PRV is a market-oriented pull mechanism that can be combined with push mechanisms such as orphan drug tax credits.

Push and pull mechanisms have well-known benefits and limitations. Push mechanisms allow direct donor control over product development and might be especially beneficial at the earliest stages of the research process, when scientific and commercial risks are substantial and the feasibility of the product is uncertain. On the other hand, push mechanisms that are controlled by a central agency can suffer from asymmetric information and a misalignment of incentives across donors and developers, leading to resource inefficiencies.

Pull strategies reward output and do not require donor funding except at specific milestones, such as regulatory approval or market distribution. Pull strategies are designed to create market incentives through commitments to particular outcomes. Two potential limitations, however, are the credibility of the commitment and the substantial time involved in pharmaceutical R&D programs, which 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 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 a pneumococcal vaccine for disease strains prevalent in developing countries. This pilot program provides for seven to ten years of funding with the goal of creating sustainable supply conditions in developing countries. It is 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 uses both push and pull incentives is the U.S. Orphan Drug Act (ODA), passed in 1983. This provides tax credits, subsidies, and other benefits such as market exclusivity to stimulate R&D of treatment for diseases not prevalent in the United States (Grabowski 2005). It has been very successful in encouraging new drug treatments for rare illnesses such as Gaucher’s disease and Wilson’s disease. Neglected diseases also qualify for orphan drug status because of their rare occurrence in the United States, but there have been relatively few drugs developed under the ODA for tropical diseases—even widespread killers like malaria.⁵ The combination of orphan drug subsidies, together with the prize of a transferable PRV, could provide a more powerful set of incentives to increase R&D in this area.

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 PDPs support a portfolio of development projects dedicated to particular

neglected diseases. A PRV could be a valuable addition by providing resource support and incentives to private partners. For example, nonprofit foundations engage a variety of 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 for further research.

The PRV also complements the charitable and good-will activities of for-profit corporations. Some important drugs that target 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 corporate initiatives in progress target filariasis, trachoma, and leprosy (Grabowski 2005). The PRV could help broaden the scope of R&D on neglected diseases and complement the philanthropic motivation of these programs.

The PRV could reinforce other pull mechanisms as well, such as AMC programs that provide purchase guarantees for malaria or TB vaccines that meet particular specifications (Berndt and Hurwitz 2005). However, the PRV's most important function might be to encourage R&D of treatments for lower-profile neglected diseases without large, dedicated funding. In particular, the voucher could encourage drug developers to apply what they have learned about one set of neglected diseases to another set. It could also allow smaller biotech firms to demonstrate the importance of innovative new therapies.

The FDA's Role in Administering the PRV

To earn a PRV, researchers must develop a molecule (pharmaceutical or biological) that contains an active ingredient 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. To use the PRV, however, the bearer must notify the FDA 365 days before 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 drugs. The user fee for new drug applications requiring clinical data was \$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 NDA submission. This does not mean that the application must be accepted or rejected in this period. Rather, the FDA can approve, reject, or deem the drug "approvable," in which case the drug application is returned to the sponsor to correct deficiencies and perhaps perform additional tests (Berndt and others 2005). The FDA, therefore, retains considerable discretion in the review of all drug applications.

FDA actions in administering the priority review of voucher drugs will affect the value of the voucher. If, for example, FDA reviewers tend to label these drugs approvable rather than approved—whether because of minor deficiencies or excess risk aversion—this would significantly diminish the value of the PRV and its efficacy as an incentive for R&D. Such a risk appears to be the biggest concern of companies that are considering participating. Given that R&D is high-cost, high-risk, and can stretch over long time periods, there must be a credible expectation that the PRV will in fact speed drug approval. Many companies might wait to see if this is the case before initiating new R&D programs targeting neglected diseases—and the markets for vouchers could be slow to develop.

Potential Unintended Consequences

There are concerns that the PRV program could slow the review of other drugs or, alternatively, that the faster reviews will not be thorough, with the consequence that voucher drugs pose greater safety risks. Charging the special user fee and requiring 365-day advance notification for PRV drugs should provide the FDA with sufficient resources to handle the extra workload and not delay the review of other drugs. In addition, since priority review does not lower the approval criteria for safety or efficacy, it should not increase safety risks, provided that adequate resources are available to undertake the faster reviews.

Several recent studies investigate whether the fast review track, established under the Prescription Drug User Fees Act (PDUFA), has led to greater safety risks. The legislation introduced review time targets and also gave the FDA significantly more resources to undertake new product reviews. Berndt and others (2005) find that the proportion of new drug withdrawals remained unchanged after the implementation of drug user fees in 1994. Similar findings are 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, finds that drugs with faster review times are subject to more adverse events. But 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, controlling for global launch lags, drug novelty, and utilization. Their results indicate that drugs first approved abroad are subject to fewer adverse events than those first approved in the United States. This suggests that FDA reviewers benefit from spillover knowledge of the drug's effects in actual clinical practice with large patient populations—in addition to the data obtained from controlled patient trials. From a policy perspective, however, PRVs are unlikely to affect the country of initial launch, since the vast majority of commercially important new drugs since the mid-1990s have been either launched in the United States or worldwide (Grabowski and Wang 2008). After controlling for global launch lags and 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, and there is evidence of significant health benefits from the timely access to new medicines under user fees (Philipson, Berndt, Gottshalk, and Sun 2008). So instead of rolling back these targets, Congress chose to institute new post-marketing safety measures. This is consistent with the recommendations of an array of experts including the Institute of Medicine (2007) and former FDA commissioner Mark McClellan (2007).⁶ The 2007 law dedicates a significant percentage of drug user fees to enhancing post-market surveillance and information disclosure. It also gives the FDA expanded risk-management tools.

The Value of PRVs

The PRV is valuable from three perspectives. First, the company awarded the voucher can either choose to enjoy its benefits or, upon sale, their monetary equivalent.⁷ Second, the company that uses the voucher receives a speedier drug review. Third, people around the world benefit from the new drugs and vaccines encouraged by the PRV program.

The Value of a Priority Review

In an earlier analysis (Ridley, Grabowski, and Moe 2006), we considered the corporate advantages of obtaining a PRV. We showed that roughly half the blockbuster drugs introduced in the 1990s—that is, drugs that had \$1 billion in annual sales by the fifth year after launch—received a standard rather than a priority review. But between 1992 and 2002, priority reviews were, on average, twelve months faster than standard reviews. To estimate the value lost in those twelve months, we used as our baseline the after-tax stream of income for the representative top-decile product from a comprehensive sample of new drugs introduced in the period 1990–1994 (Grabowski, Vernon, and DiMasi 2003). We found that getting such a product to market a year earlier was worth more than \$300 million (Ridley, Grabowski, and Moe 2006).

The value of the voucher decreases as the difference between the priority and standard review times decreases. In 2006 the difference in median review times was seven months, not twelve (table 20.1). The PRV' value would be positively affected, however, if the voucher (1) increased a drug's time on the market (rather than just shifting it forward), and (2) created early mover advantages vis-à-vis a competitor. Given the workings of the Hatch-Waxman Act on patent restorations, we assume that effective patent life will remain unchanged. Specifically, we assumed that a faster FDA review time will be exactly offset by less patent term restoration under the rules of the Hatch-Waxman Act for

many products. In Ridley, Grabowski, and Moe 2006, therefore, we estimated only the time value of money, assuming the voucher product's income stream was unchanged and shifted forward in time by exactly one year.

There are many situations in which effective patent life will be increased by a product's earlier entry into the market. In several scenarios, the PRV will effectively put the product on the market sooner and increase its patent life by the time difference between the priority and standard review—that is, the drug will have an earlier market entry but the same patent expiration date. A longer patent life could be worth a substantial amount in the case of a top-decile product.

Early-mover advantages are another source of value that we abstracted from our 2006 analysis. These advantages, which accrue to companies that beat competitors to introduce a new class of therapeutics, can be substantial in the pharmaceutical field. The fact that the PRV is transferable and can be sold to the highest bidder could greatly enhance its value if a bidding war were to occur between rival firms developing competing drugs in the same class. We will now consider the increase in PRV value from extra patent life and early-mover advantages in more detail.

Effective patent life

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. Half the time lost in clinical development and all the time lost during FDA review is added to the effective patent life—subject to two constraints: (1) the maximum patent extension time is five years, and (2) the extension is capped by an effective patent life of fourteen 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 restoration.

As noted in our 2006 analysis, we assumed that the earlier market entry afforded by a PRV will be exactly offset by reduced patent restoration time (Ridley, Grabowski, and Moe 2006). For example, drugs subject to the fourteen-year cap on effective patent life will have a fixed fourteen-year effective patent life with or without the PRV. This fixed effective patent life would also hold true when the extension is relatively short and neither of the Hatch-Waxman constraints hold (for example, restored patent time is less than five years and effective patent life less than fourteen 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 fourteen-year effective patent life. Such products would gain an extended patent life from a PRV.⁸

There are several other scenarios in which a product could gain a longer patent life from a speedier FDA review. Especially relevant examples are products whose market exclusivity periods are not determined by their effective patent life expiration date. For example, a product's life could be ended prior to the

expiration of its extended patent period if it were successfully challenged by a generic competitor. Alternatively, a product's sales could be significantly curtailed if a superior product were introduced. In other cases, a product's effective patent life might extend beyond that determined by the patent extension formula due to other patents or regulatory factors.

Empirical analysis of effective patent life

To determine the relevance of these patent-life scenarios, we examined the experiences of blockbuster products encountering initial generic competition in the five-year period 2002–2007. In particular, we focused on the sub-sample of all new molecular entities that received a standard FDA review. We then selected products that had \$1 billion in sales or more in the year immediately preceding generic entry. There were eleven products that met these criteria in 2002–2007 (see table 20.2)⁹

Of these eleven products, four had an extended patent life of fourteen years under Hatch-Waxman, plus an additional six months for undertaking pediatric clinical trials.¹⁰ As discussed, the patent life for these projects would have been the same with or without the PRV. On the other hand, two products (Coreg and Ambien) reached the five-year constraint prior to a fourteen-year effective life. These products would have obtained increased patent life from an earlier launch with a PRV.¹¹ In the case of another five products listed in table 20.2 (Paxil, Celexa, Allegra, Norvasc, and Protonix), the outcome is less clear. This is because their generic entry points were determined by patent litigation rather than the Hatch-Waxman patent life formula.

An earlier launch date also shifts forward the first point in time that a generic firm can file an abbreviated new drug application (ANDA) with a patent challenge (a so-called Paragraph Four certification, indicating that the generic firm believes the patent is invalid or noninfringed). Under Hatch-Waxman, the first generic firm that files an ANDA and successfully challenges the innovator's patent receives an 180-days of exclusivity (Berndt and others 2007). The earliest permitted filing date for an ANDA with a patent challenge is four years after the FDA approves the innovator's product.¹² But the actual timing of ANDA challenges depends on a variety of factors, including the size of the commercial opportunity, the perceived vulnerability of the innovator's patents, regulatory considerations, and the parties' resources and constraints. As shown in table 20.3, the timing of generic entry from a successful patent challenge spans a wide spectrum from 6.3 to 14.7 years after the introduction of the innovator's product. This range reflects the myriad factors at work in these situations.

In their analysis of market exclusivity periods for new molecular entities challenged by generic entry in the period 1995–2006, Grabowski and Kyle (2007) suggest that many would have obtained increases in effective patent life from a PRV. In particular, the mean annual market exclusivity for drugs with sales above \$100 million varies between ten and twelve years (Grabowski and

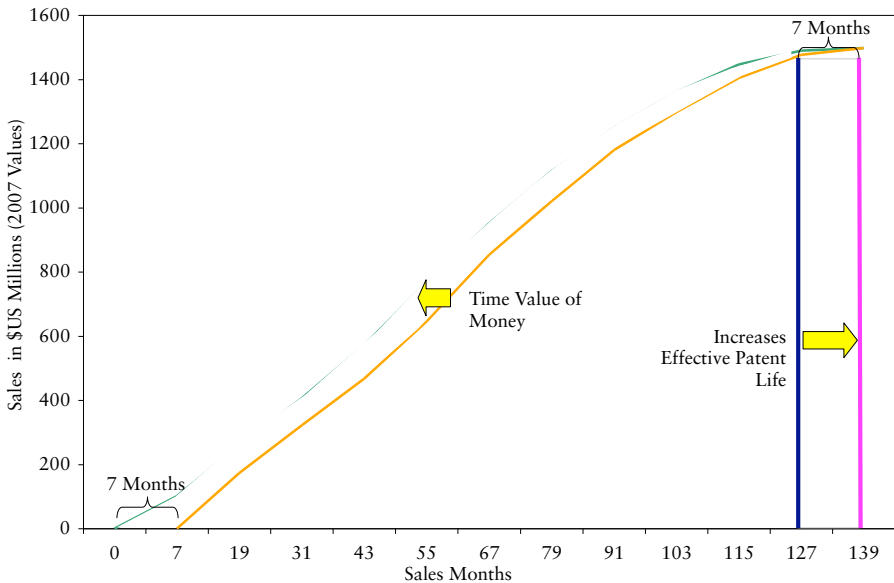
Kyle 2007). Most products had shorter lifetimes than the fourteen-year effective patent life extension limit (or the limit of fourteen years and six months with pediatric exclusivity), due to a variety of factors including licensing delays, lengthy preclinical or clinical development times after the core patents were filed, regulatory delays, and successful patent challenges.

Based on our historical analysis, many products can expect to increase their effective patent life through the priority review voucher. Because the PRV can be traded, the evidence of longer exclusivity increases the voucher’s market value.

A stylized example

To obtain further insights into the expected values associated with increased patent life from a PRV, we developed a stylized example, illustrated in figure 20.2. In this example, we assume that a product without a PRV will have a lifetime of eleven years, at which point the product loses the entire market to generic competitors.¹³ The PRV is assumed to permit the innovator company to gain entry into the market seven months earlier (this is the average difference between the priority and standard review, given in table 20.1).

Figure 20.2 The Priority Review Voucher Shifts Sales Forward and Increases Effective Patent Life



Source: Authors’ stylized example based on sales patterns of blockbuster drugs.

Table 20.1 Approval Time (Months) for Priority and Standard NMEs and New BLAs, 2000–2006

| Year | Total standard review median | Total priority review median | Differences in total median time | Standard FDA review median | Priority FDA review median | Differences in median FDA review |
|------|------------------------------|------------------------------|----------------------------------|----------------------------|----------------------------|----------------------------------|
| 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 |

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

Notes: NME = new molecular entity; BLA = biologic license application. Beginning in 2004, these figures include new BLAs for therapeutic biologic products. Total review time is the full time from an NDA's filing date to FDA approval. FDA review time refers to the subperiod when the NDA is under active review (i.e., not counting the period when an NDA is returned to the sponsor to clarify issues or correct omissions prior to a decision.)

Early-Mover Advantages

The advantages of first entry have long been recognized. Theoretical work by Schmalensee (1982) shows that once consumers use a new product and become familiar with it, they might be reluctant to use a newly introduced competitor. In the case of pharmaceuticals, being first to market means that physicians will have time to become familiar with the therapeutic qualities of a drug before competitors enter the scene and, even after, they will often think of the first entrant as the best.

Research on the pharmaceutical industry also provides empirical evidence that first-movers have an advantage over later entrants, all else 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 serotonin-specific reuptake inhibitors (SSRIs) and H2-receptor antagonists, Berndt and colleagues

found that order of entry had significant effects on market share (Berndt and others 1997, 2002). Their analysis of the H2 blockbuster market, for example, finds that all else being equal, the $(n+1)$ th entrant can expect sales about 40 percent lower than those of the n th entrant (Berndt and others 1997).

Table 20.2 Standard Review Drugs with More than \$1 Billion in Sales in the Year Before Generic Entry

| | Chemical name | Generic entry | FDA approval | Market exclusivity ^a | Generic trigger event |
|----|-------------------------------|---------------|--------------|---------------------------------|-------------------------------|
| 1 | Zestril/Prinivil (lisinopril) | 06/2002 | 12/1987 | 14 years, 6 months | 14-year Hatch-Waxman EPL |
| 2 | Paxil (paroxetine) | 09/2003 | 12/1992 | 10 years, 8 months | Litigation |
| 3 | Celexa (citalopram) | 10/2004 | 07/1998 | 6 years, 3 months | Litigation |
| 4 | Allegra (fexofenadine) | 09/2005 | 07/1996 | 9 years, 2 months | Litigation |
| 5 | Pravachol (pravastatin) | 04/2006 | 10/1991 | 14 years, 6 months | 14-year Hatch-Waxman EPL |
| 6 | Zocor (simvastatin) | 06/2006 | 12/1991 | 14 years, 6 months | 14-year Hatch-Waxman EPL |
| 7 | Zoloft (sertaline) | 08/2006 | 12/1991 | 14 years, 6 months | 14-year Hatch-Waxman EPL |
| 8 | Norvasc (amlodipine) | 03/2007 | 07/1992 | 14 years, 8 months | Litigation |
| 9 | Ambien (zolpidem) | 04/2007 | 12/1992 | 14 years, 4 months | 5-year Hatch-Waxman extension |
| 10 | Coreg (carvedilol) | 09/2007 | 09/1995 | 12 years | 5-year Hatch-Waxman extension |
| 11 | Protonix (pantoprazole) | 12/2007 | 02/2000 | 7 years, 11 months | Litigation |

Source: FDA website, Drugs@FDA; Company Annual Reports and Press Releases.
Note: ^a All the products in the table except Protonix were granted a six-month pediatric exclusivity extension to their patent expiration date; this is reflected in the values for market exclusivities.

To the extent that companies are involved in a competitive race to introduce a new class of therapies, the value of a PRV—especially for a bidder firm projected to be second in the race—could increase significantly with the expected long-term gains in market share from an earlier introduction. In certain scenarios, the value of the early-mover status could be substantially higher than either

the time value of money or increased effective patent life. Since the PRV can be banked and sold to the highest bidder, its market exchange value will depend on the demand for and supply of vouchers at any point in time. As discussed, expectations and attitudes toward risk as well as the negotiating and bargaining strength of the participants in this market are likely to play an important role in the market value of the PRV.¹⁶

The PRV's Value to the Developer of a New Tropical Medicine

To motivate the 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 percent tax credit that comes with an orphan drug designation. Sale of the voucher to a third party would, in turn, be subject to the corporate income tax. These revenues total several hundred million dollars and would obviously support many neglected disease programs.

In the case of nonprofit PDPs, 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 stated 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 could then plow back the revenues into further work on other components of its R&D program. In either event, the PRV could become a major source of R&D funding for PDPs with programs targeting neglected diseases.

As discussed in our 2006 analysis, we believe the cost of neglected disease R&D could be significantly less than the \$800 million mean estimated cost of researching and developing new chemical entities.¹⁷ This is true even without 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 need not undergo 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 by the U.S. military to support vaccine and drug development for pathogens in foreign countries. These products could be investigated following clinical trials in these public programs. All of these factors suggest that a PRV, valued at several hundred million dollars, could be a valuable stimulus to increase R&D activity on neglected diseases, just as the ODA stimulated a dramatic increase in research targeting rare genetic diseases in developed countries.

Global Social Welfare

New pharmaceuticals and biologicals that address diseases for which adequate treatments are not currently available offer immense societal benefits. A common threshold for health interventions in the poorest countries is \$100 per disability-adjusted life year (DALY), a fraction of the value used 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 sixteen neglected diseases targeted by the Food and Drug Administration Amendments Act of 2007. In addition, other diseases that disproportionately affect developing countries—as shown in figure 20.1—are likely to be added to the list of targets for the PRV in future regulatory actions.

Another potential benefit is that drugs sped to market by the PRV will be sooner available in the United States. Several of the blockbuster drugs that received standard reviews in the 1990s went on to be leaders in their therapeutic class (including Zocor, Norvasc, and Ambien). If people in the United States are given access to a voucher-applied product seven months earlier than expected, this could lead to significant increases in consumer and producer surplus. Quantifying these potential gains is an empirical task for future researchers.

Conclusion

In 2007 Congress created a novel voucher award program to stimulate the R&D of treatment for neglected diseases. The PRV program became effective in September 2009. The first voucher has been awarded to Novartis in conjunction with the FDA approval of the anti-malarial drug, Coartem, in April 2009.¹⁸ We estimate that in a well-functioning market, a PRV could be worth hundreds of millions of dollars based on the value of faster reviews, increases in effective patent life, and early-mover advantages vis-à-vis competitors. The vouchers therefore could be a powerful stimulant for developing and filing new FDA drug applications relevant to neglected diseases.

The voucher program complements other push and pull mechanisms such as PDPs and AMC incentive programs. Given that drugs targeting tropical diseases such as malaria and dengue fever are eligible for orphan drug status in the United States, a 50 percent 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 due to the faster reviews of voucher drugs. But users of the priority review program will pay an additional user fee and must give the FDA 365 days' advance notice to allow the agency time to allocate its resources for the expedited reviews. Furthermore, priority review does not involve a lower standard for approval and does not

entitle the bearer to an actual approval in six months, only a decision in that time period. 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, and that voucher drugs will not be subject to inordinate delays unrelated to a product's efficacy or safety.

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.

As the FDA approves more medicines for tropical diseases, these drugs will likely be eligible for support by both governmental and nongovernmental initiatives (such as that of the Gates Foundation) to improve the welfare of people in developing countries. The U.S. government has also announced a \$350 million program over five years for Neglected Tropical Disease Control 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, or STHs (hookworm, roundworm, and whipworm). This program is being coordinated by USAID in collaboration with the CDC and World Health Organization (USAID Health, 2009). As was true for the U.S. Orphan Drug Act, Europe and Japan could pass their own variants of the PRV.¹⁹ These initiatives could also be integrated with other evolving programs for the distribution of established therapies to countries with low ability to pay.

Notes

¹ We appreciate helpful comments from Toshiaki Iizuka, Karen Eggleston, Hector Rincon, and participants at the Pharmaceuticals in the Asia-Pacific Stanford University Conference.

² Section 1102 of the Act titled Priority Review to Encourage Treatments for Tropical Diseases.

³ 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, onchoceciasis, schistosomiasis, soil transmuted helmithiasis, and yaws.

⁴ 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.

⁵ As of July 2003, there were only 12 orphan drugs approved in the United States targeted specifically to tropical diseases (Grabowski 2005; Kettler 2000).

⁶ 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).

⁷ The company awarded the voucher and its user are not necessarily the same company, since the firm that generates the PRV might choose to auction or trade it to another company rather than utilize the PRV itself.

⁸ 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.

⁹ 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 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.

¹⁰ 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).

¹¹ 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 by a PRV would only be 2 months before it reaches the 14 year 6 month constraint under Hatch-Waxman.

¹² There is a period of between 5 to 7½ years before an ANDA filed with a patent challenge can be effective. Under the Hatch-Waxman Act there is a five year period (the innovator's "data exclusivity" period) in which a generic can not enter with an ANDA filing. In addition, for ANDAs filed with a patent challenge, there is a stay of up to 30 months while the matter is being resolved in the courts. If the matter is still active after this stay, the generic firm may enter at risk or wait until a District Court rules on the validity and/or infringement of the innovator's patents. (Gryta 2008).

¹³ Products with sales in excess of \$1 billion typically lose more than 90 percent of their sales to generic competitors within a matter of months (Grabowski 2004; Silver 2007). But where only a generic product enters with a six month Hatch-Waxman exclusivity because of a successful product challenge, the innovator firm will typically license an authorized generic (Berndt et al 2007). This strategy 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 the originator firm loses all of the product's sales at the time of generic entry.

¹⁴ 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 percent 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. The value of the additional sales in this stylized example before discounting is \$874 million.

¹⁵ To obtain present values of income, one would need to subtract the variable costs of production, marketing, taxes, and other fees (see Grabowski, Vernon, and DiMasi 2002). A company-specific pre-launch analysis for a new product correspondingly would need to include the product's forecasted sales revenues over its expected lifetime as well as the relevant contribution margins, cost of capital, marginal tax rates, etc.

¹⁶ 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.

¹⁷ This estimate includes discovery research and clinical development expenses as well as the costs of failed candidates, all capitalized to the date of marketing.

¹⁸ Since the program was only implemented in September 2008, the initial approvals are expected to be products already approved elsewhere, or in the late stages of development, prior to their introduction here or abroad. Coartem had been approved outside the United States prior to 2009, and Novartis has made it available on a nonprofit basis in several low-income countries. For Coartem, one potential benefit of this initial voucher award is to provide information to market participants on the FDA's behavior toward priority review under the PRV program. Novartis has not indicated yet how it plans to utilize the voucher.

¹⁹ In Japan, for example, priority review is granted for drugs treating orphan and other serious diseases (Japan Pharmaceutical Manufacturers Association 2007, 32–33).

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