

seminar briefing no8

PRIORITY REVIEW VOUCHERS TO ENCOURAGE INNOVATION FOR NEGLECTED DISEASES

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Lunchtime seminar by Professor Henry G. Grabowski which took place on Wednesday, 3 June 2009 at the Office of Health Economics, 12 Whitehall, London SW1A 2DY

Introduction

I am going to talk today about Priority Review Vouchers (PRVs), an idea that my colleagues David Ridley and Jeffrey Moe had to encourage research and development for treatments for tropical diseases. I will first provide some background on PRVs, then I will talk about the features of the PRV law and how it could be used to complement other incentives for tropical diseases, how they may be valued and finally, some issues about the PRV law: what is in it, what is not and some potential adverse consequences.

This law came into being as an amendment to the FDA Amendments Act of 2007. In the US there is a law called the Prescription Drug User Fee Act (PDUFA) that has to be renewed every five years. It was first passed in 1992 and it basically increased the resources available to the FDA for the regulatory approval process by charging companies a user fee that allows the FDA to conduct reviews within a target time frame. As part of this renewal, in 2007 an amendment was attached establishing the award of a PRV to a company for obtaining a new drug approval in the United States for one of the 16 named tropical diseases listed in the legislation.

The voucher therefore is essentially a prize that a company receives if it gets a new drug approval for a tropical neglected disease. This entitles the holder to priority review of another drug of the bearer's choice; for example, this could be a drug for hypertension or diabetes, it does not have to be for a tropical disease. There are therefore two classes of drug approvals at issue: one is the tropical disease drug or vaccine and the other is a drug from the standard queue that could be put in a priority queue when the voucher is used.

There are 16 disease categories that are referred to in the law, including some that are 'major' neglected disease targets: tuberculosis, malaria, leishmaniasis, leprosy, etc. These particular diseases were targeted by the law, based on consultation with the Sabin Foundation. The intent was to stimulate R&D on drugs that will mainly be used in developing countries and that do not really have much of a market outside of those countries. The FDA has discretion to add any other diseases not currently listed in the legislation for which there is not a significant market in developed countries, and that disproportionately affects poor and marginalized populations. At the time the law was passed by Congress, the Secretary said that they were not going to consider adding other diseases for the time being, but in the future they would look at this question.

Background to the legislation

Figure 1, below, is a diagram taken from our 2006 Health Affairs article¹ where we first described the concept of PRVs. The X axis shows the share of DALYs within the countries that are designated by WHO as developing countries and the global disease burden is on the Y axis. Most of the diseases that are on the far left are those that are included in the law. The main idea here is that there could be substantial global social value generated for new medicines addressing these diseases, and that new medicines could be developed through this incentive. At the same time there could also be a benefit to US consumers and the developing firms from the use of the Voucher to gain quicker approval for selective drugs in the U.S. However, these benefits must ultimately be balanced against increased R&D expenditures, including government financed tax credits. Some of the research expenditures for tropical diseases fulfil the criteria for orphan drug status and are therefore eligible for research supports such as tax credits.

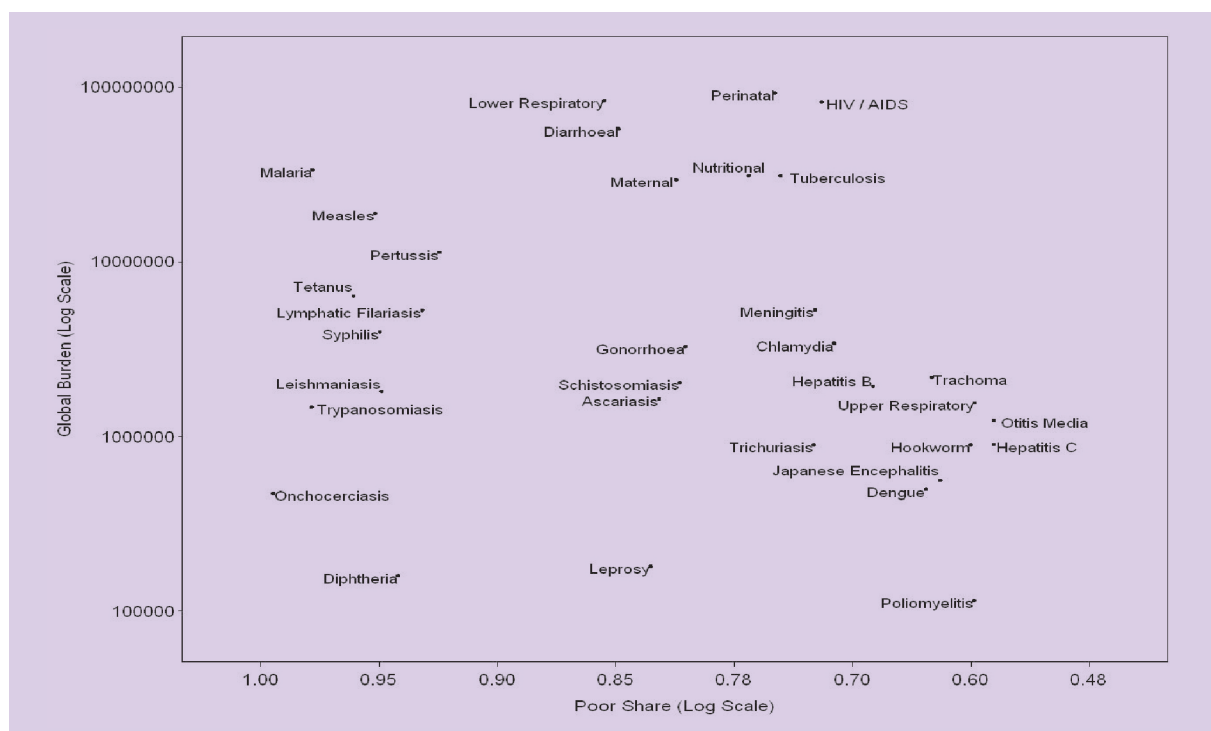
Let me, however, start by describing the background behind the legislation. In 2002 the Glaxo Foundation gave the public policy school at Duke University a grant for research on access to medicines not only in the Third World but also to impoverished areas in the US. My colleague, Jeff Moe, who has a PhD in Social and Organisational Psychology, but who has also spent time in the industry, along with David Ridley, a professor at the Fuqua School of Business, and myself were awarded a portion of that grant. We began brainstorming ideas

that could be market orientated incentives to encourage research or neglected diseases. It was actually Jeff Moe who came up with the idea of a priority review voucher.

I was a little sceptical at first, in the sense that I thought it might be a useful idea but that the FDA would not support it. In any case, we developed the idea and presented it at a few seminars, including one at the American Economic Association dedicated to considering this incentive along with others. We talked to John Iglehart, the editor of *Health Affairs*, about submitting an article. The timing worked out well for us because they had just received a grant from the Gates Foundation to increase their coverage of global health issues and were going to have a special issue focused on neglected diseases. David Ridley became the lead author and the article that was published was the one I referenced earlier. In addition, *Health Affairs* held a press conference in Washington, DC to commemorate its greater focus on global health issues, where David Ridley gave a briefing on our paper to staffers and journalists who attended.

One of the journalists at the press conference mentioned that Senator Brownback of Kansas was interested in this issue and we started discussing the priority review concept with his staffers. Senator Brownback had been pushing a similar incentive to stimulate R&D for neglected diseases except in that case the voucher would grant a six-month patent extension on any drug of the bearer's choice as a reward for obtaining an approval for a neglected disease drug or vaccine. The basic idea was similar to pediatric exclusivity where six months of

Figure 1: Annual global burden of disease (DALYs) vs. share of burden in developing countries, 2005



¹ Ridley, D. B, Grabowski, H. G, and Moe, J. L. (2006) "Developing Drugs for Developing Countries," *Health Affairs*, 25(2): 3134-324.

additional patent time is granted for the approval of a pediatric indication based on new clinical trials.

A counterargument on the patent extension concept was that such a transferable voucher would delay price and generic competition. Ultimately, this particular incentive approach did not gain traction. Senator Brownback found our alternative idea attractive. He skilfully involved another Senator, Sherrod Brown, from the opposite end of the political spectrum, as an advocate for the priority review voucher concept, as well as Senator Joseph Lieberman. The three of them co-sponsored an amendment to the renewal of the user fee legislation, and that was enough to get it passed with little opposition in the Senate.

As this amendment worked its way through the House, it got caught in some political back and forth. Some Congressmen said this is basically an incentive for the pharmaceutical industry and we are not sure we can support it, while from the other end of the spectrum, some Congressmen said this is basically for Africa and the Third World and we have bigger issues in the U.S. So there was some resistance on the far ends. In addition, as it gained support, some of the stakeholders started to think about broadening the voucher incentive to other areas of targeted research. In particular, some companies suggested adding HIV/AIDS and various other diseases that already have significant amounts of research, or at least that is true for the HIV strains that are present in the First World. So there was some attempt to expand the diseases beyond tropical diseases.

There was also an attempt to take out the transferability of these vouchers so that only the company that conducted the neglected disease work could use the voucher. My co-authors and I had to go to Washington a few times and conduct mini seminars explaining why this was a very important provision. A transferable voucher is desirable on economic grounds because some of the stakeholders that are doing the work, like a biotech firm, would still obtain value even if it had no products coming out of the pipeline in the foreseeable future. It could use the voucher as an instrument to raise funds from VCs, or sell it, or auction it. Similarly, the voucher could be used to generate funds for a private development partnership (PDP). Eventually the legislation was passed in September 2007 with a transferable PRV. I was amazed, delighted and very surprised to go from an article and press conference in 2006, to a law in 2007.

Priority review vouchers: features

PRVs can be transferred or banked and companies must pay a supplemental user fee to utilize them. In the U.S. a company must pay a user fee for any new drug that is reviewed. Currently, that fee is over \$1.2 million. To use the PRV and change from a standard review to a priority review a company will have to pay an additional fee that is equal to the average cost of doing a priority review. The FDA will annually determine how large the extra user fee will be to submit an application with a priority review voucher. In our paper, we estimated that a likely fee would be a few million dollars more to use the voucher, based on our preliminary calculations on the FDA's expected costs to do a priority review.²

The FDA inserted a clause into the law that could provide some complications: the company using the voucher has to give the FDA 365 days notice that it is going to use it in a new drug application. Problems may arise because in most cases Phase III trials may not be completed a year in advance of an application and the company may not know all the parameters of the drug trials and it may be that the drug could qualify for priority review, negating the need for the voucher. The FDA wanted this clause added to stabilise their workload and ensure they have enough resources to conduct the priority review and Congress agreed to it.

Some other features of the Bill were included to address concerns about the possibility of companies obtaining a voucher for products that offered little or no therapeutic advances. For example, pharmaceutical companies might try to get multiple vouchers from different formulations of the same active ingredient. To avoid this, a novelty criterion was inserted in the law. It stipulates that the tropical disease drug must itself be eligible for priority review; it cannot just be a variation of an existing drug. In particular, new indications, formulations or combinations of approved drugs are excluded from the PRV scheme. While a novelty criterion has merit, we thought research on new indications for some established anti-infective drugs could be an important pathway to obtain new treatment regimes for tropical diseases. Unfortunately, Congress ruled that option out. Interestingly, they did not rule out that the drug had to be first approved in the U.S. There are, therefore, some provisions in this law that are not ideally designed from an incentive perspective, but we believe it is still a very valuable law.

The first Priority Review Voucher has already been issued. There was a one year period before any products could apply for the PRV and a few months ago (April 2009) Novartis received the first Voucher for Coartem®, an anti-malarial drug that has been around for almost a

² On September 13, 2010, the FDA announced the PRV user fee would be \$4.582 million for Fiscal Year 2011 (beginning October 2010).

decade. It was approved in Switzerland in the early 2000s. Coartem[®] is a very important drug, and Novartis has made it available on a non-profit basis in the Third World and now it has been approved in the US.

Novartis has not indicated how it is going to use the voucher. Presumably it is going to bank it and use it for a Novartis drug. One point of criticism is that Coartem[®] is not a new drug. However, this is the first wave of drugs and it has only been a year since the law was passed. Inevitably, there will be drugs that are already available in one form or another outside the United States that will be awarded a PRV. Awarding a PRV to Novartis can be thought of as a reward for good work, and also as a test case for the FDA. While this is not the ultimate objective of the program, the value of this first awarded PRV will be to see how the FDA acts and whether PRVs really result in faster reviews compared to standard reviews. This could be an important signal to the market on the value of this incentive mechanism for increasing research on tropical diseases.

Sources of value

I am going to talk a little bit about some of the features that I think add value to developers of new drugs for the 16 listed tropical medicines in the law. I mentioned that the transferability of the voucher adds value for both for-profit and non-profit enterprises. For example, a start-up biotech firm working in the relevant infectious diseases can utilise the voucher to improve its funding support from venture capital investors or to enhance its partnership terms with a large pharmaceutical or biotech company.

Correspondingly, if a PDP develops a new tropical disease drug and receives a voucher they could then auction it off and use the funds for R&D. PDPs could also transfer the voucher rights in exchange for funding of more expensive Phase III trials. This could be a quid pro quo for the companies to do the Phase III clinical trials and obtain the rights to the voucher.

A voucher can also add value in the portfolio decision making process within a large company. For example, it could be used internally to justify in part the resource costs of engaging in infectious disease R&D for neglected diseases. In addition to doing R&D on neglected diseases for strategic and philanthropic purposes, a company can make some money by using or selling the voucher. It can also complement or add some value to negotiations between a small biotech and a big pharmaceutical company.

When we came up with the idea of PRVs, we never intended them to be the basis for a whole program the way an advance market or guaranteed price commitment is often designed. We envisaged PRVs as a complement to other “push” and “pull” incentives. Some public incentives that are already in place that complement PRVs are orphan drug incentives. In the U.S. a drug qualifies for orphan status if it is for a disease that affects less than 200,000 patients. This includes many tropical diseases. Orphan drugs are eligible for a 50 percent tax credit on clinical trial costs. A company could obtain the orphan drug tax credit as part of a voucher-eligible development project on a neglected disease.

There could be spillovers from Project BioShield, a program set up by the federal government for drugs to combat terrorism. Some of these drugs that would be useful to counter bioterrorism could also potentially be used for neglected Third World diseases as well. However, there might be some interesting issues that arise. For example, one company person mentioned that they have some drugs that potentially could qualify for both programs, but because of the PRV they have an incentive to get it approved for a neglected disease indication first.

Figure 2 lists various push and pull incentives available for neglected disease that PRVs could complement. There is a lot of discussion in the literature about the pros and cons of push versus pull and Professor Michael Kremer and others have discussed them in detail. Push incentives provide funding either through foundations or through the government, are particularly suited to early stage R&D where there are lots of possibilities and options as well as lots of uncertainty. However principal-agent problems often arise with push incentives, primarily because of asymmetric information and the non-alignment of incentives between developers and funders.

Donors such as the Gates Foundation have become much more sophisticated in terms of how they monitor their contracts and they are better able to address a lot of the principal-agent problems.

Pull incentives like advance market (guaranteed price) commitments have the advantage of an efficient market design to the extent that the purchaser is able to specify terms of the guaranteed price or advance market commitment. However, pull incentives suffer from time consistency issues. In the case of an advance market commitment, the creditability of a prize fund that may be several years in the future can be critical.

As a pull incentive, the voucher for extended patent life has a lot of value. If you can get a voucher that gives you six more months of Lipitor[®], that is an enormous

Figure 2: Push and pull mechanisms

MECHANISMS	PROS			CONS	
	Drugs for neglected diseases	Donor pays only if drug	Other Pros	Rewards serendipity	Other Cons
1. Push: \$ for R&D	+		+ Earlier stage R&D		<ul style="list-style-type: none"> • Donor pays in advance • Principle agent issues
2. Pull: Guaranteed price	+	+	+ Efficient market design	-	<ul style="list-style-type: none"> • Time consistency problem • Specification issues
3. Pull: Voucher for extended patent life	+	+		-	<ul style="list-style-type: none"> • Higher premiums • Some deadweight loss from generic delay
4. Pull: PRV	+	+	+ Speeds potential blockbuster	-	<ul style="list-style-type: none"> • Uncertain value • Drug safety issues?

prize. But this prize also comes with deadweight loss from generic delay and higher insurance premiums. As a result, it does not seem to be a viable policy alternative.

PRVs are also a pull incentive. They are essentially prizes that have the advantage of complementing these other incentives. Their values are derived from speeding up the review for a new drug of the bearer's choice. This also can provide benefits to consumers in the United States. In one of the tables in our 2006 article we looked at commercially important drugs (i.e. drugs that had billion dollar sales within five years) launched in the 1990s to determine which had received standard review and which were priority reviewed. What we found was that many of the drugs that were first in class received priority review, but there were quite a few other important drugs, like Zocor®, the leading statin medication until Lipitor® came out, that received standard review. Other examples include Zyprexa® which became a leading schizophrenic drug as well as Paxil® and Celexa®, SSRIs that came onto the market after Prozac®. Our idea was that drugs with potentially large markets, such as the ones just listed, that would normally receive standard review would be exactly the kind of drug where this voucher would be particularly useful and also provide some benefits to patient groups in the United States. For example, the tolerability of different SSRIs varies significantly across individuals, and some patients could have benefited from earlier access to drugs such as Paxil® and/or Celexa®.

What is the value of the voucher?

What are the conditions that make the PRV programme a viable incentive mechanism for stimulating research on neglected diseases? From the buyers' side, if the voucher is traded, the incremental returns from a priority review over a standard review would have to be greater than what a company paid for the Voucher plus its extra user fee. From the seller's side, or the development side, the Voucher price plus any push subsidies like orphan drug tax credits and goodwill would have to be greater than the expected R&D cost of developing the treatment for neglected disease. These are also the conditions that must be satisfied when a single entity does the research on the tropical disease and utilizes the voucher itself as well as in a market transaction where the rights to the PRV are sold or transferred. These conditions are discussed in more detail in our *Health Affairs* paper.

A key driver of this incentive mechanism is therefore the value to a company of a speedier review of a new drug application. What is the potential value of priority review over standard review? In the U.S. we have regulatory approval targets as part of the user fee legislation. If a drug is classified as a standard review, the FDA had a 12-month target (it is now a 10-month target) and its goal is to review 90 percent of the applications within 12 months (now 10 months). For a priority review, the target is a review within six months. Traditionally, drugs that qualified for priority review represent important therapeutic gains in terms of efficacy, reduced side effects, or compliance. There is an established basis within the FDA for determining whether a drug should receive priority review.

Figure 3: 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	Difference 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	-0.1	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
2007	12.9	6	6.9	12.9	6	6.9
2008	13	6	7.0	13.0	6	7.0
Mean	18	7	11	14	7	7

Source: <http://www.fda.gov/cder/rdmt/NMEapps93-06.htm>
 Notes: NME = new molecular entity; BLA = biologic license applications.
 Beginning in 2004, these figures include new BLAs for therapeutic biologic products.

The FDA does not have to approve the drug within the targeted times, but it has a mandate to render an initial decision within these time periods. There are three possible outcomes: 1) the drug is approved, 2) the drug is approvable but the company has to conduct additional tests or provide additional information to get approval; or 3) it is rejected. The FDA's mandate is therefore to review a new drug application and give the applicant a decision within the specified period of time. As I mentioned earlier, about half of the largest selling drugs in the 1990s received standard reviews. A transferable voucher has optimal value for drugs with high expected sales and expected standard review.

Figure 3 shows the kind of data we have available from the FDA. According to FDA data, the average difference between a standard review and a priority review is about 11 months. There are some outliers affecting these averages' value, so we focused on the median review times based on what the FDA considers to be a complete application. As shown in Figure 3, the median difference between standard review and priority review is seven months: 14 months for standard review and seven months for priority review. In our analyses of the value of a PRV to a company, we assumed, as an initial starting point, that the FDA would treat a PRV application as they do other priority review applications, and thus a company could expect to get, on average, a seven months faster review.

Components of the value from priority review

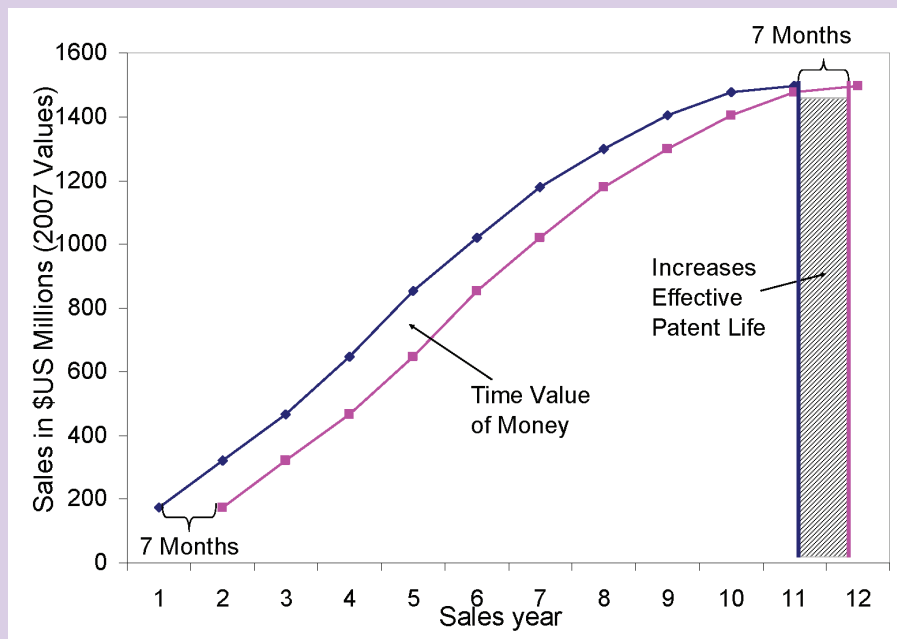
What is the value of seven months to a company using a voucher? In our initial article we concentrated on the

time value of money as the key factor. In addition, there is potential for increases in effective patent life and there are also cases where two companies could be in a race to produce a new generation of products and one could use the voucher to gain early mover advantage. To illustrate these concepts, I am going to discuss some stylized examples to determine what the value would be under alternative scenarios.

Figure 4 shows the sales curve for a product that is worth, at its peak, one and a half billion dollars (\$1.5 billion). Assume the product reaches that sales peak in 11 years and with a PRV, one gets approval seven months earlier. Even if the product's patent then expires at an earlier point in time, there is the discounted time value of revenues from this extra seven months, represented in Figure 4 by the area between the two sales curves. This is the value of getting on the market sooner even if your patent life is also shortened. Patent life could be shortened because of the Hatch-Waxman Act, which I will discuss in more detail shortly.

In the first scenario considered, the patent life would expire seven months earlier, but the present value of revenue flows with priority review compared to the present value of revenue flows without priority review is worth a significant amount of money. In addition, in some circumstances (our second scenario), patents would expire at the same time, and the fact that one's new drug got on the market seven months earlier would give the company seven more months of patent life, and so one also has this whole shaded area on the right in Figure 4. To reiterate, in these stylized examples, the

Figure 4: U.S. sales profile with voucher



initial conditions are that the expected patent life is 11 years, sales are expected to peak at \$1.5 billion in the U.S., and the cost of capital is 11 per cent for a representative pharmaceutical firm. For a biotech firm the cost of capital could be significantly higher.

Doing the math from these scenarios, the present value of the time value of money area in Figure 4 is over \$300 million and the present value from the increased patent life, if you can add that on, is about \$277 million. That is the value of the sales revenues, but a company is concerned about after tax profits. If you take some ballpark numbers and you assume that what falls to the bottom line is 50 per cent of the sales before taxes and you pay taxes at 35 per cent, then the expected value is between \$150 and \$200 million if one gets both an increased patent life and time value of money. If a company only obtains the time value of money component, it would be around \$100 million.

To stress, this is probably not what companies would pay for the voucher. This is a maximum willingness to pay estimate based on the voucher's value before discounting for various uncertainties: In particular, your drug might not get approved in its first submission, the actual sales could be lower than expected, and most importantly, there is the risk that the FDA would not give you the full seven months of faster reviews that is associated with other priority review drugs.

In terms of the patent life component, it is also relevant to ask whether a company could really expect to get extra patent time. In the U.S. we have the Hatch-Waxman Act that allows for abbreviated pathways for

generics, and for patent extensions for new molecular entities, given their patent extensions are designed to compensate for the fact that patents usually are granted early in the clinical development process and much of the initial 20-year period has expired by market approval. Patent extensions are calculated as half the development time plus the FDA review time. If your review time is shorter because of the voucher, it potentially offsets the patent term extension. However, the law is a little more nuanced than that, and there are some constraints that will influence whether one can expect to obtain longer patent lifetimes from a PRV.

The main constraints are that the maximum patent restoration time is five years and effective patent life from an extension cannot exceed 14 years. However, companies can receive an extra six months of paediatric exclusivity for testing the use of the drug in children. Suppose a company is subject to the first constraint, the five-year limit. Even if its drug is priority reviewed from a voucher, it is still subject to that five-year limit. In this case, in Figure 4, one is not just pulling the whole curve forward. In particular, the company's new drug will be subject to patent expiration at the same point of time even with this faster review, and it obtains an extra seven months of patent life. On the other hand, if one is subject to the 14-year effective patent life cap, then the 14 years are pulled forward on the graph and the drug does not get any extra patent life from a priority versus standard review. It is also worth pointing out that if there is no increase in effective patent life (scenario one), there is an extra benefit to society in terms of increased price competition, given that generics will be eligible to get on the market at an earlier point in time.

We conducted an analysis to try to gain some insight into this issue by looking at drugs that received standard review and had billion dollars or more in sales before generic entry. We examined how much patent life they obtained and what was the constraining factor (see Figure 5). Some of these drugs are constrained by the 5-year limit on patent extensions, others by the 14-year cap on effective patent life and still others by outcomes of patent challenges and litigation. The bottom line is that some drugs would get effective patent life increases and some would not from exercising a PRV, based on how patent extensions are constrained and related factors.³

Then, finally, there is a less frequent benefit brought up by some of the companies interested in PRVs. Assume a company is in a race for a new therapeutic class of drugs with another company, and the other one is somewhat ahead. For example, Company A is a few months ahead in submitting its new drug application and will get a priority review because it will be first to the market with a drug that has a new mechanism of action, and Company B, will receive standard review and have a lag of nine months, given the slower review time targets for these reviews. In that nine months, without direct competition from Company B, Company A could realize substantial first mover benefits.

A fast second company could eliminate many of these

early mover advantages if it had access to a PRV. I have sketched out an example (Figure 6). There are two companies: Company A is a first mover and Company B is a 'fast second.' They are going to split a market that is worth \$4 billion. The first mover gets 60 per cent of the market and the second mover gets 40 per cent of the market because of its nine month lag. The two drugs have fairly comparable characteristics.

Now, suppose that the 'fast second' drug can get a PRV, enabling it to get onto the market in seven months earlier. As a result, the first mover advantage is only two months now rather than nine months (Figure 7). Using hypothetical numbers, Company B's market share increases from 50 percent to 55 percent and the value of getting an extra five percent of the market increases its peak sales by \$200 million and, as one can see from the curve, the advantage would be larger than what one would get from time value of money and effective patent life components of value. It may be that this situation does not occur very often, but when it does, having this voucher could be very valuable.

This then gives some alternative scenarios regarding the value of the voucher. Some companies have said it could be worth less than \$50 million, others say more than \$100 million, but most of them want to see how the FDA actually treats PRVs before making hard estimates.

Figure 5: Standard review drugs with more than \$1 billion in sales before generic entry

BRAND (CHEMICAL NAME)	GENERIC ENTRY	FDA APPROVAL	MARKET EXCLUSIVITY	GENERIC TRIGGER TREATMENT
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

Notes: A six-month pediatric exclusivity period was added to the listed patents for all these products except Protonix®

³ Details of this analysis are presented in Grabowski, H. G., Ridley, D.B., and Moe, J.L. (2009) "Encouraging innovative treatment of neglected diseases through priority review vouchers" in Karen Eggleston, editor, Prescribing Cultures and Pharmaceutical Policy in the Asia Pacific, Brooking Institution Press, Washington, DC, 347-365.

Figure 6: First mover advantage

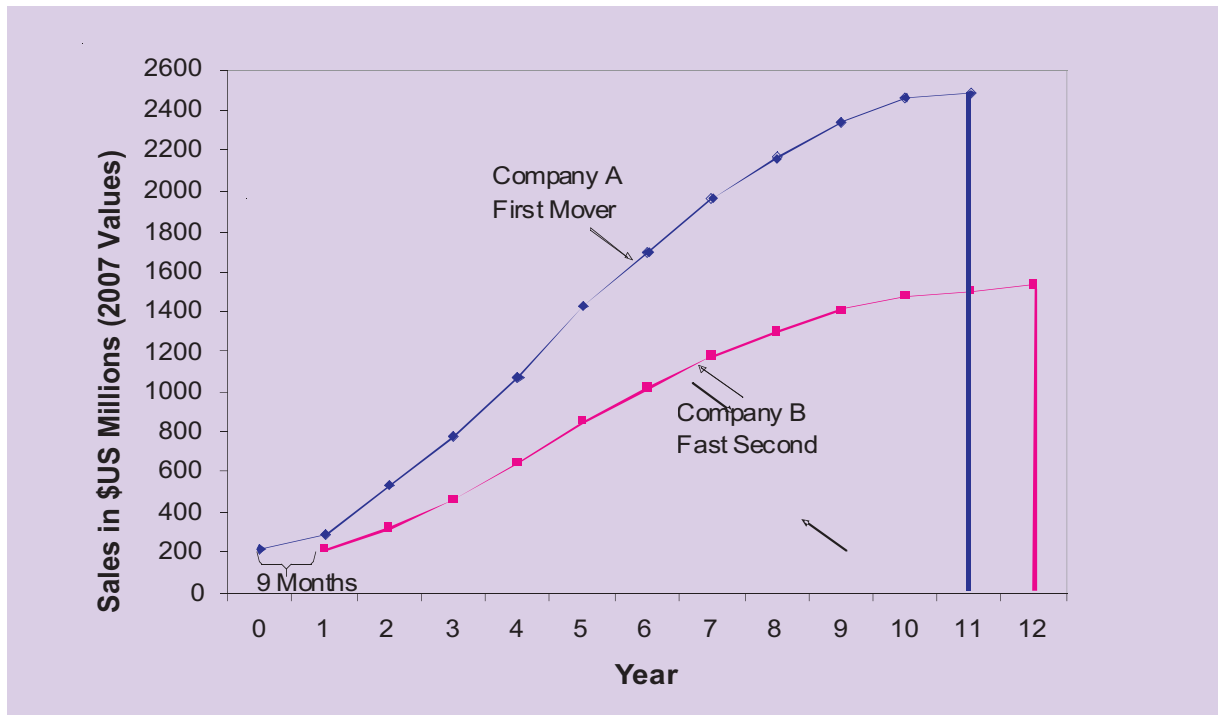
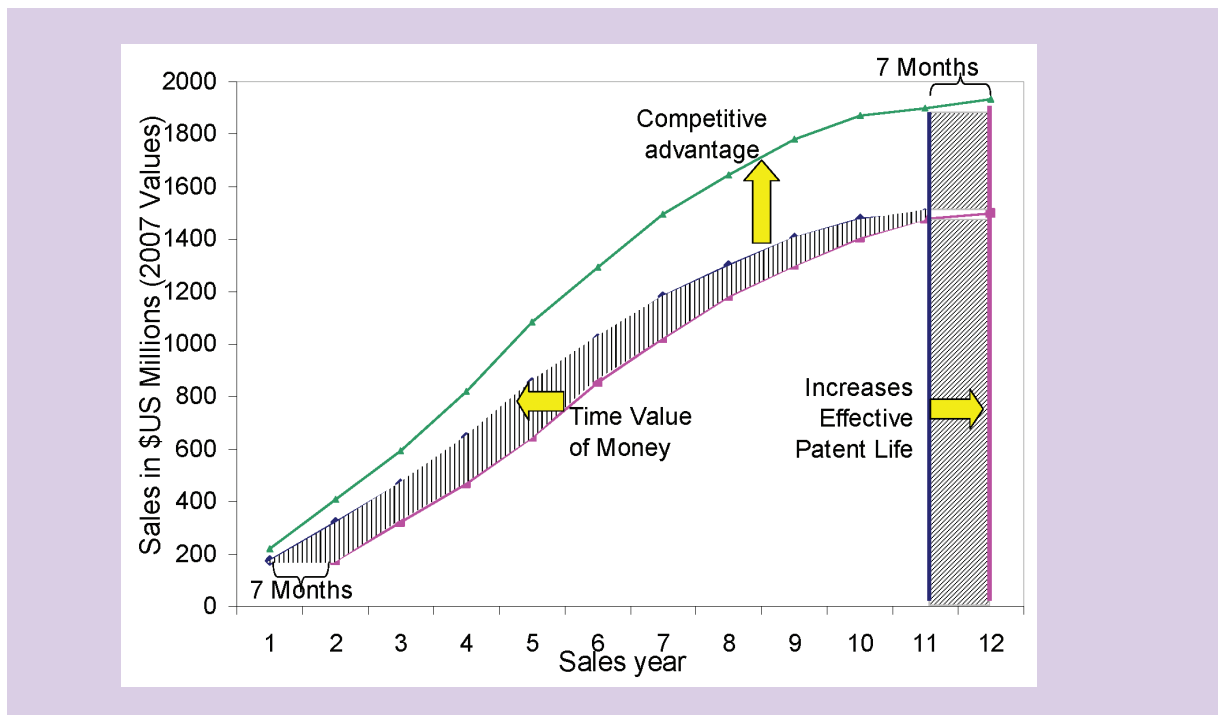


Figure 7: Second entrant has priority review voucher reduces delay from 9 to 2 months



Some Additional Regulatory Issues with Respect to PRVs

Earlier, I said that if a company receives approval for a neglected disease drug, it has to be judged to be eligible for priority review by itself to obtain a PRV. In other words, the FDA must consider the neglected disease drug to be novel in some way and it must provide significant therapeutic benefits in terms of efficacy, safety

or compliance. So a company with a project in the early stages of development has to determine if their drug meets these criteria and if they will be eligible for a PRV. This is an issue about which we had some initial interchanges with the FDA. Its response was that it cannot guarantee that if a drug is approved five years from now the drug sponsor will definitely get a PRV, because some other drug with similar characteristics may be approved first.

However, the FDA indicated that it would be able to tell a company that if it is the first with a drug with particular characteristics, there is a high probability that it will be awarded a PRV. Some of these drugs for tropical disease indications may also be eligible for other programmes such as fast track or accelerated approval reserved for drugs for 'serious' and 'life threatening' diseases. These programmes allow a new drug to get on the market with substantially less clinical trial evidence than normal. In order to qualify for fast track the FDA must determine that there are not adequate safe and effective alternative therapies available for a patient population with a life threatening or disabling condition. Fast track review differs from priority review in that you can get on the market with a new drug without doing all the pivotal tests that are normally necessary.

As discussed, the FDA can also significantly influence the market value for vouchers. The way the process works is that if a company has a drug for an infectious or tropical disease, it is reviewed by the division associated with infectious diseases within the FDA. The voucher generally will be used in a different division of the FDA and that division may have a queue of some drugs for standard regulatory review and some for priority review. The FDA's goal is to review 90 percent of priority drugs in that queue within six months, but depending on resources and on their preferences, will they actually deliver?

Some of the top people at the FDA say they are committed to this program. One such champion is Tim Cote, who heads the Office of Orphan Drugs and is on the General Guidance Committee for PRVs. However, there may be reviewers in other divisions that are less enthusiastic about PRVs. Getting drugs to the Third World is a meritorious criteria and the FDA appears to be very much in accord with this objective. On the other hand, suppose the FDA gets a voucher for a new drug in a class that already has several good alternative drugs. Will they actually review this PRV application in six months? It could be that they will treat PRVs on a case by case basis. In some cases, one may have a reviewer that really sees the purpose of this, believes in it, and delivers a decision within six months. In other cases this may not be true, and the PRV drug may get no benefit or only a few months faster review than a standard application. There is a lot of discretion within the FDA and I think this is the single biggest factor causing concern. One VC investor likened the situation to the Peanuts cartoon with Lucy holding the football and just as Charlie Brown runs up to kick the ball, Lucy pulls it away. Until this FDA uncertainty is resolved, the value of these vouchers may be significantly reduced, as there is a risk premium associated with FDA actions.

The public health community has raised some concerns about faster review time targets at the FDA as an incentive instrument. First, will PRVs slow the approval of other drugs? I think not, because there is an extra user fee and a 365-day notice period. In addition, there are probably not going to be enough of these vouchers being used in the foreseeable future to slow down the approval of other drugs. The second issue is will PRVs create greater safety risks? My view is that the FDA does not have to approve any of these voucher-based applications within six months; it just has to make a decision, so that should not be a problem. I will discuss this general issue of how user fees and time targets affect drug safety in more detail shortly.

Another concern raised by advocates for Third World causes is will these new U.S. approved medicines for tropical diseases actually be distributed in developed countries? In our article, we specified that this prize is awarded after a company gets an approval for a neglected disease, but it must also contract out to a manufacturing facility and make sure the drug is available in developing countries. Unfortunately, Congress felt that it does not really have the power to enforce this internationally, and therefore did not include this criterion in the law. So another issue is will the money come from somewhere to actually buy the drug and distribute it? I hope government as well as non-profit organizations will assume this funding task.

Based on some of my recent research work, I would like to touch on the broader issues raised by user fees. These fees have shortened the US review time from 24 months to 14 months for all drugs and by even more for priority reviews. Critics of user fees that have argued that getting drugs out faster creates safety risks. During the last renewal of the Prescription Drug User Fee Act (PDUFA), they sent a letter to Congress urging the abolition of user fees in favour of going back to a more deliberate pace for reviews. Neither the FDA nor Congress was persuaded, but what they did do was dedicate more of the user fees from PDUFA to post-market safety. The idea behind that change is that one is not going to know all the safety risks when the drug is approved. So as patient populations expand dramatically after a drug's approval, it is important to have good post-marketing reporting systems on adverse events as well as risk management programmes in place to deal with unexpected events.

Richard Wang and I published an article about a year ago on whether or not faster reviews have led to patient safety problems⁴. We looked at adverse drug reactions and compared them to review times, controlling for drug utilisation, novelty and the therapeutic category. Our general finding was that if you control for all these other factors the impact of faster review times on

⁴ Grabowski, H, Wang, R (2008). Do faster FDA drug reviews adversely affect patient safety? An analysis of the 1992 Prescription Drug User Fee Act. *Journal of Law and Economics* 51: 377-406

adverse events was not statistically significant. We also found that the U.S. is typically the first country to get either a commercially or therapeutically important new drug. There is some evidence that drugs that are approved and distributed in other major markets first have less adverse events in the U.S. With respect to PRVs, I do not think that they are going to affect the order of global approvals in a manner that would substantially increase the likelihood of unexpected adverse events.

I will conclude this presentation with a quick evaluation of PRVs as an incentive mechanism using criteria laid out by Towse and Kettler⁵. The first criterion states that it should incentivise new research without wasting resources. I think PRVs are a fairly lean, efficient way to do that. The government does not have to put in money like it does in some of the other areas and that is one of the appeals of PRVs. Congress is besieged with all kinds of requests for substantial tax credits for cancer prevention or for various other worthy causes. By contrast, this is a mandate to the FDA to review a drug faster and award a prize. It does cost something in terms of additional public resources, but these are rather modest. The second criterion is that the incentive specifies which treatments are eligible. The new law does do that explicitly with its list of 16 disease categories. The third criterion is that the incentive is credible in the eyes of the developers. It remains to be seen if PRVs will satisfy this criterion, but I think if the FDA behaves in accordance with the law's objectives

PRVs will have credibility within drug development companies and organizations. With regard to the fourth criterion, specifying treatment of follow-on drugs, the FDA has stated that follow-on drugs that do not provide some incremental benefit will most likely not get a PRV. So, on these first four criteria, I think the PRV law does fairly well.

The final criterion is that it creates products that are available to the intended consumers, i.e. the drugs get to the Third World and provide social welfare. As I discussed earlier, if an important drug is developed, the Gates Foundation and governments will have to create mechanisms for access. PRVs do not take you all the way to the market, but I think they will provide others with an incentive to step up and help take it all the way.

If this incentive mechanism is successful in stimulating research or neglected diseases, one would expect other countries and regions of the world to adopt it.⁶ This was true of the legislation to stimulate research on rare diseases. The Orphan Drug Act was passed in the United States in 1984, and comparable legislation eventually followed in Japan and Europe. Expansion of PRVs to other countries would amplify their value to developers of medicines for neglected diseases. I think it will be exciting to see how this incentive will evolve over time, and what other market-oriented incentive mechanisms might be enacted by legislators to increase R&D for neglected diseases with high global disease burdens.

⁵ Towse A, Kettler H (2005). Advance price or purchase commitments to create markets for treatments for diseases of poverty: lessons from three policies. *Bulletin of the World Health Organization* 83(4): 301-307.

⁶ David Ridley and Alfonso Calles -Sanchez have recently advanced a proposal for European PRVs. Ridley, D. B. and Sanchez, A. C. (2010) "Introduction of European Priority Review Vouchers to Encourage New Medicines for Neglected Diseases," *The Lancet* 27(3): 463-473.

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