DEVELOPING DRUGS FOR DEVELOPING COUNTRIES

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ABSTRACT

Infectious and parasitic diseases create enormous health burdens but because most of those suffering from these diseases are poor, little is invested in developing treatments. We propose that developers of treatments for neglected diseases receive a "priority review voucher." The voucher could save an average of one year of FDA review and be sold by the developer to the manufacturer of a blockbuster drug. In a well-functioning market, the voucher would speed access to treatments that consumers and payers value more. Thus, the voucher could benefit consumers in both developing and developed countries at relatively low cost to the taxpayer.

INTRODUCTION

Infectious and parasitic diseases accounted for more than half of healthy years lost in Africa in 2002, but only 3 percent of healthy years lost in developed countries.[1] Communicable diseases that disproportionately affect people in developing countries include malaria, leishmaniasis, Chagas disease, tuberculosis, dengue, and African trypanosomiasis. Lack of scientific knowledge is not the major barrier to drug development for many of these diseases. Scientists know more about the biology, immunology, and genetics of leishmania and trypanosomes than any other parasites.[2] Successful compounds often do not enter costly clinical development.[3] The barrier is a lack of financial incentive. Because most people suffering from these neglected diseases live in low-income countries,[4] there is little financial incentive for private pharmaceutical companies to invest in R&D for new treatments.

We propose a "priority review voucher" as an incentive to pharmaceutical companies to develop therapies for neglected diseases. To receive a voucher, a therapy must meet the following criteria: 1) treat neglected diseases such as African trypanosomiasis, Chagas disease, leishmaniasis or Dengue fever,[5] 2) receive approval by the United States Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products,[6] 3) be clinically superior to existing treatments, 4) forego patent rights,[7] and 5) find at least one manufacturer for the product. The awarded transferable voucher would entitle the bearer to priority FDA review for another drug (or possibly multiple drugs) and orphan drug tax credits.

Currently, the FDA awards priority status to drugs according to perceived novelty. In the 1990s, fourteen of twenty-nine "blockbuster drugs" (those with sales of $1 billion in their fifth year on the market) were classified as priority (Exhibit 1). Drugs that did not receive priority review but went on to be market leaders include Norvasc (amlodipine) for hypertension, Zyprexa (olanzapine) for schizophrenia, Zocor (simvastatin) for cholesterol, and Cozaar (losartan) for hypertension. Had priority review vouchers been available, these drugs could have helped patients sooner and earned higher returns. We estimate that a priority review voucher would be worth more than $300 million for a potential blockbuster drug, because it would shorten the time the FDA takes to analyze data from an average of 18 months to about 6 months.[8]

Insert Exhibit 1 here

Priority review does not entail lower standards for safety and efficacy. It does, however, require that the FDA have additional resources to analyze data more quickly. We estimate that the cost to the FDA of changing a drug's status from standard to priority is approximately $1

million, a cost that could be recovered through a user fee to the voucher holder. With this extra user fee it should not be necessary for the FDA to slow other drugs in the queue.

A variant of our proposal is to auction the priority review right to a manufacturer.[9] The proceeds of the auction could then be paid (as a push or pull mechanism) to the developer of a treatment for a neglected disease. This mechanism would also operate as shown in Exhibit 2, except that there would be no transfers between the manufacturer of the potential blockbuster drug and the developer of the treatment for the neglected disease.

Insert Exhibit 2 here

The priority review voucher provides two separate benefits: faster access to blockbuster drugs in developed countries and faster access to cures for infectious diseases in developing countries. There are several reasons to link the benefits. First, the voucher creates a market mechanism that identifies drugs for which priority review would be particularly efficient. Second, the two benefits are more likely to achieve government approval when linked, because they appeal to different constituencies.

In this paper, we briefly discuss the diseases that primarily affect people in developing countries. Next, we describe push and pull mechanisms designed to increase funding for R&D. We then estimate the costs and returns to funding R&D for neglected diseases using transferable priority review rights at the FDA. We then examine six potential limitations of the voucher. We conclude with a discussion of extensions.

DISEASES OF DEVELOPING COUNTRIES

Average spending for health services in low-income countries was just $23 per capita in 2001.[10] Pharmaceutical manufacturers do not expect to earn positive returns on R&D from the private market for diseases of developing countries.[11]

Diseases with the greatest burden include HIV/AIDS, malaria, and tuberculosis (Exhibit 3).[12] Manufacturers do invest in R&D for HIV/AIDS, because there is a market in both developed and developing countries for these therapies.[13] In contrast, there is less incentive to invest in R&D for malaria, because more than 99% of disability-adjusted life-years (DALYs) lost to malaria are among people in developing countries. A pipeline of new, more effective vaccines and therapies are needed to treat these diseases, because resistant strains develop and because there is a high failure rate for early-stage compounds. Other diseases with a burden of more than 1 million DALYs -- predominantly in developing countries -- include tetanus, lymphatic filariasis, trachoma, ascariasis, schistosomiasis, and African trypanosomiasis.

Insert Exhibit 3 here

MECHANISMS FOR STIMULATING DRUG DEVELOPMENT

Mechanisms that subsidize research inputs (i.e., those that decrease R&D costs) are known as "push strategies." Mechanisms that reward research output (i.e., those that increase financial returns) are known as "pull strategies." Many of these mechanisms can be regarded as complements rather than substitutes, particularly pull strategies that do not require funding unless a treatment reaches the market. Furthermore, donors that provide push funding could receive some of the pull reward from the development of a successful product.

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The Orphan Drug Act (ODA) includes both push and pull mechanisms. First, the ODA provides seven years of marketing exclusivity upon FDA approval. Second, drug makers can qualify for tax credits for up to half of their clinical testing expenses. Third, developers can receive modest grant support from the FDA for the investigation of treatments for rare diseases. Fourth, FDA provides counseling regarding conditions for approval.[14] The ODA was followed by laws in Japan (1993) and the European Union (2003) that include similar incentives.[15]

Neglected diseases qualify for orphan drug status because of their low disease prevalence in these countries. In the U.S., a company can qualify for U.S. tax credits for drugs requiring foreign testing when there is an insufficiently large testing population in the U.S. As of July 1999, FDA had granted 25 U.S. orphan designations for tropical diseases.[16]

One type of push strategy is the public-private partnership (PPP).[17] PPPs use philanthropic funding to contract with public and private sector entities that develop drug candidates for neglected diseases.[18] For example, in 2005 the Global Alliance for Vaccines and Immunization received $750 million from the Gates Foundation and $290 million from Norway to increase access to existing vaccines and accelerate R&D efforts for treatments for neglected diseases.[19] Push mechanisms reduce the developer's risks and initial costs and can allow the donor greater control over product development. On the other hand, push mechanisms can suffer from asymmetric information, because the donor has less information than the developer about which projects are the most promising and which costs are appropriate.

Whereas push mechanisms subsidize research inputs, pull mechanisms reward research output. Funders commit to finance drug and vaccine purchases for poor countries prior to

product development. The Advance Market Commitment Working Group proposed a guaranteed price for a new vaccine for malaria, tuberculosis, or AIDS. Countries would provide a small copayment to insure that new vaccines meet the market test. They estimate that a market size with present value of sales of $3 billion (in 2004 dollars) would be necessary to motivate manufacturers to initiate projects aimed at these diseases. In 2004 Britain's Chancellor of the Exchequer and other donors committed to purchase a malaria vaccine if one is developed.[20]

Another pull mechanism is the transferable patent exclusivity right. A developer that licenses a product for a neglected disease would receive additional time on patent for a different product, and this right could be sold to another company.[21] For a risk-averse manufacturer, a voucher for extended patent time might be more valuable than a voucher for priority review, because the manufacturer would be more confident about the value of a product that is already on the market. On the other hand, the voucher for extended patent life would delay access to generic drugs, so the incentive for R&D for neglected diseases would be paid by consumers of a different drug and their insurers.

BENEFITS AND COSTS

For the priority review voucher to succeed in enhancing global welfare, it must satisfy three conditions. First, to create a market for the voucher, the expected net benefit for the manufacturer that purchases the voucher must be nonnegative. Second, to induce investment in R&D for neglected diseases, the expected net benefit for the developer that earns a voucher must be nonnegative. Third, the expected net global welfare benefit must be positive. In this

section we provide an illustration of costs and benefits of the voucher. Actual figures will depend on the products in question. Detailed calculations are provided in the online methods appendix.

Condition 1: Value to the Manufacturer

Benefit of Priority Review over Standard Review. Manufacturers are willing to spend resources speeding drugs with potentially high market value through the development and approval process.[22] We estimate that changing a top-decile compound's classification from standard to priority is worth $322 million on average for the manufacturer. This estimate is based on changing the review time from 18.4 months to 6.4 months[23] for a top-decile drug with net present value of $2.92 billion (in 2004 dollars) and a discount rate of 11%.

The voucher is purchased before commercialization, so we assume that the manufacturer is risk-neutral and believes that the product will earn average returns for a top-decile drug. If manufacturers are risk-averse and/or there is greater uncertainty, priority review will be worth less than $322 million. Alternatively, if the manufacturer is risk-neutral and believes that the product will be in the top 5% in sales, priority review will be worth more.

We assume that cash flows will be realized one year sooner and that effective patent life and market life will be constant. This is an appropriate assumption for most drugs, given the formula on Hatch-Waxman patent term extensions.[24] Because the patent life would be shifted forward by one year, both the pioneer drug and the generic drug will reach the market one year earlier than under standard review. Our estimate of the benefit to the manufacturer is conservative, because the marginal benefit will be even greater in a situation of rapid technological change in which new products displace products with remaining patent life.

*Cost of Priority Review over Standard Re*view. We assume that the additional costs to the FDA are passed on to the voucher holder as an additional user fee. We estimate that the cost of priority review is $2 million and the cost of standard review is $1 million. Hence, the additional cost of moving from standard to priority review is $1 million. These estimates are based on an average review cost (user fee plus FDA budget) of $1.2 million for all drugs (standard and priority), a cost elasticity of time of –1.2,[25] and 18.4 months vs. 6.4 months for standard vs. priority review. Given that the value of priority review is $322 million for a top-decile drug and the voucher holder would be assessed an additional user fee of $1 million, the manufacturer of an average top-decile product should be willing to pay up to $321 million for a voucher.

Condition 2: Value to the Developer

To motivate development of a drug for a neglected disease, the selling price of the priority review voucher(s) plus goodwill must exceed half of the R&D costs to develop the drug, because the other half of the R&D costs would be covered by ODA tax credits.

The selling price of the voucher would be approximately $321 million. The developer also receives community recognition. Pursuit of goodwill has motivated manufacturers such as Merck to donate ivermectin for river blindness, but additional incentives are need to motivate further R&D. Furthermore, the voucher provides scientists with an economic justification for pursuing projects that attract them for intellectual and social reasons.[26]

The R&D development program would be eligible for the push incentives included in the ODA, including tax credits for up to half of the clinical testing expenses. If drugs for neglected diseases have the same clinical R&D costs as the average new drug candidate in the 1990s,

capitalized clinical costs would be $191 million (in 2000 dollars).[27] We include the cost of successful and failed trials because all drugs receiving orphan drug status are eligible for tax credits, even those that are not approved. Adjusting using the GDP implicit price deflator, the mean clinical trial cost would be $504 million (in 2004 dollars). Thus, a 50% tax credit would be $252 million.

We believe, however, that the cost of developing a drug for a neglected disease could be considerably lower than the mean case. First, given the likely acceptance into the FDA's accelerated approval program, orphan drugs might be approved on the basis of a pivotal phase 3 clinical trial (or a combined phase 2/3 trial). We expect fewer trials, because a drug for a neglected disease would not undergo the extra trials needed for formulary acceptance and reimbursement.[28] Second, as a result of advances in biotechnology and genomics, there is a greater understanding of the molecular basis of pathogens,[29] and thus higher probability of success and lower R&D costs for these infectious disease indications.[30] Third, R&D efforts associated with bioterrorism should create positive spillovers for research for neglected diseases. Fourth, research started for other indications can sometimes yield information for the treatment of neglected diseases.

If one voucher is not sufficient to generate significant research on neglected diseases, then multiple vouchers could be awarded. For example, two vouchers for two blockbuster drugs could be awarded for every one treatment for a neglected disease.

Condition 3: Social Welfare

The social welfare gains to patients (both consumers of the drug for the neglected disease and consumers with earlier access to potential blockbuster drugs) plus the net gains to

manufacturers (both of the drug for the neglected disease and the potential blockbuster drug) minus the cost to the government of FDA review and orphan drug status should be positive.

Producer Surplus. Assuming that expected net economic returns to the developer are zero (i.e., the value of the vouchers will equal R&D costs in long-term equilibrium) provides a lower bound on the social value of the priority review voucher. In fact, producer surplus will be positive if the value of priority review for a potential blockbuster drug exceeds the net R&D costs of orphan drug credits for the developer of a drug for a neglected disease.

Consumer Surplus from a Drug for a Neglected Disease. The consumer surplus from a drug or vaccine for a neglected disease will depend on the quality of the product, how many people can be treated with it, and the value that society places on human life. As illustrated in Exhibit 3, 46 million DALYs are lost each year to malaria. A common cost-effectiveness threshold for health interventions in the poorest countries is $100 per DALY.[31] For comparison, health interventions are considered cost-effective in the U.S. at up to 500 to 1000 times this amount.[32] Thus, the burden is at least $4.6 billion per year. A product would be worth $1 billion if it could alleviate 22% of the burden of malaria for just one year. (Of course, the benefits would extend beyond one year.) Other parasitic and infectious diseases have smaller burdens than malaria (e.g., 6 million DALYs lost each year to lymphatic filariasis), but treatments could be worth $1 billion in net present value, given that benefits extend over time. As we demonstrate below, although the benefits to people in developing countries could be enormous, they need not be to justify the priority review voucher, because of the benefits of faster review for people in developed countries.

Consumer Surplus from Faster Access to a Potential Blockbuster Drug. Consumers in the U.S. will benefit from faster access to new drugs. The manufacturer's price does not extract the entire consumer surplus. Consumer surplus is approximately equal to half of the manufacturer's surplus,[33] so if the producer surplus from faster review (gross of R&D costs) is $322 million, then the consumer surplus would be $161 million. This does not include the additional consumer benefit of earlier access to generic drugs resulting from shifting patent life forward by one year.

Government Costs. By motivating a manufacturer to create a new treatment for neglected diseases, the U.S. government will bear the additional cost of drug review and of orphan drug status. We assume that the FDA will deem the treatment for neglected disease worthy of priority review on its own merits (in addition to giving the developer a priority review voucher) at a cost of $2 million. We expect that the orphan drug tax credit would cost taxpayers less than $252 million, although the amount will be lower if developers can use efficiencies and spillovers from other projects.

Global Welfare. We assume that one voucher per drug for neglected disease is a sufficient incentive, expected producer surplus equals zero (i.e., manufacturers earn normal profits), and consumer surplus for blockbuster drugs is approximately half of producer surplus. Thus, global welfare equals the consumer surplus from the treatment for a neglected disease plus half of the producer surplus from faster review (approximately $161 million) minus the cost of orphan drug tax credits (approximately $252 million) and other push mechanisms minus the cost of priority review for the drug for a neglected disease (approximately $2 million). If the social value of a treatment for a neglected disease is worth at least $100 million in net present

value, the priority review voucher would enhance global welfare. In fact, we believe that the social value of treatments for neglected diseases could be in the billions of dollars.

LIMITATIONS

First, a voucher worth $321 million plus orphan drug tax credits of $252 million is considerably smaller than the $3 billion Advance Purchase Commitment (APC). The difference exists, in part, because the priority review voucher uses after-tax profits (sales net of production and distribution costs), whereas the APC estimate is based on pre-tax sales revenues gross of any costs. Another difference is that the APC covers R&D, manufacturing, distribution, and introduction costs. For the APC there is an explicit incentive for the developer to ensure consumer access. Nevertheless, a primary difference between the proposals is the generosity of the prize, so the voucher might encourage developers to salvage existing projects that were initiated for other diseases. With a lower cost to the sponsor (e.g., taxpayers), the priority review voucher could be applied to more neglected diseases and still meet a given cost-benefit criterion. Thus, the APC might be available for diseases for which there are significant donor resources (e.g., malaria, tuberculosis, HIV/AIDS), while the priority review voucher could be applied to a wider class of neglected diseases. If the goal were more development then the number of vouchers awarded per product discovered could be increased.

Second, the incentive mechanism has little value if treatments are developed that do not reach patients. The developer should work with global and local stakeholders prior to FDA approval to ensure that the product will be used. It is the responsibility of the developer to

insure that someone manufactures the drug, perhaps through technology transfer to a developing country.[34] Additional charitable efforts might be necessary to support access.

Third, developers might fear that the government will not award a voucher as promised. Fortunately, the government is likely to keep its promise since the program is low cost. Like other pull mechanisms, however, it is important to write enforceable contracts.[35]

Fourth, poor people might prefer cash over medicine. We believe that many donors would prefer to give medicine because health is viewed as meritorious, whereas cash can be siphoned by corrupt intermediaries.[36] Furthermore, medicines have spillover effects and may be international public goods.[37]

Fifth, a voucher might speed the approval of a product with high potential sales but limited clinical benefits. Given FDA approval we assume that the product has clinical benefits, but if these are small (and yet expected sales are high) then U.S. benefits will be smaller.

Sixth, drugs given priority review might be less safe. Priority review, however, does not entail lower standards for safety and efficacy; it requires that the FDA have additional resources to analyze the data in about 6 months. According to FDA data, shortening review times does not increase the withdrawal rate. From 1971 to 1993 the withdrawal rate was approximately 2.7%, and from 1994-2004 when review times were dramatically lower the withdrawal rate was 2.3%.[38] On the other hand, Olson (2004) finds that drugs with faster review times are subject to more adverse drug reactions (ADRs).[39] However, Olson's data were limited by a short time period (1990-1995) and limited information on drug utilization. A 2005 Tufts study finds no correlation between review times and withdrawal rates across therapeutic classes.[40] The

voucher's political viability might be enhanced by a revamped system of post-approval surveillance, currently under review by FDA and the Institute of Medicine.[41]

CONCLUSION

We propose a novel pull mechanism in which a voucher is awarded for creating and licensing a drug that treats neglected diseases in the developing world. The transferable voucher would give the bearer priority review status at the FDA for another drug. If the voucher speeds FDA approval by a year, it could increase the present value of sales of a blockbuster drug by more than $300 million. In addition to this reward the developer would be eligible for orphan drug tax credits. In a well-functioning voucher market, drugs that consumers and payers value more would reach the market sooner. We estimate that the additional cost of faster FDA review would be $1 million and could be passed on to the manufacturer. The cost to the government would be the additional cost associated with any drug for a neglected disease (i.e., orphan drug tax credits).

The concept of a priority review voucher could also be applied to diseases associated with bioterrorism. A bill introduced in the U.S. Senate in 2005 proposes that the developer of a drug that prevents or treats a bioterrorism-related illness would receive a voucher for extended patent life for a different product.[42] Whereas a patent extension delays entry of generics, the priority review voucher speeds entry of generics, because it speeds the launch of the branded drug and likely moves forward its patent expiration.

Given its relatively low cost, the priority review voucher could be part of a larger tool kit including push and pull mechanisms. Whereas the voucher could motivate developers to

continue with existing programs, awards such as the proposed $3 billion APC could motivate

entirely new programs. Furthermore, if the APC is directed at malaria, tuberculosis, and HIV-

AIDS, then the voucher could be applied to African trypanosomiasis, Chagas disease,

leishmaniasis or Dengue fever.

The priority review voucher could provide benefits in developing countries and the U.S.

at relatively low cost. These two benefits are separable in theory, but we believe they are more

politically palatable when linked. The voucher would appeal to pharmaceutical manufacturers,

consumers (who appreciate faster access to blockbuster drugs), the military (whose personnel

operate in developing countries and may be exposed to neglected diseases), and advocates for

health in developing countries.

ACKNOWLEDGMENTS

TECHNICAL APPENDIX

In this section we list three necessary conditions for the priority review voucher to succeed in enhancing global welfare. We also provide illustrative calculations.

CONDITION 1: VALUE TO THE MANUFACTURER

The net benefit for the manufacturer that purchases and uses the voucher must be nonnegative. We can represent condition 1 as follows:

$$\pi_b = (\pi_p - \pi_s) - (\phi_p - \phi_s) - v \geq 0 \ \forall N$$

where π_b is the expected producer surplus from faster review for a potential blockbuster drug; π_p is the return from priority review; π_s is the return from standard review; ϕ_p is the user fee from priority review; ϕ_s is the user fee from standard review; and v is the voucher price. π_b must be nonnegative for all N vouchers.

Benefit of Priority Review. The additional expected producer surplus from changing from standard to priority review is as follows:

$$(\pi_p - \pi_s) = ((1 + r)^{(ts-tp)} - 1)\vartheta$$

where r is the annual discount rate; t_s and t_p are the median approval times for standard and priority drugs (measured in years); and ϑ is the expected net present value of the product in 2004 dollars.

Based on research by Grabowski et al. (2002), the expected net present value of a top-decile drug is $2.7 billion (in 2000 dollars), and a reasonable value for the discount rate is 11%. Adjusting for inflation using the Gross Domestic Product implicit price deflator yields a net present value of $2.92 billion (in 2004 dollars).

According to Berndt et al. (2005) (with additional data from A.H.B. Gottschalk), the median FDA approval time was 18.43 months for standard drugs and 6.4 months for priority drugs from 1997-2002. Under the second Prescription Drug User Fee Act, the FDA's goal is to complete the review of 90% of new drug and biologic license applications within 6 months for priority drugs and within 10 months for standard drugs. Completion of drug review means that the FDA approves, disapproves, or issues an action letter detailing necessary steps to obtain approval. In fact, the benefits of the priority review voucher would have been even greater in 2003. The FDA reported that in 2003 the median time was 6.7 months for priority drugs and 23.1 months for standard review.

Based on these assumptions, the value of faster review of one year (π_p - π_s) for a top-decile drug is approximately $322 million (in 2004 dollars).

Cost of Priority Review. Berndt et al. (2005) report that applications with clinical data in fiscal year 2004 were assessed a one-time fee of $573,500. In 2002, 47% of the cost of processing human drug applications was paid by user fees and 53% from Congressional appropriations. Hence, the private plus public cost of review is approximately $1.2 million.

According to the FDA, 39% of drugs approved between 1997 and 2003 had priority status (FDA 2004).

According to Carpenter and Fendrick (2004), "a 10% increase in staff was always associated with least a 12% decline in expected review time, and as much as a 25% decline in expected review time." To yield a conservative estimate, we use the 12% figure, which gives us an elasticity of –1.2.

As discussed above, Berndt et al. (2005) report that the median FDA approval time was 18.4 months for standard drugs and 6.4 months for priority drugs from 1997 to 2002.

Using these data, we estimated two equations with two unknowns:

$$0.39c_p + 0.61c_s = \$1.22 \text{ million} \tag{1}$$

$$\text{Arc elasticity: } -1.2 = ((6.4 - 18.43) / (0.5(6.4 + 18.43))) / ((c_p - c_s) / (0.5(c_p + c_s))) \tag{2}$$

where c_p is the cost of priority review status and c_s is the cost of standard review. Solving the system of two equations and two unknowns, we find that $c_p = \$1,849,000$ and $c_s = \$785,000$. For simplicity, we round them to one significant digit each: $c_p = \$2$ million and $c_s = \$1$ million. Thus, the cost of priority review is $2 million, and the cost of standard review is $1 million, so the additional cost of moving from standard to priority review is $1 million.

Returning to condition 1, if $(\pi_p - \pi_s)=\$322$ million and if $(\phi_p - \phi_s)=\$1$ million then the voucher price (v) must be less than or equal to $321 million for expected producer surplus from faster review to be non-negative.

CONDITION 2: VALUE TO THE DEVELOPER

The net benefit for the developer that earns a voucher must be nonnegative. Condition 2 can be represented as follows:

$$\pi_n = v\,N + \omega + \gamma - c \geq 0$$

where π_n is the expected producer surplus from a drug for a neglected disease; v is the voucher's selling price; N is the number of vouchers awarded; ω is the value of orphan drug status (assumed to be equal to the tax credits); γ is the value of goodwill; and c is the R&D cost of a drug for a neglected disease. Condition 2 can be rewritten as $v\,N + \gamma > a\,c$ where a is the fraction (0<a<1) of the R&D costs that are not covered by ODA or other push mechanisms.

Given the price estimate in condition 1 and given that $N=1$, the fraction of the R&D costs paid by the developer must be less than $321 million plus goodwill.

CONDITION 3: SOCIAL WELFARE

Condition 3 requires that the net global welfare benefit must be positive. It can be represented as follows:

$$W = \sigma_n + \pi_n + N \sigma_b + N \pi_b - \omega - \phi_p > 0$$

where W is social welfare; σ_n and π_n are expected consumer surplus and producer surplus from a new treatment for neglected disease; σ_b and π_b are expected consumer surplus and producer surplus from faster access to a potential blockbuster drug; N is the number of vouchers awarded; and ω and ϕ_p are the costs to the government from orphan drug status and priority review for a drug for neglected disease.

We assume that one voucher per drug for a neglected disease is a sufficient incentive, that expected producer surplus equals zero (i.e., manufacturers earn normal profits), and that consumer surplus for blockbuster drugs is approximately half of producer surplus.

Consumer surplus is equal to half of producer's surplus if the demand curve is linear and marginal costs are constant. Consider an inverse demand function p = a - b q where p is price and q is quantity. Total cost=cq+F where c is marginal cost and F is fixed cost. The consumer surplus is the area between the demand curve and the price: $(a-c)^2/8b$. Producer surplus is the area between price and marginal cost: $(a-c)^2/4b$.

Hence, global welfare can be rewritten as follows:

$$W = \sigma_n + (\pi_p - \pi_s)/2 - \omega - \phi_p = \sigma_n + \$161m - \$252m - \$2m = \sigma_n - \$93m$$

For global welfare to be positive, the gains from a treatment for neglected diseases must exceed \$93 million. If we use a discount rate of 3% rather than 11% then $W = \sigma_n + 112.5m - 176m - 2m$, so the gains from a treatment for neglected diseases must exceed \$65 million.

Notes to the Appendix

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EXHIBITS

Exhibit 1. Priority ratings for drugs launched in the 1990s that achieved sales of $1 billion dollars by the fifth year following launch. Source: Drug sales data from May issues of MedAdNews. Review classifications from FDA data provided by Adrian Gottschalk. Note that FDA used a three-tier (i.e. 1-A, 1-B, 1-C) rather than two-tier (i.e. priority, standard) review classification prior to October 1992. For drugs approved prior to October 1992, the authors converted 1-A and 1-B to priority and 1-C to standard.

Trade Name	Approval Date	Review Classification
Pravachol	Oct-91	Standard
Biaxin	Oct-91	Priority
Zocor	Dec-91	Standard
Zoloft	Dec-91	Standard
Norvasc	Jul-92	Standard
Taxol	Dec-92	Priority
Paxil	Dec-92	Standard
Imitrex	Dec-92	Priority
Claritin	Apr-93	Standard
Propulsid	Jul-93	Standard
Glucophage	Dec-94	Priority
Cozaar	Apr-95	Standard
Prevacid	May-95	Standard
Fosamax	Sep-95	Priority
Allegra	Jul-96	Standard
Zyprexa	Sep-96	Standard
Diovan	Dec-96	Standard

Lipitor	Dec-96	Priority
Seroquel	Sep-97	Standard
Plavix	Nov-97	Priority
Rituxan	Nov-97	Priority
Singulair	Feb-98	Standard
Viagra	Mar-98	Priority
Celexa	Jul-98	Standard
Remicade	Aug-98	Priority
Celebrex	Dec-98	Priority
Avandia	May-99	Priority
Vioxx	May-99	Priority
Actos	Jul-99	Priority

Exhibit 2. Priority Review Voucher Schematic. Source: authors

Government

1. Voucher + orphan credits

Treatment

3. Voucher + user fee

Priority review

Developer of treatment for neglected disease

2. Voucher

Payment

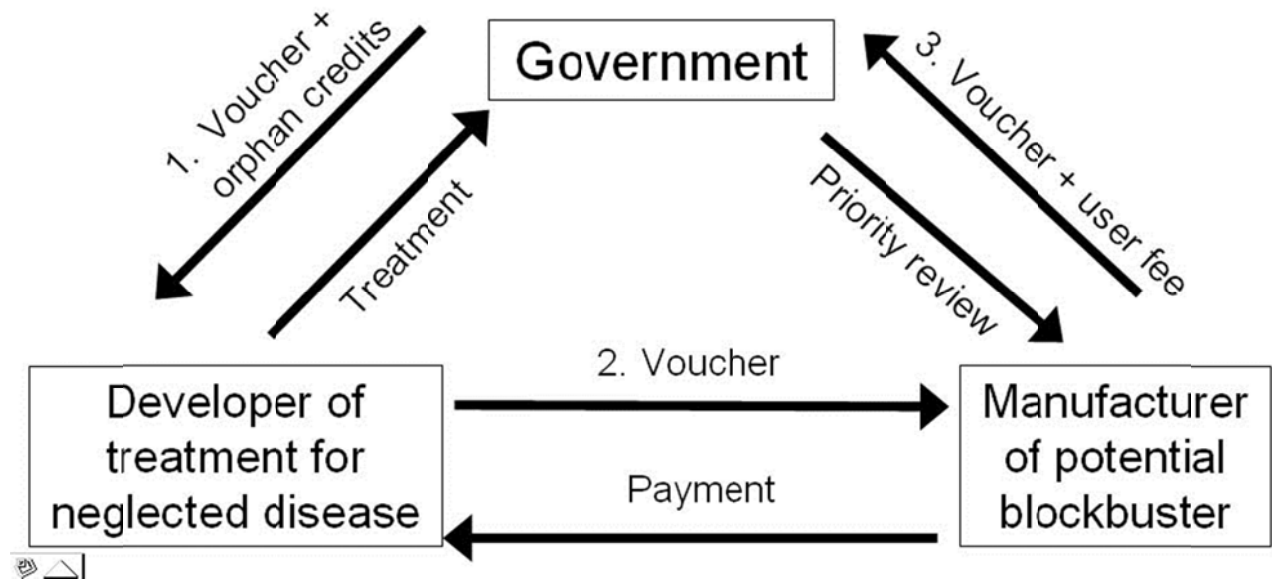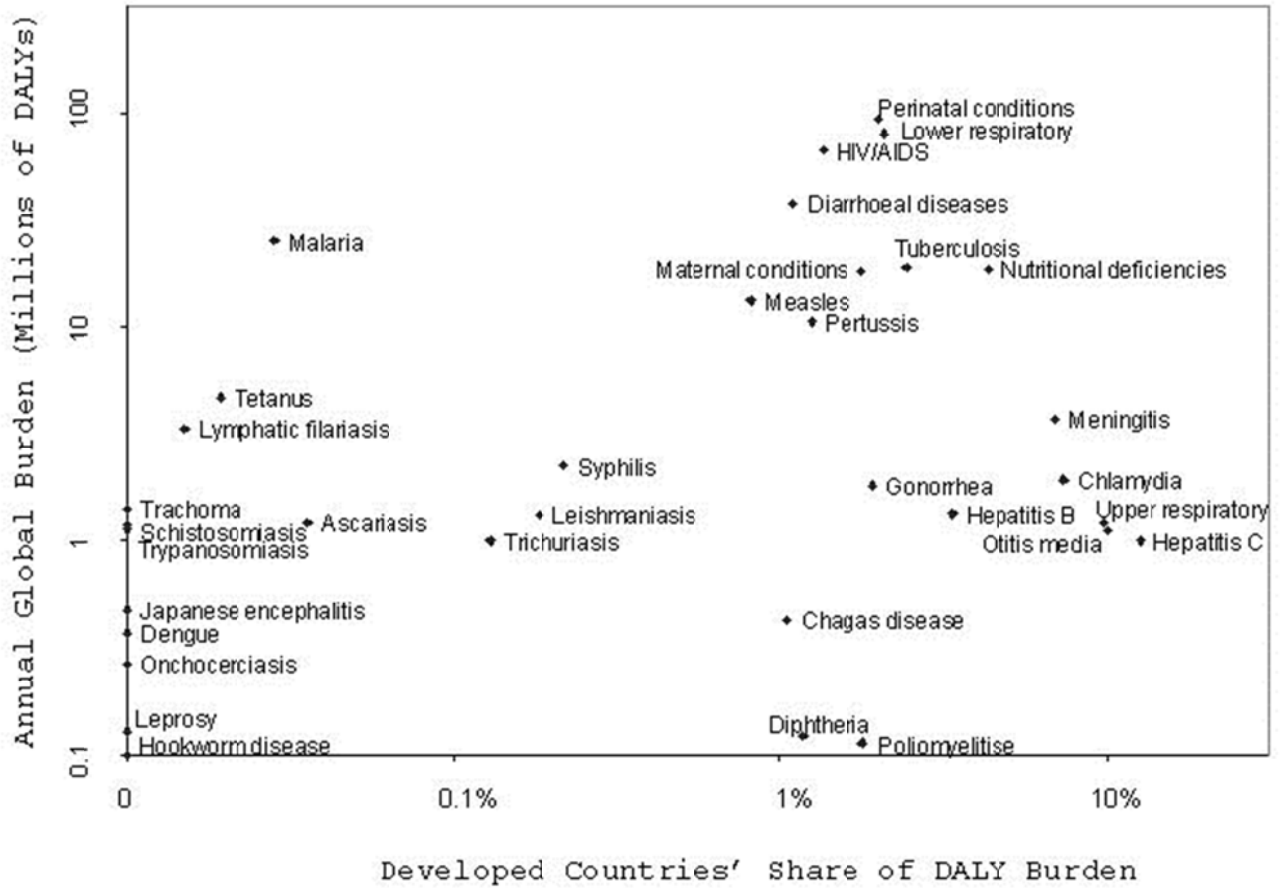Manufacturer of potential blockbuster

Exhibit 3. Global Disease Burden and Distribution. Source: authors' calculations based on data
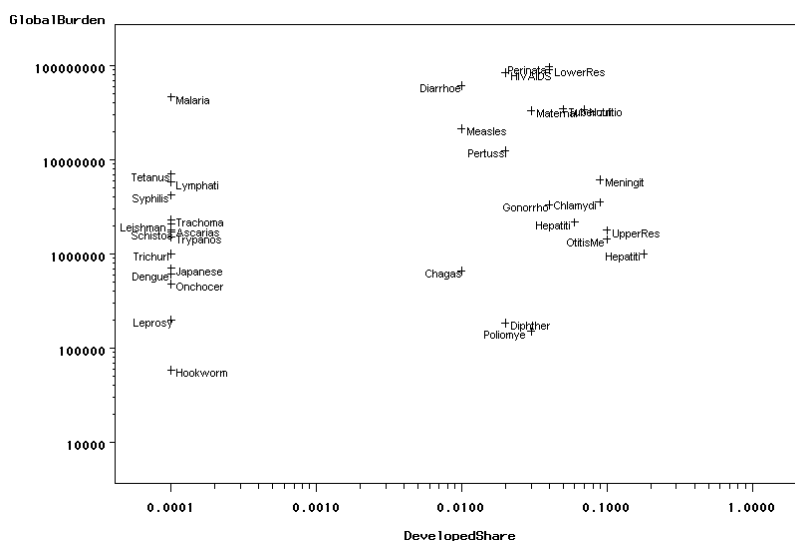
from the *World Health Report 2004*.

Following are the data for the above figure. Note that because the data are skewed, we

recommend a log scale for the figure.

Cause	Share in Developed Countries	Global Burden
Hepatitis C	0.18	1004000
Otitis media	0.10	1435000
Upper respiratory infections	0.10	1795000
Chlamydia	0.09	3571000
Meningitis	0.09	6192000
Nutritional deficiencies	0.07	34417000
Hepatitis B	0.06	2170000
Tuberculosis	0.05	34736000
Lower respiratory infections	0.04	91374000
Perinatal conditions	0.04	97335000
Gonorrhoea	0.04	3365000

Poliomyelitise	0.03	151000
Maternal conditions	0.03	33632000
HIV/AIDS	0.02	84458000
Pertussis	0.02	12595000
Diphtheria	0.02	185000
Diarrhoeal diseases	0.01	61966000
Chagas disease	0.01	667000
Measles	0.01	21475000
Syphilis	0.00	4200000
Leishmaniasis	0.00	2090000
Trichuriasis	0.00	1006000
Ascariasis	0.00	1817000
Malaria	0.00	46486000
Tetanus	0.00	7074000
Lymphatic filariasis	0.00	5777000
Trachoma	0	2329000
Schistosomiasis	0	1702000
Trypanosomiasis	0	1525000
Japanese encephalitis	0	709000
Dengue	0	616000
Onchocerciasis	0	484000
Leprosy	0	199000
Hookworm disease	0	59000

Following is an alternative version of Exhibit 3 created in SAS.

Annual Global Burden of Disease (DALYs) vs. Share of Burden in Developed Countries

ENDNOTES

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[1] Calculation using table 3 of *World Health Report 2004: Changing History* (Geneva, World

   Health Organization, 2004), http://www.who.int/whr/2004/en/ (18 May 2005).

[2] D. Wirth. "A Harvest Not Yet Reaped: Genomics to New Drugs in Leishmania and

   Trypanosomes." DND Working Group Expert Paper, September 2001.

   http://www.dndi.org/pdf_files/harvest.pdf (23 September 2005).

[3] R. MacDonald. "Prioritising Neglected Diseases Related to Poverty." *British Medical Journal*

   331, no. 7507 (2005): 12.

[4] *World Health Report*.

[5] These neglected diseases were identified independently by the International Federation of

   Pharmaceutical Manufacturers Association (http://www.ifpma.org) and by a Médecins

   Sans Frontières (http://www.neglecteddiseases.org) working group.

[6] FDA approval is a conservative requirement, because the FDA might reject a vaccine that

   would not pass a risk-benefit test in the U.S. but would pass such a test in a developing

   country (Kremer 2002).

[7] Some developers will not hold all patent rights, but the voucher creates a financial incentive

   for the patent holders to negotiate. John Walsh and colleagues find little empirical basis

   for claims that patent thickets impede biomedical research. J.P. Walsh, C. Cho and W.M.

   Cohen. View from the Bench: Patents and Material Transfers. Science. Vol. 309.

   September 23, 2005.

[8] The voucher would grant the bearer the same treatment as other priority drugs, so review time would be 6 months on average, but not guaranteed.

[9] Pharmaceutical R&D Policy Project, Wellcome Trust-LSE, "Fast Track Options as a Fundraising Mechanism to Support R&D into Neglected Diseases," January 2005. http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/documents/PRPP/FastTrackOption(FTO%20January2005.pdf (23 September 2005)

[10] *World Health Report*.

[11] With little revenue at stake most manufacturers forgo patent protection for essential drugs in developing countries. A. Attaran, "How Do Patents And Economic Policies Affect Access To Essential Medicines In Developing Countries?" *Health Affairs* 23, no. 3 (2004): 155-166.

[12] *The World Health Report 2004* classifies the following countries as developed: all countries in Europe (including Israel and Turkey), parts of North America (Canada, Cuba, and the United States), and parts of the western Pacific (Australia, Brunei, Japan, New Zealand, and Singapore) (p. 157).

[13] For research on access to drugs with markets in both developed and developing see J.O. Lanjouw (2003) "Opening Doors to Research: A New Global Patent Regime for Pharmaceuticals," *Brookings Review*. Brookings Institution Press. Vol. 21, no. 2, Spring 2003.

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http://www.cmhealth.org/docs/wg2_paper9.pdf (5 October 2005); H. Kettler,

"Narrowing the Gap between Provision and Need for Medicines in Developing

Countries," London: Office of Health Economics, 2000.

[16] Kettler, "Narrowing the Gap."

[17] VG Hale, K Woo, and HL Lipton. "Oxymoron No More: The Potential Of Nonprofit Drug

Companies To Deliver On The Promise Of Medicines For The Developing World." Health

Affairs 24, no. 4 (2005): 1057-1063.

[18] H.E. Kettler, S. Marjanovic, "Engaging biotechnology companies in the development of

innovative solutions for diseases of poverty," Nature Reviews Drug Discover, Volume 3,

February 2004, 171-6.

[19] *The Economist*, "Foundation," 27 January 2005.

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"Advanced Purchase Commitments for a Malaria Vaccine: Estimating Costs and

Effectiveness," NBER Working Paper, May 2005, http://www.nber.org/papers/w11288 (3

December 2005); E.R. Berndt and J.A. Hurvitz. "Vaccine Advance-Purchase Agreements For

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[21] Kettler, "Narrowing the Gap."

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[23] A.H.B. Gottschalk provided data on median review times under PDUFA-II. See also E.R. Berndt, A.H.B. Gottschalk, T.J. Philipson, and M.W. Strobeck, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates." *Nature Reviews Drug Discovery* 4 (2005), 545-554.

[24] Moving the launch date forward by one year moves the patent expiration forward by one year for most drugs. Under the Hatch-Waxman Act, most drugs are eligible for compensatory increases in effective patent life equal to the time lost in regulatory review. H. Grabowski and J. Vernon, "Effective Patent Life in Pharmaceuticals," *International Journal of Technology Management* 19, no. 1/2 (2000): 98-120.

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[33] Consumer surplus is equal to half of producer's surplus if the demand curve is linear and marginal costs are constant. This method of calculating consumer surplus applies when the manufacturer has market power. In the case of the drug for neglected diseases, we assume that the drug is available as a generic, so the price would be near marginal cost and consumer surplus would be much greater.

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