An Efficient Reward System for Pharmaceutical Innovation

Aidan Hollis
Department of Economics, University of Calgary; Institute of Health Economics[1]
email: ahollis@ucalgary.ca
Draft – updated 17.01.2005

This paper is frequently updated. Please check against the most recent version at http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf

Abstract
Because pharmaceutical markets function poorly, the patent system does not effectively stimulate drug research and development. Instead, it induces large amounts of research into drugs with relatively little incremental therapeutic value, while providing inadequate incentives to innovate in some areas of great therapeutic value. At the same time, patents result in high prices which exclude many users from access to potentially life-saving therapies. In this paper, I propose a novel reward system for pharmaceutical innovation, in which innovators are rewarded based on the incremental therapeutic benefits of their innovation. This would align innovators' incentives with social objectives, and lead to the best possible allocation of research investment. With rewards paid directly to innovators, patents could be compulsorily licensed to enable competitive pricing, thus solving problems of drug access. Government expenditures on rewards could be largely funded through reduced expenditures on patented drugs, and pharmaceutical innovators could continue to earn a healthy return on their investments.

1 Introduction

The global system of drug development and marketing is broken. Research spending is misdirected into products which add little therapeutic value to the medicine chest; and high prices for patented drugs are preventing access to life-saving drugs and distorting international trade. These worldwide problems – which are of immense importance – are results of the way the patent system is implemented, but they are not inevitable. In this paper, I describe an alternative implementation of the patent system to reward innovation

[1] The author began this research while TD MacDonald Chair of Industrial Economics at the Competition Bureau, Ottawa for the year 2003-4. The comments in this paper are his private views and are not purported to reflect the opinions or position of the Commissioner of Competition, the Competition Bureau, or the Government of Canada. I am very grateful to James Love, who suggested research on this topic to the author, and to Michael Abramowicz, Aslam Anis, Dean Baker, James Boyle, Jillian Clare Cohen, Cam Donaldson, David Feeny, Merrill Goozner, Joel Hay, Richard Kingham, Josh Lerner, Joel Lexchin, James Orbinsky, Kevin Outterson, Finn Poschmann, Suzanne Scotchmer, Don Willison, Greg Wolbring and participants in numerous seminars (CEA 2004, ACEA 2004, Universities of Alberta, Calgary, McMaster, Toronto, Victoria, UBC) for helpful comments, questions, and critiques which forced me to clarify my thinking.

and to provide prescription medicines at their cost of production. The key to unblocking the impasse of high drug prices is to reward drug innovators based on the therapeutic value their products create through a national government-funded Pharmaceutical Innovation Fund. Depending on the size of the fund, incentives for pharmaceutical innovation could be made stronger or weaker than at present, but total annual rewards on the scale of $120bn a year globally would provide more and better directed incentives for effective pharmaceutical innovation than exists under the current system. The incremental cost to governments of such a scheme would be relatively small – if anything – since they would save so much on pharmaceutical purchases. And because therapeutic benefits of drugs can be reasonably identified using standard techniques, it is possible to make rewards proportional to therapeutic benefits in a predictable, meaningful way. This is exactly the outcome that the patent monopoly system is designed to obtain, but which it fails to achieve in the pharmaceutical market. In this paper, I describe how to implement such a system.

The proposed approach is intended to be complementary to the patent system. It maintains the institutions of patent system but replaces the existing patent reward (the right to profits obtained through exclusive use of the innovation) with a new type of patent reward (a payment based on the incremental therapeutic benefit of the product). In the existing implementation of patents, government involvement in the market is through preventing other firms from using the patented innovation, but there are no direct government payments for innovation. Governments also intervene in pharmaceutical markets in most countries through extensive regulation, price controls and purchases. In the proposed system, government would not be involved in the market at all, but would retrospectively determine the therapeutic benefit of an innovation in order to make a payment to the patentee. So it should not be assumed that the proposed system somehow involves "more government" than the existing system, which depends on very substantial intrusions into competitive markets. Indeed, it is comparable in some respects with the commonly observed system in which the government provides drug insurance and controls prices.

This proposal applies only to pharmaceuticals whose primary purpose is to improve health outcomes, since this is the proposed basis for determining rewards. There are a number of widely used techniques for measuring health outcomes such as Quality Adjusted Life Years, or QALYs. These measures can be used to roughly aggregate health effects of medicines across individuals with different levels of health. While imperfect, the use of QALYs enables a comparison to be made between the therapeutic benefits of different drugs in a standardized way and thus to find a meaningful measure of the social value of an innovation. The implementation of the QALY technique in deciding which pharmaceuticals are covered by government insurance in a number of jurisdictions around the world has been highly successful, and it offers strong encouragement for a broader application of QALYs to determining how to reward pharmaceutical innovations.[2] While there are problems with QALYs (as discussed in Section 5.4 below), they are also a reasonable measuring stick for health outcomes.

[2] Indeed, there is a sense that in countries such as Canada, Australia, NZ, the UK, and some others, where cost-utility evaluation of pharmaceuticals is common, that rewards already are in part determined on the basis of QALY analysis.

There are two reasons for thinking that innovation in pharmaceutical markets should be treated differently from innovation in other areas. First, patents are exceptionally important in pharmaceuticals, more so than in almost all other industries. Second, pharmaceutical markets are extraordinary because the person choosing the medicine (the physician) is not the consumer, and often the consumer does not pay, at least directly. Thus similar but not identical medicines do not typically create strong price competition. So the usual incentives to control costs appear to be ineffective in pharmaceutical markets and there is a mismatch between the rewards to the innovator and the therapeutic benefit of the product.[3] The current system makes the incentives for innovation dependent on this seriously dysfunctional market, whereas the proposed system rewards innovation based on health outcomes.

There have been a number of other proposals for change to patent systems. The two principal directions for reform are funding research through direct grants from a government agency such as the NIH and replacing patents with government-funded prizes or rewards (Wright, 1983; Baker, 2004). Evidently, this proposal falls into the latter category. Scotchmer (2005, chapter 2) offers a discussion of the issues that arise in systems of prizes, and a review of their interesting history.[4] Gallini and Scotchmer (2001) argue that a system of prizes is the best possible mechanism for eliciting innovation "if the size of the prize could be linked to the social value" of the innovation, exactly what is proposed here.[5]

The main problem with prize and reward systems is in determining how large the prize should be: historically, prizes and rewards have typically been a small fraction of the social value of innovations (DiMasi and Grabowski, 2004). Proposals for alternative ways of setting up prizes have therefore focused on enabling adequate (but not excessive payments) to be made to innovators, in exchange for placing their patents in the public domain. Kremer (1998) suggests a "patent buyout mechanism", with a prize amount determined by the price at which firms would be willing to purchase the patent. Shavell and van Ypersele (2001) propose a system of optional patent rewards, in which government could offer a reward greater than the patentee's monopoly profits, but smaller than the social value of the innovation. Such a system would increase innovation and – if the rewards were not excessive – welfare. Guell and Fischbaum (1995) propose that governments pay a reward based on the profits obtained by a product in a test market.

Abramovicz (2003) offers a comprehensive discussion of these and other proposals, and argues that, whatever mechanism is used, retrospectively assessed rewards could be helpful, and that the problem of under-rewarding of innovations could be avoided by requiring the rewarding agency to disburse all its funds while at the same time allowing firms the option of choosing between a reward and a patent monopoly. The key contribution made in my proposal is identifying an efficient method of determining the payment to be made to innovators, based on the therapeutic contribution of their

[3] The limited effectiveness of competition in pharmaceutical markets is of course one of the reasons that so many countries impose price controls only on pharmaceuticals.
[4] See also Kremer and Glennerster (2004, chapter 6).
[5] Will Masters (2004) proposes a more modest use of prizes as a supplement for patents in agricultural innovation. He suggests that prizes should be awarded with the amount to be equal to a fixed fraction of economic value of the innovation over a pre-determined time period.

innovation. Unlike the other proposals, mine offers both a way of alleviating inefficiencies caused by high drug prices and a method of directing pharmaceutical research towards the most socially valuable innovations. I agree that a fixed sum of rewards should be determined in advance (to avoid the problem of inadequate rewards), but defer the question of whether the reward program should be optional for firms.

Kremer and Glennerster (2004) and the Center for Global Development (2004) propose a system of purchase commitments for vaccines. This system resembles prizes in some respects, but requires the authority to be able to specify the nature of the vaccine and eligibility requirements in advance. Kremer and Glennerster (pp. 64-65) argue that "pull" programs, of which my proposal is an example, "offer the opportunity to harness the … energy and creativity of the private sector. … It is an open, transparent approach that is difficult for special interest to capture. Private sector R&D would be attracted to worthwhile products though a market-oriented approach…" However, they argue that the pull programs they describe have a number of limitations: "In particular, they must specify the desired research outputs beforehand, and coming up with the right specification and eligibility requirements may be difficult." An important characteristic of my proposal is that it requires no such anticipatory specification; instead, it offers a rule for how a fixed pie is to be divided, based on the characteristic of medicines which is chiefly valued – their effect on health outcomes.

In the following sections, I begin by describing the special problems inherent in the interaction between the pharmaceutical market and the patent monopoly system. I then present the details of the proposal, and finally address both how it could create value and what obstacles there could be to its implementation.

2 The Patent Monopoly System and Pharmaceuticals

The patent monopoly system functions particularly poorly for pharmaceuticals. As I describe in this section, it leads to misdirected innovation and marketing, to inefficiently high prices, to high volumes of counterfeit drugs, to parallel imports, and, indirectly, to price controls.

2.1 Misdirected Innovation

It is well known that monopoly exploitation of innovations under the patent system can reduce the benefits or "surplus" available to society from an innovation. This inefficiency is tolerated because the monopoly profits create an incentive to innovate, and in the absence of innovation, even less social surplus is created. Underlying this trade-off between high prices and innovation is the understanding that willingness to pay a high price for a good indicates high value. The greater the value to consumers, the higher the price the innovator can charge, and the greater the profits. This means, in turn, that the incentive for innovators is to undertake research that is valuable to society, since such innovations will earn high rewards. If rewards are not proportional to the social value, then the patent system cannot work well: it will lead firms to invest in innovations which have little social value, while ignoring avenues of investigation which could be of immense social value.

Unfortunately, pharmaceutical markets are among the least well functioning of all markets, undermining the connection between value and reward. Doctors prescribe medications based on their beliefs as to the best medicine, somewhat influenced,

presumably, by the extensive detailing and advertising focused on them. Since doctors do not pay for the medicines they prescribe, price is not an important component of their decision-making process. Consumers are typically ignorant of possible choices, and of the differences between various therapies and medicines and how these would relate to their own physiology, and may be paying only a fraction of the price of any medicine, or may pay nothing at all. The other part will be paid for by an insurer – possibly government or a private company – which has limited influence over the medicine prescribed.[6] In these circumstances, price is a relatively unimportant strategic variable for competition between drugs – detailing of doctors may be more important. In addition, prices in many countries are regulated by government. The result is that prices may be either too high or too low compared to the ideal market (one in which consumers are informed about the choices they make and then bear the full cost of those choices).

Since prices in pharmaceutical markets do not necessarily reflect value to consumers, profits are not likely to be proportional to the social value of an innovation. There are four types of problems which arise here, which I will discuss in turn. First, the pricing of pioneer drugs may bear no particular relationship to value. Second, "me-too" drugs may be able to generate large profits even though they offer little or no therapeutic advantage over prior therapies. Third, firms may find it very profitable to develop minor modifications to their own existing drugs, as a sort of evergreening strategy. Fourth, profits from developing and showing new uses for non-patented compounds will be small and may not support investing in clinical trials to demonstrate efficacy.

Pioneer drug pricing

When a pioneer drug enters a market, how is it to be priced? (A pioneer drug is a drug which offers a substantial improvement in therapeutic effectiveness compared to previous therapies.) This will depend largely on the willingness of insurers to provide coverage for the drug, but it can obviously be very difficult to deny coverage when a given therapy is much better than the alternatives. For example, the drug Fabrazyme is superior to other therapies for Fabry's disease, and the manufacturer Genzyme is as a result setting a yearly treatment price of approximately $275,000 in Canada, with the expectation that provincial drug insurance plans will still be willing to pay for it.[7] While for the small number of Fabry's disease patients coverage seems financially manageable, this does raise the question of whether the market is able to determine reasonable prices for medicines.

Where markets are distorted by price controls, the same question applies: are price controls leading to reasonable prices? Most OECD countries have some price control mechanisms in place which evidently distort pricing from the market, and it is not clear that the direction of the distortion is always correct. Without reasonable prices, the reward to innovation is not necessarily going to be proportional to its social value.

[6] Agency problems in drug markets have been well-understood for a long time: Senator Kefauver noted in his 1959 hearings into drug pricing that "The drug industry is unusual in that he who buys does not order, and he who orders does not buy." (Cited in Maeder 2003)

[7] CBC, "Province ponders costly Fabry drug coverage." Available at http://novascotia.cbc.ca/regional/servlet/View?filename=ns_fabrydrugs20040213 accessed on November 11 2004.

Celebrex presents another example of this sort of problem. This pioneering drug used a novel approach to help suppress pain. Despite early hopes that it would reduce the incidence of gastric bleeding, it has never been shown to be more effective at relieving pain or to have less serious side effects than other low-cost drugs. Despite this, it has been successful in charging a price about 10 times as high as comparable drugs. In other markets, one might expect that if two products had similar characteristics, and yet one cost 10 times as much as the other, that the more expensive product would have low sales. Pharmaceuticals markets, however, don't work like this, and Celebrex has generated billions of dollars in annual sales revenue. Pfizer has devoted substantial resources to marketing this product to doctors and consumers, and it has consistently been one of the most heavily advertised drugs. The lesson one must draw from this example is that, under the current system, it is not necessary for a drug to be better in any measurable sense for it to generate billions of dollars in profits.

Me-too drugs

Many commentators have been very critical of what appears to be an increasing number of "me-too" drugs (sometimes also called "follow-on" drugs). Me-too drugs are products which largely duplicate the action of existing drugs. For example, there are now many "statins" to help fight cholesterol, and, as some commentators have observed, it is not evident that there is much social gain from so much variety.[8] Me-too drugs can be valuable in providing therapeutic choice, and perhaps also gains from competition; but they also may harm the returns available to the break-through drug in a class by capturing market share (diMasi and Paquette, 2004; Calfee, 2000; Lee, 2004; Hollis, 2004). It is arguable that firms have devoted an excessive share of innovative research into developing me-too drugs, which have relatively little incremental therapeutic value, but which harm the returns available to the first drug in the class.

It is not clear what proportion of research spending is devoted to these so-called "me-too" products, as the industry does not release data on spending by product. It is possible to obtain some insight into this question by examining data on clinical testing, which consumes over 50% of drug R&D spending (DiMasi, Hansen, and Grabowski, 2003). Public data on the number of subjects in clinical tests suggests that only 20% of the R&D budget allocated to clinical testing is used for drugs which the FDA categorizes as offering a "significant improvement" compared to marketed products – the other 80% is used for products which do not offer a significant improvement (Love, 2003). Estimates of R&D spending in pharmaceuticals consistently show that a large fraction of expenditures are targeted at products offering little or no therapeutic improvement over existing drugs.[9]

It is hard to understand the standard industry defence of me-too drugs, which consists of arguing that they are good *because* they lead to price reductions and competition before patent expiry (Kaitin 2004). If price reductions are desirable in themselves before patent expiry, why are patents so desirable?

[8] Angell (2004, p. 90) argues that many me-too drugs are never tested at equivalent doses to show that there are significant differences in outcomes for some patients, and claims that "the idea that patients respond differently to me-too drugs is merely an untested – and self-serving – hypothesis."

[9] Love (2003), Lexchin (2003), and National Institute for Health Care Management Research and Educational Foundation (2002).

Line Extensions on Existing Drugs

When drug companies are facing patent expiration and generic competition, a standard approach is to develop "line extensions" to existing drugs. Typically, line extensions are some sort of minor enhancement to the drug which is adequate to enable the company to switch many of its buyers from the old version to the new version before generic competition for the old version arrives. A good example of this strategy is Nexium, which though therapeutically extremely similar to generically available versions of omeprazole, is able to command a significant premium in the marketplace, and makes billions in sales revenues.[10] Clarinex, a slight variation on Claritin, has been successful in extending its franchise. Avorn (2004, p. 206) notes that "the clinical benefits of [line extensions on existing drugs] may be trivial, but the cost of that activity is not, since it must include all the expensive toxicology studies, clinical trials, and regulatory compliance requirements that a real innovation would entail."

Low profits from new uses of existing compounds

While drug companies actively seek out new uses for high-priced patented drugs, there are no incentives to find and test new uses for existing non-patented compounds. The reason is that if an innovator discovers a new use for an old drug, such as aspirin, the innovator would likely find it very difficult to make any profits from selling the drug. Even if the innovator could obtain a patent for the use of aspirin to treat some condition, competition in the product market would make it impossible to make profits from this patent. Given that clinical testing costs can run into the tens or hundreds of millions of dollars, the inability to make profits from existing non-patented compounds implies that they will not be tested. A good example of how this problem can operate is given by the story of Dr D. Faustman, whose approach to curing diabetes involves "an inexpensive, readily available drug."[11] No pharmaceutical company has been willing to invest in clinical tests, in part because it would likely be impossible to earn substantial returns even if Dr Faustman's approach turns out to be correct.

2.2 "Deadweight losses"

The patent system as now implemented also causes substantial welfare losses because consumers who would buy the product if it were priced at somewhere nearer production cost do not buy it at the monopoly price.[12] The welfare loss caused by this is called by economists the "deadweight loss" (DWL) of monopoly pricing, since there is a pure loss

[10] Nexium had US sales of $3.1bn in 2003, supported by direct-to-consumer advertising of $260m. ("The media business: selling prescription drugs to the consumer." New York Times, October 12, 2004, p. C1.) On the therapeutic value of Nexium, see Therapeutics Letter, June-September 2002, at http://www.ti.ubc.ca/PDF/45.pdf, last accessed June 13, 2004. The preference for many consumers of high priced branded products over essentially identical (but much lower priced) generics also provides interesting evidence for the weak role of price competition in pharmaceuticals. Another interesting case in which small (or even negative) therapeutic benefit has led to huge profits is the case of the two pain-relievers Celebrex and Vioxx (Juni, Rutjes and Dieppe, 2002).

[11] Gina Kolata, "Diabetes Researcher Forges Her Own Path to a Cure" *New York Times*, Section F, November 9, 2004.

[12] Avorn (2004, p. 262) discusses how deadweight losses can occur even when there is full insurance. Insurers may be unwilling to cover certain medicines, such as osteoporosis drugs, whose benefits mainly appear only after some years.

to society when consumers do not obtain a product which they value more than the cost of producing it. Guell and Fischbaum (1995), using highly aggregated data, claim that the scale of deadweight loss in the US drug market is on the order of $3bn- $30bn annually; in a more detailed paper (1997) the same authors estimate deadweight losses of $5bn on $8bn of sales, which indicates very large DWL for the market overall.[13] Baker and Chatani (2002) construct a very rough estimate for DWL of $5bn - $20bn annually for the US. Globally, the DWL is certain to be many times this figure, because in many markets, drug insurance is unavailable and so consumers are more price-sensitive.

Hollis and Flynn (2003) show that the incentives to innovate generated by monopoly pricing in developing countries may be very small in comparison to the deadweight losses created by high prices. The 2003 WTO Doha agreement to allow compulsorily licensed drugs to be supplied to developing countries is testament to the importance of finding a solution to the welfare losses (including death and suffering) caused by high pharmaceutical prices. The problem of "access" to drugs worldwide is also creating a crisis of confidence in the pharmaceutical system worldwide, particularly as so many people in developing countries have been unable to afford drugs for HIV/AIDS, aggravating a humanitarian disaster.

2.3 Counterfeit Drugs

The high prices of patented drugs compared to production costs, and the difficulty of verifying the legitimacy of products, have led to a flood of counterfeit medicines.[14] Counterfeits comprise a substantial share of the global market for pharmaceuticals.[15] Many counterfeit products are ineffective, do not contain the claimed amount of the active ingredient (if any), or are produced under unsanitary conditions, and may therefore have adverse health effects on consumers. Counterfeits also harm the innovating drug company by stealing their sales and, if the counterfeit product is ineffective, damaging their reputation. Counterfeits can thus also reduce the incentives to innovate.

2.4 Price Controls

Because of agency problems in drug markets, as well as the substantial deadweight losses caused by high prices discussed above, most developed countries with extensive government health insurance programs have implemented price controls. These price controls require extensive government interference in drug markets and are likely to be cause a variety of market inefficiencies.[16]

---

[13] Douglas and Guell (2004) use US and Canadian data to argue that the DWL in the US market for a large number of drugs is at least 25% of sales.

[14] A recent statement of the US Assistant Attorney General in a vaccine price-gouging case claimed that an "exorbitant market price … may increase the incentive for counterfeiters to manufacture fake, ineffective, and potentially unsafe" drugs. (Statement of Interest of the United States, in Office of the Florida Attorney General v. ASAP Meds, Inc., Broward County Circuit Court, October 22, 2004.)

[15] Lybecker (2003) claims that counterfeits may constitute up to 10% of the global market for pharmaceuticals. See Outterson (2004) for a discussion of counterfeiting in pharmaceuticals. The counterfeit drug problem may be solved in developed countries within the next few years through the use of RFID tags on individual bottles of pharmaceuticals (Gardiner Harris, "Tiny Antennas to Keep Tabs on U.S. Drugs" *New York Times*, November 15, 2004).

[16] A problem related to the difficulty of setting price controls is determining how to allocate very expensive drugs (Avorn, 2004, p. 261). When there are limits to the resources available to a government-funded health insurance program, doctors need to be aware that the simple act of writing a prescription may lead to

Even in the United States, where the government has emphatically rejected the use of price controls, special price mechanisms regulate the prices at which pharmaceuticals are bought for some government departments (such as Veterans Affairs). The frequent legislative attempts in recent years to allow imports of drugs from other countries with some form of price controls is of course another mechanism for introducing price controls; and comparisons between US and foreign prices are a constant reminder to Americans that other countries seem to benefit from price controls. This suggests that even in the US, there is a possibility that price controls may eventually be introduced in various guises.[17]

2.5 Excessive Marketing

The problems in pharmaceutical markets that lead firms to undertake huge investments in order to develop products with relatively little therapeutic benefit can also lead to excessive marketing of the same drugs.[18] A product which offers little therapeutic benefit compared to other available products, but is sold at a high price, may nevertheless be marketed aggressively. Evidently, such marketing may be profitable for the firm, but it does little to generate real benefits for society to the extent that it reflects only competition for market share. Such competition for market share may even hurt real innovation, since the pioneer drug in a market must also engage in competitive marketing.[19] Looking forward, the pioneer firm knows that it will make less profits than if it were less likely to face such competition, and so the competition (which, recall, offers little additional therapeutic benefit) harms the incentives to innovate in the first place.

To put the amount of marketing into context, the industry employs approximately 88,000 sales representatives to visit doctors in their offices, or about one for every five or six practicing physicians in the US. Such an investment in marketing would not be made if the representatives had no effect on sales.

---

hundreds of thousands of dollars of costs to the program, which in turn may lead to inadequate resources to care for other patients. But individual doctors, while they are in the position of gatekeepers of prescription medicines, are not in a good position to make resource allocation decisions on this scale, because they cannot know either the constraints or the opportunity costs in other parts of the system.

[17] For example, Pfizer's recent reduction of prices for low-income and uninsured consumers was widely seen as a strategic move to counter "legislative momentum behind price controls." ("Pfizer to discount drugs for the Poor," July 8 2004, *Financial Times*, p.1) At the same time, large private sector buyers have recently been active in establishing "buyer groups" in order to create leverage for price discounts ("Big Employers Join Forces in Effort to Negotiate Lower Drug Prices" by Milt Freudenheim, *New York Times*, June 12 2004). There is also the interesting claim of Secretary of Health and Human Services that firms should be prohibited from "charging unconscionable prices not reasonably related to the fair market value of the pharmaceuticals sold." (Statement of Interest of the United States, in Office of the Florida Attorney General v. ASAP Meds, Inc., Broward County Circuit Court, October 22, 2004.)

[18] Marcia Angell (2000) argues (plausibly, but without additional support) that "The fact is that marketing is meant to sell drugs, and the less important the drug, the more marketing it takes to sell it. Important new drugs do not need much promotion. Me-too drugs do."

[19] Note that competitive marketing is different from marketing when the firm is in a monopoly situation: monopoly marketing provides information to encourage prescribing of the drug and is presumably therefore useful. To the extent that competitive advertising is greater than monopoly advertising, it is likely that it is socially excessive. Note also that competition through marketing does not confer the same benefits on consumers as competition through price reductions.

2.6 Dangerous "Me-too" Drugs

Drugs sometimes have unforeseen, undesirable side-effects. When new medicines are introduced, it is not always possible to know the long-term impacts. This is, for example, the case of the pain-relief medicine Vioxx which was recently withdrawn from the market after new evidence showed that it appeared to increase the incidence of heart attacks. If a new drug offers substantial benefits compared to other existing therapies for a given condition, the risk that unknown adverse side-effects may occur in the future is at least balanced by those benefits. However, to the extent that many "me-too" type drugs do not offer any such substantial benefits, but only the risks, the current system in which me-too drugs are richly rewarded is an invitation to introduce new, risky medicines.

An outstanding example of such an effect is the introduction of calcium channel blockers (CCBs) as a treatment for high blood pressure. CCBs were very expensive, costing up to $900 per year for treatment, and were, as a result, heavily marketed. The heavy marketing led to widespread prescribing, even though, as Avorn (2004, pp. 298-9) points out, "essentially no large-scale clinical trial had been published proving that the CCBs could actually prevent the strokes, cardiovascular disease, and kidney damage that were the main reasons for treating high blood pressure in the first place." In the ALLHAT double-blind trial of anti-hypertensive medicines, it was eventually found that inexpensive diuretics of a type that had been available on the market for many years were more effective as a first-line therapy for most patients with uncomplicated hypertension. So those patients who were buying CCBs were not only paying more, they were using a less effective medicine which had been less extensively tested. Doctors were prescribing CCBs because the extensive marketing and educational programs focused on them are effective, not because there was evidence that CCBs were more effective than existing therapies. In this example, we see a combination of misdirected innovation, heavy marketing the purpose of which was to switch patients from one therapy to another, and misdirected prescribing.[20]

2.7 Summary

As shown above, the patent monopoly system does not serve the pharmaceuticals market very well – it leads to misdirected innovation, to substantial deadweight losses, to counterfeit drugs, to price controls, and arguably to excessive marketing and unnecessary risks to patients. These features are not observed to the same extent in other markets.[21] This suggests that there are two crucial requirements for an effective system of funding innovation in pharmaceuticals. First, the rewards for innovation in pharmaceuticals

[20] Avorn (2004, p. 175) offers another example of the same sort for the product Xigris. This product was found to be slightly more effective for treating septic shock than placebo, although it slightly increased the risk of hemorrhage. The FDA approved use of the drug, after weighing the medical benefits and costs. Later, it was discovered that Xigris was only more effective than placebo for the sickest patients; while for less sick patients, its only medical impact was to increase the risk of (potentially devastating) bleeding. The manufacturer, however, priced Xigris at thousands of dollars per treatment, meaning that it had strong incentives to market it for the widest possible use.

[21] For example, in automobile markets, consumers are relatively competent to assess product quality and to make informed decisions about purchasing based on prices, quality, and their own budgets. Automobile makers therefore have incentives to develop differentiated products which respond to consumers' demands. Deadweight losses are relatively small in automobile markets because prices are close to the average cost of production, counterfeits are relatively rare, and price controls are not used.

should be proportional to the social value of the innovation. And second, prices should be near average production cost, in order to minimize deadweight losses and counterfeit drugs, and to eliminate the need for price controls. The following section details a proposal for a system which meets these requirements.

3 The Proposal

This section describes a method for rewarding patented pharmaceuticals with payments or rewards paid out of a government-financed Pharmaceutical Innovation Fund (PIF). When a drug is approved for use in a country, it would be registered by a firm, normally by the owner of related patents required in the production of the drug.[22] The PIF would make payments to registrants, and in exchange for such payments, registrants would be compelled to grant zero-priced licenses for all listed patents when used to make and sell the drug. The payments would be annual during the period in which the registrant's drugs were patented. Rewards might also be paid for patented cost-reducing process innovations, and for court verdicts of invalidity or non-infringement which allowed for generic production without a compulsory license, as discussed in the appendix (S. 8). The purpose of this section is to outline how the fund should determine the reward for a given innovation.

Payments from the PIF would be made based on the proportion of points attributable to a drug. Each patented drug would be given points reflecting the gain in average therapeutic value less costs of treatment over that of the next best pre-existing treatment, for *all* units of the drug sold by the registrant and by other manufacturers in a given year. Therapeutic value is determined by multiplying the incremental QALYs generated by the drug by the "dollar value" of a QALY.[23] (In determining the next best pre-existing treatment, the PIF should exclude patented medicines registered by the same firm and medicines relying on the same patented innovations as the medicine under consideration.)

In other words, the PIF agency will determine the net benefit of a drug, and then compare it to the net benefit of the next most effective pre-existing therapy, and award points based on the improvement. These points would be awarded to the registrant for each year in which the registrant's patents would, in the absence of compulsory licensing, be sufficient to prevent other firms from producing bio-equivalent products. Evaluation would be undertaken annually or as needed, based on the available information about a drug.[24] See the appendix (S. 8) for more details on quantifying this amount. Each registrant would obtain a payment equal to the total reward fund multiplied by its share of the total points allocated. The total amount available to be paid should be fixed, with the share of the payment to each registrant being determined by its share of points. (I discuss an alternative mechanism for determining the payments, where each QALY is rewarded by a fixed dollar payment, in S. 8.1.)

The registrant would obtain points for every sale of its drug, no matter who produced or sold the product, so that the reward is really for the innovation, clinical

[22] It is possible that a registrant might not own all the required patents, in which case registration would require the registrant to obtain a license to the patents from the patentee.
[23] Note, however, that it is not essential to be very precise about such a value.
[24] Annual analysis would be useful mainly in cases where the therapeutic benefit of a product is not fully understood when it is introduced.

testing, and marketing of the drug. In principal, the innovator need not produce or sell the drug at all, though it would have an incentive to market the drug so as to increase the volume of sales on which it could earn points. In many cases, drugs are given for a variety of different conditions, and so the therapeutic value, as well as the next best therapies, would be different for different conditions. This implies that it would be useful to obtain evidence from prescribing doctors on what conditions drugs were prescribed for, through random sampling of doctors.[25]

In the next two sections, I describe the possible gains from this proposed system, and some of the substantial, obvious problems that would arise in its implementation.

4 Benefits of Implementation of the Proposal

The potential benefits of the proposal are immense, including making drugs more widely accessible, eliminating inefficient pricing, improving the direction of research spending, and making marketing incentives more efficient.

4.1 Better direction of research expenditures

The proposal would make the incentives to innovate proportional in a meaningful way to social value, since the award given to the drug registrant would be commensurate with the net benefit created by the drug. Firms that developed products with high incremental therapeutic value would be highly rewarded, and firms that developed products which offered little incremental therapeutic gain over existing treatments would obtain relatively small rewards. This would increase the incentives to find new products with large incremental therapeutic value, and decrease the incentives to find new products which offered little extra benefit. (And with fewer me-too products, and less incentive to advertise them, as discussed in section 2.5, profits of pioneer innovators would be even higher.) At the same time, it could become profitable to demonstrate the therapeutic value of old, unpatented compounds for new uses, if rewards were paid to patentees who had shown the therapeutic value of the patented use of the compound.

One feature of the proposed reward system is that because only the first drug in a class is likely to make really large profits, the incentive to "race" is much higher. Often me-too drugs are in development over the same period, but only the one that gets to market first is the pioneer. The proposal would somewhat change the incentives in this situation, compared to current framework. Currently, being second is certainly a disadvantage, but the later-arriving firm may still make considerable profits if its product is equal or better and its marketing is effective. The proposal would restrict the potential profits of the second entrant, even if its product was slightly better. This increased incentive to race has both good and bad properties – it may lead to wasteful expense to win the race, but it also may lead to quicker arrival of new treatments. Firms would also likely want to avoid getting into racing situations.[26]

---

[25] This would be particularly important for some drugs which have extensive off-label uses (uses for which the FDA has not approved the product). There are claims that up to half of all prescriptions are written for off-label uses. "How Drug Directory Helps Raise Tab for Medicaid and Insurers", *Wall Street Journal* Oct. 23, 2003. IMS Health already conducts in the US a survey of this sort entitled the "National Disease and Therapeutic Index."

[26] One possible response to this might be to push back the date of "pre-existing therapies" when calculating the incremental benefits of a new drug. For example, one might a reward new drug for its incremental

While it is difficult to estimate the possible gain in terms of innovation, it would likely be substantial, since the incentives for socially valuable innovation would be increased. (My rough guess is that it would improve the allocation of up to $10bn a year in R&D spending, which could have a substantial cumulative effect in the long term on development of new therapies.) Thus it is no defence of the existing implementation of the patent system that the proposal would "undermine incentives for innovation."

4.2 Lower Prices and Elimination of "Deadweight Loss" (DWL)

Prices of medicines under this proposal would fall to approximately the average cost of production. Based on experience with drugs facing generic competition today, this implies that patented drug prices would decrease by on average 50% to 80%. This would obviously be beneficial for consumers and insurers, with total savings in the US of on the order of $100bn annually. Globally, savings might be on the order of $200bn. Much of this saving would however be used up in paying for rewards.

Aside from the reduction in total expense to consumers, there would be a welfare gain from increased consumption of lower-priced medicines. The deadweight loss (DWL) from the current patent system is certainly immense in pharmaceutical markets. The efficiency gains from reducing drug prices to approximately the average cost of production could easily be over $100bn, and the gains in terms of saved lives would likely be very large.

4.3 Reduction in counterfeit products

The proposal would substantially lessen the incentive to produce counterfeit drugs, since prices would fall to close to average production costs. Of course, some counterfeiting might still take place for products with relatively high production costs, but with lower prices, the profits from counterfeiting would be lower.

4.4 Elimination of price control regimes

The proposed system would allow for the elimination of price control regimes in countries where they exist, since prices would be near average production cost, and no significant gains could be realized by trying to push prices lower. There are several reasons why the patent plus price controls approach is inferior. Price controls, first of all, imply at least as much government interference and lobbying as the mechanism I have proposed, without all the corresponding benefits. Price controls are typically not sufficiently sensitive to the net therapeutic contribution of a new product, thus distorting incentives to innovate. Price controls are usually determined only on the basis of clinical trials before the drug is approved, and do not benefit from demonstrations of effectiveness (or ineffectiveness) during the period of commercial sales. Price controlled drugs are not usually priced near production cost, but may nevertheless fail to provide a sufficient reward to innovation. There is a more extensive discussion of how this proposal relates to price controls in Section 6.7.

---

therapeutic contribution compared to the best therapy available as of one year before the approval of the new drug.

4.5 More efficient marketing

The proposed system of rewards would not prevent marketing by the drug registrant. Indeed, promotions which expanded demand could be profitable, since the registrant obtains points for additional sales, based on the average net benefit. However, the effect of this marketing would be wholly beneficial: marketing which increased sales such that the net benefit was negative would decrease the reward obtained. So firms would have an incentive to promote the drug to obtain the largest number of users with a positive net benefit. However, the amount of promotional activity would be reduced under this proposal because there would be fewer copycat drugs competing to attract a limited number of prescriptions.

Note that this is another important respect in which my proposal differs from those of Kremer (1998) and Shavell and van Ypersele (2001): under their proposals, government buy-out of patents would effectively eliminate any private incentive to undertake marketing and commercial development of drugs after their patents had been bought out. As Kieff (2001) discusses, commercial development of patented products often requires the spur of monopoly: in the sort of proposal suggested by Kremer and Shavell and van Ypersele, it seems unlikely that there would be any detailing of doctors or other non-patentable attempts to improve the commercial value of the drugs whose patents had been bought out.

4.6 Reduction in total costs

The current system is wasteful, as described in Section 2, since it leads to large expenditures in marketing and in research into copy-cat drugs and line extensions. The proposed system could therefore actually cost less in total, with substantial savings to consumers. Criticisms of the proposal based on the assumed inefficiency of the management of the PIF should counterpoise this inefficiency against the immense inefficiency of the current system.

5 Obstacles to Implementation

There are a number of obvious difficulties in implementing the proposed mechanism. First, substantial government resources would be required to finance the rewards. Second, there is a legitimate concern over how large the PIF would need to be to induce the efficient amount of innovation. Third, a large federal agency would be required to perform comparative analysis of the therapeutic effectiveness of medicines and their costs. This would be costly and fraught with the risks of bureaucratic inefficiency and collusion. And fourth, there is a concern that it is not possible to identify therapeutic benefits of medicines with enough precision to make judgements over how to allocate rewards from the PIF. I address these in turn.

5.1 The cost of financing the reward fund

The PIF would require substantial investment to finance the rewards. If the fund for the US were set to pay out $60bn annually, that would represent approximately 3% of the US federal government budget for 2005.[27] To the extent that the proposed system required increased expenditures by government, it would require additional taxes to pay for the

[27] An alternative calculation used below would base each national PIF on a fixed share (perhaps around 0.3%) of GDP: under this formulation, the US PIF would be approximately $40bn annually.

PIF. However, the government would also reap considerable savings from paying lower prices on the drugs it buys, and consumers could in principle pay higher taxes given lower personal drug spending and insurance costs.

The savings to governments from lower pharmaceutical prices would be substantial and could allow even a very large PIF to be approximately revenue neutral. Currently, US federal, state, and city government spending on pharmaceuticals is approximately $80bn[28], of which around $10bn is spent on drugs available generically. Under the proposed plan, assuming modest expansion of the quantities of drugs financed, and a 65% decrease in average price for branded products, government spending on pharmaceuticals would fall to approximately $35bn annually, for a savings of $45bn. Suppose that the US financed its own national PIF of $60bn (with other national governments funding their own PIFs for another $60bn, approximately in line with current global pharmaceutical revenues). Then US governments would require only a small increase in revenues under the proposed system. Consumers would benefit from substantial savings. In other countries, where the government share of pharmaceutical spending is higher, savings could likely be realized even with very substantial contributions to the PIF.[29]

5.2 The problem of setting the fund at the right amount

In order to make the proposed system credible, it is necessary that the incentives be large enough to stimulate at least as much R&D as occurs currently; and so I suggest here some rough figures to determine what amount would be necessary globally.[30] Evidently the size of the PIF would be related to the rate of innovation: I guess that global funds of about $120bn – or approximately 0.3% of global GDP – annually would likely be large enough to provide incentives for more spending on innovation than we currently observe. The fund would need to finance three major items: R&D, marketing, and profits.

The current scale of private-sector research spending *globally* is on the order of $50bn annually (Fleck, 2004), so we need to include at least that much for financing R&D. However, as noted above, the $50bn of R&D under the proposal described here would be better directed to generate real gains to health than under the current patent monopoly system. It is difficult to estimate how much total investment in R&D should be; but even if it does not generate the "optimal" amount, it is also true that the current system does not generate the optimal amount of R&D.[31] The uncertainty over the optimal

[28] This is a very raw guess – but Medicaid spending on retail pharmaceuticals is around $40bn, so including hospital spending plus city and state governments, $80bn seems in the ball park. There is likely to be a substantial increase in spending starting in 2006.

[29] For example, in Canada, the government share of drug expenditures is approximately 47% of US$14bn, so a reduction of 50% in brand prices would save the government around US$2.5bn, enough to pay for a PIF equal in size to 0.3% of GDP.

[30] I am using very crude guesses on current drug expenditures and costs at present and these are not intended to be more than illustrative.

[31] Economists sometimes assume that in order to induce the efficient amount of R&D spending, it is necessary for the reward to innovation to be equal to the entire social surplus created by the innovation. This is of course not true: all that is necessary to achieve efficiency is that the marginal reward should be equal to the marginal social surplus, implying that consumers obtain no surplus from the marginal dollar of R&D investment. Neither the proposal in this paper, nor the current implementation of the patent system, nor any other known mechanism, can make any pretension to being able to achieve efficiency in this sense. See Outterson (2004) for more on the question of the optimal amount of pharmaceutical R&D.

size of the PIF is comparable to uncertainty over the optimal period of patent protection in the current system.

Second, under the proposed system, marketing would continue to be important, as described in Section 4.5, since the innovator would earn more profits if the drug was used more. The incentive to market the drug is desirable because the informational content of marketing, whether through physician detailing, free samples, journal advertising, study sponsorship, or directly to consumers, can be valuable. Globally, pharmaceutical marketing expenditures are on the order of $30bn.[32] Under my proposal, marketing expenditures would likely fall substantially as "copycat" drugs would have little incentive to advertise, and, in response, market leaders would also advertise less. In order to leave some room for marketing expenditures by innovators, the fund should be increased by approximately another $20bn.[33]

Finally, there are substantial assets employed in the pharmaceutical industry on which a return is required. Currently, global innovator profits are on the order of $50bn annually. This implies that, in order to sustain the current level of expenditures on R&D, allowing for marketing and a healthy return on capital employed in the industry, the global sum of national annual rewards should be on the order of $120bn. Note that there is not any inherent notion here of paying firms for marketing or profits; but successful drug firms do promote their products and need profits. Those with highly valuable drugs would obtain payments large enough to pay for innovation, to market their products, and to reward investors, just as under the patent monopoly system.

One problem that arises is that the value of pharmaceutical innovation may vary over time (see, e.g. Calfee, 2000, chapter 4). However, if the average number of QALYs generated by pharmaceutical innovation appeared to be changing, that would provide a useful signal that the size of the PIF should also change.

5.3 Bureaucratic/Political Control of the PIF

Putting a large reward system in the hands of a bureaucracy is fraught with risks. Experience with regulated industries suggests that bureaucracies are liable to collude with regulated firms ("regulatory capture"); political interference leads to questionable decision-making; and government agencies may lack well-defined objectives and cost-saving incentives, leading to bureaucratic inefficiency. It is possible to mitigate some of these problems, but not, perhaps, to avoid them altogether.

In order to lessen the risks of "regulatory capture", the PIF should be of a fixed amount. Each firm could put forward its best case of how many points it should be awarded, and perhaps even present evidence to show why other firms should get less. The

[32] This is only a crude guess. I guess current global revenues at $400bn with expenses of $30bn on marketing, $50bn on R&D, and around $50bn in profits. There is a large component in the income statements of drug firms entitled "marketing and administration" which is much larger than the sum of marketing I have assumed. Angell (2004) suggests that a large proportion of this expenditure is used for "educational" activities for physicians, which may in fact be promotional in nature. I agree with Angell that it is unsuitable for drug companies to fund "education" for doctors, as it is hardly possible for such education to be unbiased. Other expenses which Angell (2004) questions include payments made to doctors for drug "surveillance studies" which have no legitimate scientific use.

[33] Note that since some marketing expenditures would continue to be profitable, firms will continue to invest in promotional activities. Therefore in order to ensure adequate R&D spending, it is necessary to build in some money to pay for marketing.

fixed total payout of the PIF would lead to a zero-sum game so that firms would compete to obtain points. In these circumstances, collusion seems more difficult to sustain, although direct bribes by individual firms to PIF employees could always be a risk. Brill-Edwards (1999) discusses some problems with regulatory capture in the context of pharmaco-economic evaluation.

Political interference with rewards might also be a concern. Government preferences for giving points to domestic firms would certainly be a problem. This suggests that the rationale for how points were to be awarded would have to be made public and fully documented. In addition, since the order of approval of new drugs could influence reward amounts, one could expect political interference on behalf of domestically developed therapies.

There would also need to be a substantial investment in analysis of health outcomes and health economics by a "Pharmaceutical Innovation Fund Agency" to enable a reasonable allocation of points. With hundreds of significant drugs under patent at any given time, substantial resources would be required for determining QALYs and costs for all these medicines. The ALLHAT study of a few anti-hypertensive medications reportedly cost some $125m (Nash and Clarke, 2003). Possibly such an agency would suffer from efficiency problems. However, there are several reasons for believing that such costs and inefficiencies are not an insuperably large problem. First, undertaking evaluations of drugs and treatments is socially valuable, since it enables better treatment.[34] At present, there is a case to be made that there is significant under-investment in "post-marketing" studies of drugs.[35] Second, the costs of drug evaluation after the drug is already approved and on the market would be relatively small compared to the huge potential gains from the proposed system. Third, the bureaucracy would be less likely to suffer from inefficiency given a well-defined mandate of measuring therapeutic benefits and costs. Fourth, such an agency would to some extent simply replace existing pharmaco-economic evaluation and price-control agencies in countries where they already exist, and indeed, one option would be to conduct head-to-head trials along with placebo trials during phase III testing of drugs.[36]

Aside from the expense of creating a PIF agency, such a process would inevitably engender significant lobbying efforts from innovators seeking to obtain the largest possible share of the pie, and even possibly outright corruption. While this is undoubtedly true, it is also true that in most countries, there is already an active regime of price controls of pharmaceuticals, which must be subject to similar lobbying already. And even in the US, where price controls are not formally used, there is very substantial lobbying

[34] Companies rarely undertake comparative studies voluntarily, since it is "playing with fire." Bristol Myers Squibb recently financed a study which discovered that a rival's drug was more effective in certain conditions ("Head-To-Head Studies Have Their Risks," Theresa Agovino, *Washington Post*, July 9 2004). Angell (2004), Avorn (2004), Goozner (2004), and Reinhardt (2001) all propose a substantial increase in investment to undertake comparative studies of drugs.

[35] Indeed, the FDA sometimes mandates post-marketing studies of drugs; but a 2002 report found that only 882 post-marketing studies had been completed and filed with the FDA, out of the 2400 required during the period 1991 to 2000 (FDA, 2002).

[36] The burden on a PIF would be heavier than on most price-control type agencies, since it would require on-going (not one-time) assessments of therapeutic value in head-to-head tests. At the moment, most price control agencies only evaluate data submitted by companies, rather than commissioning their own studies. In principle, a PIF could continue to rely on such data, while requiring head-to-head studies of comparable drugs.

by the pharmaceutical industry. In addition, as discussed in Section 2.4 above, there is a serious possibility of some price controls being implemented in the US in the near future.

Government control of rewards would almost certainly be very problematic in developing countries, because the proposal depends on good data about total sales, uses, and prices. While a system which recognized the particular needs of least developed countries is discussed below, this does not deal with the problems of implementing such a proposal in lower-income (but not least developed) countries which do not have the government apparatus to collect and process the kind of data required here.

To the extent that there is a concern that this proposal would impede the workings of the free market, one should be aware that drug markets are already distorted by agency problems and government interference. This interference operates at all stages in the product lifecycle, including: early government investment into undertaking basic research (Goozner 2004); drug approval; government enforcement of exclusive rights to patent exploitation; special regulations concerning sale and pricing of drugs; special regulations concerning patent infringement; regulations concerning mandatory substitution; etc. The market for drugs is currently far from free.

5.4 QALYs and economic valuation of drugs

An important requirement for the proposed system to be effective is that it has to be possible to make reasonably good assessments of the value of a drug. There are two key components to this. First, one must be able to assess the impact of a drug on health outcomes. This can be problematic, since different individuals respond differently to identical treatments, and it is sometimes difficult to identify what effect is attributable to the treatment and what effect is due to some other feature of a patient's condition.[37] However, every drug approved by the FDA must show efficacy, and the demonstration of efficacy essentially requires the observer to measure the health effects attributable to the drug. Therefore, this aspect of determining pharmaceutical value is in fact already performed universally.[38]

The second part of the analysis is to transform these health outcomes into QALYs, or a similar measure such as DALYs (Disability-adjusted life years), HUIs (Health Utility Index), or even a willingness to pay index.[39] Essentially, this requires making judgements about the relative value of additional years of life against health levels and quality of life. Different individuals have widely varying willingness to trade-off various health outcomes, so attempting to standardize the weighting of health outcomes is not straightforward. Hedonic estimates have been extensively used to value disabilities and compromised health status in terms of QALYs, but this is not an exact science.

QALYs have been recommended as the standard measure of healthcare outcomes by a task force of experts organized by the U.S. Public Health Service (Gold et al, 1996).

---

[37] And again, note that the current patent monopoly system already suffers from this sort of problem. Many consumers who try a drug do not in fact benefit from it, but the patentee earns profits nonetheless. Other patients must benefit immensely, but pay the same as those who are, perhaps, harmed by the drug.

[38] In fact, much efficacy testing compares new drugs to placebos, which is not quite the same as showing efficacy compared to existing treatments. However, in principle the requirements for comparing against a placebo and against another treatment are the same.

[39] One of the key problems in the use of QALYs and DALYs is to avoid the inference that the life of a disabled person is worth less than the life of a person without disabilities.

Similarly, the OMB has recently been encouraging a greater use of cost-effectiveness analysis (using QALYs, DALYs, willingness-to-pay indices, etc.) in all regulatory decision-making by US government departments.[40] So the US government is already basing decisions – at least in part – on QALY-type analysis, an indication that it has found a fairly high level of acceptance both inside and outside government. There is very extensive experience with evaluating QALYs related to drug treatments, since a large number of governments and other insurers all over the world use such an approach to determine inclusion of drugs on formularies, but this does not mean that the approach has been perfected, by any means. Drug companies have also used QALY-type analysis themselves in order to demonstrate economic effectiveness of treatments (Davidoff, 2001).

Krupnick (2004) provides an up-to-date summary of issues related to QALYs and similar measurements. For an analysis of the theoretical validity of QALYs, see Doctor *et al.* (2004). A recent OECD study by Dickson, Hurst, and Jacobzone (2003) offers a guardedly positive analysis of the use of pharmaco-economic analysis, concluding that it is a "useful decision-making tool" but that there are difficulties relating to the quality of assessments, shortages of qualified staff, off-label use of drugs, and biased studies. Nevertheless, there is a strong argument to be made that the inaccuracies inevitable in valuing health outcomes would lead to much smaller distortions in determining appropriate rewards for, and providing appropriate incentives for, pharmaceutical innovation, than the current system.

The most troubling set of conditions in terms of translation into QALYs are those treated by so-called "lifestyle drugs" such as Viagra. The question of whether to reward products like Viagra through the PIF would have to reside with the PIF agency; firms seeking to develop drugs for conditions such as male pattern hair loss might seek an exemption from the PIF if they expected that consumer valuations would be high in dollars but low in QALYs. (Section 6.5 below discusses another difficult set of drugs, those with both therapeutic and lifestyle uses.) However, in any case even Viagra has been the subject of at least one pharmaco-economic study estimating its value in terms of QALYs (Smith and Roberts, 2000).

A variety of other types of pharmaceuticals, such as psychotherapeutic drugs, present another difficult class to value in terms of QALYs. However, it is important to recognize that the difficulties faced would be no worse than the problems the patent system currently faces in determining optimal pricing or investment into R&D for such drugs. Indeed, the kinds of uncertainties are exactly the same as those present in current insurance markets, which have struggled with questions of what drugs they should cover.

5.5 International Commitments

The TRIPS agreement negotiated under the WTO in the Uruguay Round requires countries to provide patent rights, including the right to exclude others from using the patented innovation. Fortunately, the proposal can be implemented without necessarily violating TRIPS. There are a number of possibilities. First, the option suggested below in Section 6.6 would not violate TRIPS. Second, countries could simply offer a choice

[40] See, for example, the speech by John Graham, Administrator of the Office of Information and Regulatory Affairs at the OMB on May 21 2002, available at http://www.whitehouse.gov/omb/inforeg/graham_speech052102..pdf, last accessed June 1, 2004.

between severe price controls or the PIF system to patentees. Since price controls do not in themselves violate international patent agreements, offering a choice between price controls and the proposed system of licensing plus rewards would not be a violation of TRIPS either.

5.6 Other Risks

There are also some other risks to be considered in the proposal. Special care would be needed to minimize the risk of collusion between doctors or other buyers and drug registrants. If consumers were bribed to buy extra, unneeded units, the drug company could obtain extra points. This is the same sort of problem already faced by insurance companies, which have been successful in controlling it.

Whatever the rate of rewarding is, a point should never be worth more than one dollar, since if a point was worth more than a dollar, drug registrants would have an incentive to set their price below the marginal cost of manufacturing, thus eliminating competitive manufacturers and leading to inefficiently low prices.[41]

Finally, an important consideration in the proposal is the risk of other unforeseen problems. New and unknown, unexpected problems would arise. We already have a good knowledge of the problems inherent in the current implementation of the patent system in pharmaceuticals.

6 Other Issues

In this section, I consider a number of other issues not discussed above: the treatment of sequential innovation; the use of the patent system; international issues; transition issues; and drugs with dual uses. This section is therefore intended for those readers who are interested in exploring the potential for practical application of the proposal.

6.1 Treatment of sequential innovation

An important feature of much current pharmaceutical innovation is small improvements in use and formulation of existing products. Therefore it is extremely important to provide appropriate incentives for such incremental improvements. At present, as discussed above, there are some very inappropriate incentives for development of small modifications to existing products since they may enable firms to effectively extend monopoly prices.

Suppose that a firm develops an improved version of its own product (e.g. once-a-day instead of twice-a-day doses, leading to improved patient compliance). If the old version of the product is no longer protected by patents, then this raises no particular problems. The firm could obtain some payment from the PIF based on the therapeutic improvement of once-a-day versus twice-a-day formulation.[42]

If the old version is still protected by patents, however, then one needs to be more careful. The net benefit of the new product is the small therapeutic benefit over the older

[41] Points could be worth more than one dollar if costs were defined to include the price of the medicine as offered by other firms only. Alternatively, drug registrants could be discouraged from manufacturing and selling.

[42] There is also some convenience value in taking a medicine once instead of twice a day. It is not clear how to value this sort of convenience beyond its value in improved compliance. Perhaps a small premium could be built in.

product. The older product might offer a large therapeutic benefit over pre-existing products and yet not generate any sales, since the newer improved version would be preferred. This would lead firms to have weak or even negative incentives to improve products currently under patent.[43] Fortunately, there is a simple solution to this problem: when calculating the points attributable to a medicine, the PIF must not include any patented medicine registered to the same firm in the set of alternative therapies.

If the sequential innovation is patented by a firm other than the registrant, then in general it will raise patent issues: that is to say, that the new improved version of the drug will infringe on patents held by the firm which registered the older drug. In these circumstances, the new company may not sell the new and improved version without obtaining a license from the patentee of the old drug. It is desirable to have improved versions of products, but if the two products are therapeutically similar, then the newer product will not obtain substantial points, unless the older one is excluded from the set of comparison therapies when calculating the net therapeutic benefit. Therefore, to encourage sequential innovations, the PIF should also not include medicines relying on the same patents in the comparison group for a given medicine.

6.2 Comments on the use of the Patent System

The proposed system employs patents as the method for determining whom the PIF rewards, and when. There are a number of reasons for using patents. First, using the patent system would allow for consistency between pharmaceuticals and other products in the administrative and judicial treatment of intellectual property. Second, there is extensive experience with patents and their litigation. Maintaining patents as the basis for rewards would allow courts to continue to use their knowledge about patent procedures and litigation. Third, this method allows for the smoothest possible transition, since it enables extension of current patent control into the new system: that is, firms that currently own or are developing technologies, based in part on their understanding of the patent system, would expect profits based on the patentability of the technologies. Fourth, the patent system would allow for effective licensing of patented innovations. For example, if the production of a given drug required the use of patents owned by two firms, the registering firm could license the other's technology using a standard license, with terms such as royalties, fixed payments, or even a share of the reward from the PIF. (Note that a firm which produces a registered drug, but is not the drug registrant, would not have to pay any license fees. License fees would only be paid by the registrant to the other firm holding a relevant patent.)

Since the proposed system uses patents as the basis for establishing property rights to a medicine (where the property right includes the right to be compensated by the PIF, and to exclude others from the use of the patented innovation in any use other than the production of the registered medicine), whatever legal and administrative problems usually attend the patent system would continue. In addition, the patent term would continue to be 20 years.

[43] To see why, suppose that the old version offers a large improvement over pre-existing therapies, while the new version offers a small incremental improvement over the old version. Doctors will prescribe the new version, leading to small sales for the old version. If the new version is awarded points based on the incremental improvement over the old version, the firm will obtain only small rewards even though it is responsible for both new and old versions.

6.3 International Issues

This model is ideal for enabling wide international access to drugs, while eliminating inefficient parallel imports between countries having different prices. Innovators could be resident anywhere; and with prices equal to the average costs of production, even developing countries would be well served. However, if not all countries adopted this model, then one could expect substantial parallel imports into the non-adopting countries. The asymmetries could lead to some problems of coordination between adopting and non-adopting countries with respect to pharmaceutical trade. But the model if adopted by many countries could be designed to allow for small contributions in developing countries, basically by assigning them a small dollar value for each QALY.

Two possibilities arise for the PIF: either it could be a full-fledged international organization, under the control of an agency such as WHO, or there could be national PIFs. A global PIF, however, seems unlikely to be attractive to many countries, which suggests that national implementation might be unavoidable. However, it would be necessary to ensure that countries did not try to shirk from carrying an appropriate burden of supporting research through their contributions to their own PIF. Hubbard and Love (2004) propose a mechanism for countries to participate in a scheme such as that envisaged here. Their proposal suggests that each country should either continue with the existing monopoly patent system or, as an alternative, agree to commit some fixed proportion of measured GDP to a pharmaceutical reward fund. The proposal outlined in this paper provides a mechanism for countries to determine how to allocate the reward fund. The mechanism is evidently beyond the administrative capabilities of many small, less developed countries, so some alternative approach would be required for such cases. (Such a mechanism is suggested in S. 6.9)

The proposal could also be implemented unilaterally by individual countries without any international agreement, although smaller countries might find it difficult to implement on their own.

6.4 Transition Issues

In general, the transition to the new system is anticipated to take the following form. The PIFA would be organized some years before the start date to begin the task of assembling therapeutic effectiveness information. This might take some years, since there is a large backlog of existing medications. Drug registrants would begin to make submissions on existing and new medications concerning effectiveness. Then as of the start date, the patents on all patent-protected medicines in the US would become compulsory licensed at zero cost. (Of course, only approved manufacturers could supply the market, given FDA safety regulations.) It would be as if all drugs suddenly lost patent protection. All producers from that date would be required to submit monthly information on sales to the FDA, and payments could be made from the PIF to drug registrants on a monthly basis. Thus, existing patented medicines could also be rewarded by the PIF; although some medicines would become less profitable and others more, depending on their relative net therapeutic effectiveness.

Some transition problems would arise. For example, existing licenses from patentees might become in effect worthless. Licensees and/or patentees might find that previously negotiated contracts were undermined. In such circumstances, if negotiation failed, arbitration might be required to ensure reasonable outcomes.

6.5 Drugs with Therapeutic and Lifestyle Purposes

Some medicines have dual purposes which span both medical and lifestyle purposes. For example, Seasonale, which suppresses menstruation, may be indicated for women with endometriosis, but it may also be used as a "lifestyle" drug for women who value its effects. While both types of uses are valuable, only the former can be reliably translated into QALYs. It is not obvious how one would deal with such situations. One option, where lifestyle uses were significant, would simply be to exempt the product from the proposed system. A second option would be to use monopoly pricing, where (1) patients who purchased the product based on a medical indication would qualify for a rebate on the product from the manufacturer, and (2) the manufacturer would receive rewards from the PIF agency for medically indicated sales. Note that this sort of problem is the same as is currently faced by insurance companies, which typically seek to provide insurance only for medically necessary – but not lifestyle – drugs.

6.6 An Option for Restricting the Proposal

One possibility in implementing this proposal would be to make inclusion in the PIF program optional for the patentee; but to tie inclusion into the PIF program to coverage under government insurance plans. Thus innovators would have a choice between exclusive exploitation of the innovation under the usual patent system, but with reduced sales since the product would not receive any coverage under government insurance plans; or submitting their product to the PIF system, losing their ability to exclude others from the use of the patented innovations, but earning a reward from the PIF and having their product covered under government insurance programs. (Private insurance plans might match the government coverage, or offer insurance for additional drugs as well, recognizing that for the most part, high therapeutic value drugs would be rewarded by the PIF and be low priced, while low therapeutic-value patented drugs would be expensive.)

This approach has some obvious benefits. First, it eliminates the problems of how to deal with products such as Viagra since the manufacturer would have to decide whether to seek awards for therapeutic value contributions or to seek high prices. Second, the rewards system would be clearly tied into the government's existing contribution to medical expenses. Thus, in areas where the government has no involvement, no government involvement would be needed. Third, it would not in any way affect national and international commitments regarding patent rights, since the decision of firms to drop their patent rights would be voluntary. Fourth, this approach would force governments to establish a large enough PIF to encourage firms to include their products in the PIF system, since if the PIF rewards got to be too small, firms with therapeutically valuable drugs would choose to forgo the rewards plus insurance coverage, providing a useful indication that the PIF rewards were inadequate.

The optional approach also suffers from some problems. First, firms choosing to opt out of the PIF could continue to invest in products with small therapeutic benefit as long as they could persuade doctors to prescribe them, leading to the same problems as discussed above in Section 2. Second, some drugs would likely not be included in government coverage, reducing the value (but also the costs) of the insurance. In general, drugs with the lowest therapeutic value would be the ones most likely not to be included in the PIF system.

6.7 Comparison with Price Control Systems

A striking perspective on the proposal is how similar it is in many respects to a system in which there is government insurance for pharmaceuticals, and price controls. Such a system is in place in most industrialized countries. In such systems, a government board typically determines prices largely on the basis of the therapeutic effectiveness of the medicine. The net result is that the revenues of the drug firm come from the government, and are equal to the price times the number of units sold, where the price is based on therapeutic effectiveness. Evidently, such a system is very similar to the proposal outlined in this paper; but it is also different in important ways.

First, price control systems still have high prices for drugs, compared to average production cost. This means that any buyers not covered by government insurance will face high prices, leading to some deadweight losses. Evidently, this problem may be small if most consumers are covered by government insurance.

Second, price controls tend to be arbitrary. In Canada, for example, prices are based on international reference pricing, with the Canadian price to be no higher than the price in a basket of seven reference countries. Prices may not increase (except for inflation) regardless of subsequent price changes elsewhere or new evidence of effectiveness. Although there is, in most price control schemes, some attention to therapeutic value, the way that it is introduced into pricing is not necessarily well conceived.

Third, in almost all such schemes, drugs with similar therapeutic effects are priced at very similar levels. This leads to inefficient research investments into copycat drugs, which are guaranteed to obtain the high price of the pioneer product, and to competitive marketing. At the same time, the inefficiently high investment into copycat drugs weakens the incentive to invest into pioneer drugs. A scheme in which rewards are based on the therapeutic contribution compared to pre-existing products will generate the greatest therapeutic progress.

Fourth, price control schemes, combined with government insurance and a fixed cap on the budget, tend to lead to exclusion of certain drugs with low benefit/price ratios. Since the price of the drug is typically not even close to the production cost of the drug, this exclusion of certain products is generally inefficient and creates deadweight loss.

Fifth, from the perspective of investors, a proposal with a rule for allocating a fixed annual reward should be attractive compared to an arbitrary system of price controls.

6.8 Medical Devices

In principle, there is no reason that innovative medical devices could not also be included in this proposal, although in practice it is questionable whether there would be sufficient competition in manufacturing to lead to large price reductions; and whether the PIF agency would have sufficient knowledge to make judgements about therapeutic value outside of the area of pharmaceutical products.

6.9 A Special Fund for Least Developed Countries

Least developed countries would typically not be expected to create their own PIFs, as the administrative burden would be large and there is a reasonable justification not to expect such countries to make large payments to innovators. However, since many diseases primarily affect people in very poor countries, this would lead to inadequate

incentives to innovate in drugs for such diseases, just as exists today. One way of resolving this problem would be to create a special internationally administered PIF for least developed countries which would give rewards on their behalf, using the system outlined above. Rewards would be allocated based on incremental therapeutic benefits of patented technologies, where the relevant patents were licensed at zero price. (Possibly the patents could be those filed in Europe or the US.) The only restriction on the size of potential rewards to an innovator would of course be the size of the total reward pool available. This approach has the benefit of not favoring any particular innovation (e.g., vaccines for HIV/AIDS): wherever large therapeutic gains were available from a drug, it would be rewarded based on the relative value of the gains, compared to other medicines.[44]

Notably, this special fund could be created independently from the adoption of the proposal in developed countries. Arguably, the need for such an approach is greatest in countries where drug insurance is rare, and so perhaps least developed countries should be the first ones to establish the type of system proposed in this paper.

It may be worthwhile to compare the proposal here to those proposals which have been made for prizes or advance purchase contracts for pre-specified solutions, such as malaria vaccines (e.g. Kremer and Glennerster, 2004). Those sorts of prizes, while perhaps desirable in themselves, are not very flexible, and hence cannot provide adequate incentives for innovation in a range of areas. The proposed special fund, however, if sufficiently large, would create large incentives to attack the entire range of health problems suffered in the least developed countries, with the greatest incentives for those drugs which would create the largest health benefits.

One option would be to designate special funds for diseases of particular interest in developing countries. For example, a malaria fund could be designed to reward only estimated gains in malaria treatment. This would have some advantages over an advance purchase contract (which would have to meet very specific technical criteria), because it would be flexible in rewarding any patented treatment, whether a vaccine or drug, without having to specify any criteria in advance.

6.10 Orphan Drugs

One of problems with the patent system is that it provides little incentive to develop so-called orphan drugs, or drugs for rare diseases. If the market is too small, firms cannot hope to recoup their costs for developing and testing drugs without extra incentives. As a result, in the United States special legislation was enacted to make developing such orphan drugs more profitable. In principle, there is no reason why exactly the same sorts of incentives could not apply to the proposal described here, including tax credits and special exclusivity rights. However, this proposal also allows for a relatively simple way of providing much more rational incentives. Special disease funds could be established which would provide additional rewards for drugs treating specific diseases.

One possible implementation of this proposal would be an optional reward scheme in which a fixed sum of money was available to any drug developer who was willing to

[44] If it were desirable to provide extra incentive particularly for those diseases which primarily affect developing countries, the award system could be calibrated (in advance) to provide extra incentives for such diseases. However, there doesn't seem to be any reason to favour a malaria vaccine over a treatment for leishmaniasis, for example, beyond their measurable effects on QALYs.

provide an open license on all the patents required to manufacture the drug. Such a reward could be paid based on the incremental therapeutic benefits of a drug, for all drugs treating diseases having a sufficiently low incidence in the population (exactly as with the Orphan Drug Act) and for which the patent holders had offered an open license.

Even charitable money could be added to the pot: donors who wished, for example, to encourage more research on a specific rare disease could designate donations which could only be awarded for drugs which resulted in greater QALYs for individuals suffering from that disease. At present, donors can in effect only give money towards push incentives (e.g. funding specific research programs), while under this proposal, they could donate towards increasing pull incentives.

7 Discussion

The proposal outlined in this paper offers an efficient method of rewarding pharmaceutical innovation which delivers two major benefits. First, it aligns private research incentives with social objectives by rewarding innovations based on their evaluated therapeutic value. This is an improvement over the ordinary implementation of the patent system, which cannot be effective in eliciting pharmaceutical innovation given that pharmaceutical markets are extraordinarily dysfunctional. The proposal can therefore be used to increase the rate of drug development. Second, it allows for drugs to be priced at approximately the average cost of production, enabling widespread access to drugs. It is possible to achieve both of these goals without increasing government expenditures on drugs, since governments are already large buyers of high-priced drugs. The proposed system is not intended to be an attack on the pharmaceutical industry: on the contrary, it continues to offer healthy profits to pharmaceutical firms which successfully bring valuable, innovative drugs to market, while removing the spectre of poorly-conceived, arbitrary price controls. These advantages suggest that this proposal deserves serious investigation.

8 Appendix

This appendix shows the exact formulation for determining the number of points to be awarded for each patented medicine.

1. The points allocated to medicine A in any year in which it had patent exclusivity for the medicine should be $\sum_i \left[\left(vQALY_i^A - c_i^A\right) - \left(vQALY_i^B - c_i^B\right)\right] q_i^A$, where i indicates the different possible conditions treated by a drug, q_i^A indicates the amount of medicine A sold to treat condition i, v is the standardized value of one QALY, $QALY_i^A$ is the average therapeutic benefit (in terms of QALYs) of a single unit of drug A when used for condition i, and c_i^A is the per-pill treatment cost using medicine A (including the price of the medicine). $QALY_i^B$ and c_i^B are the corresponding therapeutic benefit and cost of the most effective pre-existing treatment not using medicine A, for each condition i. All conditions for which the drug is prescribed should be included in this calculation, including off-label uses.
2. Points could also be allocated to cost-reducing innovations based on consumer benefits from implemented cost reductions. Suppose drug A already exists, and it is registered to firm X. Firm Y develops a new process for making the drug which enables the firm to lower the price of the medicine, so that the treatment cost using drug A falls from c_i^A to $\hat{c}_i^A$. If the new process is patented, it becomes freely available for use in pharmaceutical products, without license fees. Now firm X, firm Y and others may use the new process. Firm X continues to receive points equal to $\sum_i \left[\left(vQALY_i^A - c_i^A\right) - \left(vQALY_i^B - c_i^B\right)\right] q_i^A$, using the original cost of treatment, without the innovation. Firm Y obtains points equal to $\sum_i \left(c_i^A - \hat{c}_i^A\right)\hat{q}_i^A$, where $\sum_i \hat{q}_i^A$ is the number of units sold in which the lower cost process is used. Note that the reward is the same even if a firm improves the production process for its own medicine, i.e. if firm Y is firm X. In case all firms switch from the old process to the new process, an estimate would have to be made of the price at which the drug would have been sold in the absence of the process innovation.[45]
3. A person who was able to show in court the invalidity or unenforceability of all remaining patents on a drug should be rewarded with a share (say 10%) of the previous year's reward for that drug.

PIF payments of type (1) or (2) above should be repayable by the registrant in cases in which a court determined that the registrant's patents were invalid or insufficient to block generic competition in the absence of a compulsory license, with repayment retroactive to the date on which the registrant contested the claims of invalidity. Such repayment is

[45] I remain uncertain about the usefulness of rewarding cost-reducing patents directly, as opposed to allowing licensing to occur privately.

necessary in order to discourage firms from filing speculative patent claims or opposing invalidity claims in court when there is little expectation that a finding of validity will be made.

Category (2) awards give to the innovator rewards which are due to the development of cost-lowering techniques. Note that the innovator is not required to share the cost-reducing process – if it remains secret and is not patented, it can be used to lower only that firm's costs. If patented, then it becomes protected and other firms will want to use it if it in fact lowers their costs. Since the innovating firm benefits from cost reductions at all firms adopting the low-cost process, it would be profitable to patent the cost-reducing technique if the reward fund is large enough. Rewards for cost-reducing innovations are also important to prevent the registrant from disclosing an inefficient, high-cost process when it registers the drug and then making money through selling the medicine at a price far above its true cost of production. Some countries require the patentee to disclose the "best" mode of implementing the innovation in the patent, which is similarly intended to avoid the problem of disclosing an inefficient process. (Without category (2) awards, no independent firm would have an incentive to invest in discovering a lower-cost production method.)

Category (3) awards are necessary to provide an incentive for firms to eliminate invalid or unenforceable patents. Under the current system, generic firms have an incentive to discover invalid or incomplete patents because the first generic firm to obtain FDA approval to market obtains a 6-month generic exclusivity period in the US. Under the proposed system, any person would have an incentive to discover invalid patents, or non-infringing processes. Discovery of invalid patents and non-infringing processes would free up resources in the PIF to pay for genuine advances in drugs.[46] At the same time, however, it is important to ensure that the mechanism used would not encourage excessive, frivolous litigation in the hope of a favorable settlement.[47] There is no reason to think that the proposed system would lead to more or less litigation, if the reward for discovering invalid patents were approximately the same as today.

8.1 An Option to Replace the Fixed Fund with a Dollars per QALY reward

An alternative approach, to replace the fixed PIF, would be to reward innovators with a pre-announced amount per QALY.[48] Drugs would be assessed in the same way as described above to determine the incremental QALYs created over pre-existing therapies, and then rewarded with a fixed dollar amount per incremental QALY. Such an award might be, say, $10,000 per QALY. (In calculating this award, the incremental costs of providing this therapy should be deducted.) This alternative would have exactly the same efficiency properties as the one outlined above. It offers some advantages: first, it removes some risks from innovators, since they could more reliably predict the size of the award they would earn; second, it is plausibly more equitable, as rewards would not depend on what other innovations were in the pool. Counterpoised against these advantages is the disadvantage that governments would be less able to predict their own

[46] It is important to preserve incentives to demonstrate invalidity since the PIF agency would then not have to have the expertise to determine patent validity.

[47] The current system already suffers from a great deal of patent litigation. There is no reason to think that the proposed system would lead to more or less litigation, if the reward for discovering invalid patents were approximately the same as today.

[48] This alternative approach was suggested to me by Joel Hay.

budgetary requirements. In addition, innovators would not be playing against each other to earn rewards from a fixed pool: this would give the PIF Agency much more slack and would not allow it to benefit from the zero-sum game in which firms play against each other.[49] Possibly this option could be used to establish a ceiling on the reward per QALY.

[49] The problem of administrative inefficiency seems to me to be determinative here. If the PIF Agency does not have to make hard decisions with respect to which innovators get how many points, then it will simply allocate more dollars to everyone, resulting in huge bloat in the budget. At the same time, if the budget is unlimited, who will have any incentive to discredit exaggerated claims of effectiveness?

9 References

Abramowicz, Michael, "Perfecting patent prizes." *Vanderbilt Law Review;* Jan 2003; 56(1): 114-236.

Angell, Marcia, 2000, "The Pharmaceutical Industry: To Whom is it Accountable?" *New England Journal of Medicine* 342:1902-1904.

Angell, Marcia, 2004, *The truth about the drug companies*. New York: Random House.

Avorn, Jerry, 2004, *Powerful medicines.* New York: Knopf.

Baker, Dean, 2004, "Financing Drug Research: What are the issues?" mimeo, available at http://www.who.int/intellectualproperty/news/en/Submission-Baker.pdf, last accessed December 13, 2004.

Baker, Dean and Noriko Chatani, 2002, "Promoting Good Ideas on Drugs: Are Patents the Best Way? The Relative Efficiency of Patent and Public Support for Bio-Medical Research", available at http://www.cepr.net/Promoting_Good_Ideas_on_Drugs.pdf, last accessed December 13, 2004.

Brill-Edwards, N., 1999, "Canada's Health Protection Branch: Whose Health, What Protection?" in *Tales from the Other Drug Wars*, ed. M. L. Barer et al. (Vancouver: Centre for Health Services and Policy Research), 39–54.

Calfee, J.E., 2000, *Prices, Markets, and the Pharmaceutical Revolution.* Washington DC: American Enterprise Institute Press.

Davidoff, F, 2001. "The Heartbreak of Drug Pricing." *Annals of Internal Medicine* 134: 1068-1071.

Dickson, M., J. Hurst and S. Jacobzone, 2003, "Survey of Pharmacoeconomic Assessment Activity in Eleven Countries." OECD Health Working Papers No. 4.

DiMasi, J. and H. Grabowski, 2004, "Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D." Submission to the Commission on Intellectual Property Rights, Innovation and Public Health, June 25 2004, available at http://www.who.int/intellectualproperty/news/en/Submission3.pdf, last accessed July 2, 2004.

DiMasi, J., R. W. Hansen, H. G. Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics 22 (2003) 151-185.*

DiMasi J and C Paquette, 2004, "The Economics of Follow-on Drug Research and Development Trends in Entry Rates and the Timing of Development." *Pharmacoeconomics* 22 (Suppl. 2): 1-14.

Doctor JN *et al.*, 2004, "A new and more robust test of QALYs." *Journal of Health Economics* 23: 353-367.

Douglas K, Guell R, 2004. "The structural dynamics of the pharmaceutical industry." *The Industrial Geographer* 1(2): 74-79.

Fleck, Fiona, 2004, "Spending on neglected diseases has increased, says report" *British Medical Journal* 328:1220.

Food and Drug Administration, 2002, "Report to Congress: Reports on Postmarketing Studies [FDAMA 130]." March 2002. Available at http://www.fda.gov/cber/fdama/pstmrktfdama130.pdf , last accessed June 23, 2004.

Gallini, N., and S. Scotchmer. 2001. "Intellectual Property: When is it the Best Incentive Mechanism?" *Innovation Policy and the Economy* 2: 51-78.

Garattini S. and V. Bertele, 2002, "Efficacy, safety, and cost of new anticancer drugs." *British Medical Journal* 325: 269-272.

Gold, M. R., Siegel, J. E., Russell, L. B., and Weinstein, M. C. (1996). *Cost-effectiveness in Health and Medicine.* New York: Oxford University Press.

Goozner, M. 2004, *The $800m pill: The truth behind the cost of new drugs.* Berkeley: University of California Press, 2004.

Guell R. and M. Fischbaum, 1995, "Toward allocative efficiency in the prescription drug industry." *Milbank Quarterly* 73: 213-229.

Guell R. and M. Fischbaum, 1997, "Estimating allocative efficiency in the prescription drug industry." *Applied Economics Letters* 4: 419-423.

Hay, Joel and Winnie Yu, 1999. "Drug Patents and Prices, Can We Achieve Better Outcomes?" in Triplett J, ed. *Measuring the Prices of Medical Treatments*, Brookings Press, Washington, DC., pp.152-195.

Hollis, Aidan and Sean Flynn, 2003, "An Economic Analysis of Compulsory Licensing for Needed Medicines." Mimeo, Department of Economics, University of Calgary.

Hollis, Aidan, 2002, "The Link Between Publicly Funded Health Care and Compulsory Licensing" *Canadian Medical Association Journal* 167: 765-767.

Hubbard, Tim and James Love, 2004, "A New Trade Framework for Global Healthcare R&D." *PLoS Biology* 2(2): 0147-0150

Juni P, Rutjes A, Dieppe P, 2002. "Are Selective Cox-2 Inhibitors Superior to Traditional Nonsteroidal Anit-inflammatory Drugs?" *British Medical Journal* 324: 1287-1288.

Kaitin KI, editor, 2004. "Incremental R&D creates safer, more effective drugs & fosters competition." *Tufts Center for the Study of Drug Development Impact Report* 6(6).

Kieff, F. Scott, 2001. "Property Rights and Property Rules for Commercializing Inventions." *Minnesota Law Review* 85: 697-754.

Kremer, Michael, 1998. "Patent Buyouts: A Mechanism for Encouraging Innovation." *Quarterly Journal of Economics* 113: 1137–67.

Kremer, M and R. Glennerster, 2004. *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton NJ: Princeton University Press.

Krupnick, Alan, 2004. "Valuing Health Outcomes: Policy Choices and Technical Issues." Resources for the Future, Washington.

Lee, TH, 2004, " 'Me-too' products: Friend or Foe?" *New England Journal of Medicine* 350(3):211-212.

Lexchin, Joel, 2003, "Intellectual Property Rights and the Canadian Pharmaceutial Marketplace: Where Do We Go From Here?" Canadian Centre for Policy Alternatives discussion paper. Available at http://www.policyalternatives.ca/publications/ipr.pdf, last accessed June 22, 2004.

Love, James, 2003, "Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines," mimeo, available at http://www.cptech.org/ip/health/rnd/evidenceregardingrnd.pdf, last accessed June 22, 2004.

Lybecker, Kristina, 2003, "Rx Roulette: Counterfeit Pharmaceuticals in Developing Nations." Drexel University, Department of Economics, mimeo, available at http://www.lebow.drexel.edu/lybecker/Lybecker.pdf, last accessed May 31, 2004.

Maeder, Thomas, 2003, "The FDA Meets the 21st Century." Available at http://www.understandinggovt.org/maeder.html, last accessed September 25, 2004.

Masters, Will, 2004, "Prizes for Innovation in African Agriculture: A Framework Document." Mimeo, available at www.earth.columbia.edu/cgsd/prizes, last accessed August 29, 2004.

Nash, DB and JL Clarke, 2003, "Putting ALLHAT into Perspective." *P&T Journal* 28(9): 585-590.

National Institute for Health Care Management Research and Educational Foundation, 2002, "Changing Patterns of Pharmaceutical Innovation," NIHCM, Washington.

Outterson, K., 2004, "Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets." *Yale Journal of Health Policy, Law and Ethics*, forthcoming.

Reinhardt, U. 2001. "How to lower the cost of drugs." *New York Times*, 3 January 2001, p. A17.

Rosenthal M. B. et al, 2002, "Promotion of Prescription Drugs to Consumers." *New England Journal of Medicine* 346:498-505.

Scotchmer, S., 2005, *Innovation and Incentives*. Cambridge: MIT Press.

Shavell, S. and T. van Ypersele, 2001, "Rewards vs. Intellectual Property Rights." *Journal of Law and Economics,* XLIV: 525-547

Smith KJ, and MS Roberts, 2000. "The cost-effectiveness of sildenafil." *Annals of Internal Medicine* 132: 933-7.

Wright, Brian D. "The Economics of Invention Incentives: Patents, Prizes, and Research Contracts." *American Economic Review* 73 (1983): 691–707.